CANCER CARE DELIVERY AND WOMEN'S HEALTH

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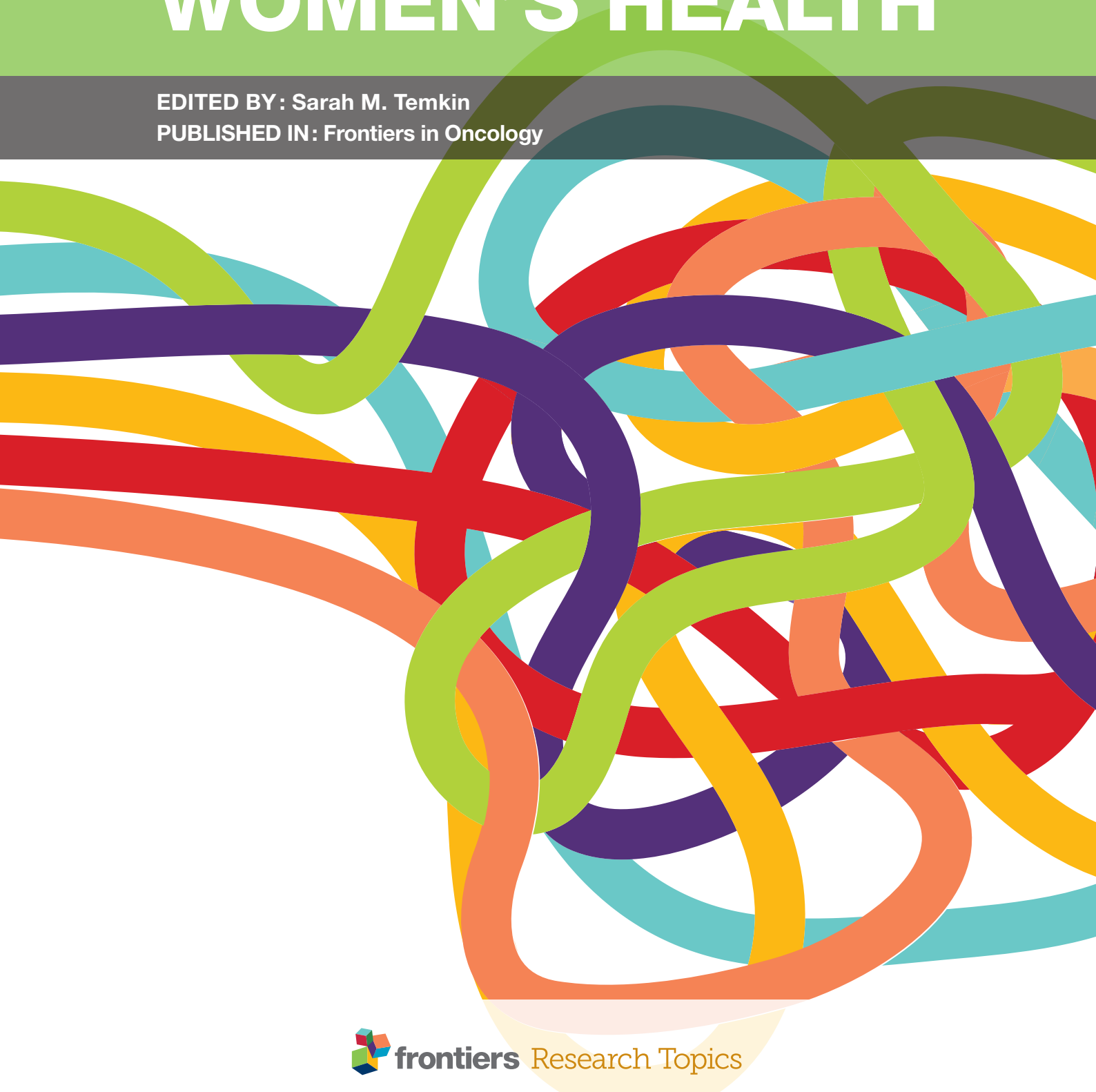

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CANCER CARE DELIVERY AND WOMEN'S HEALTH

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Cancer care delivery refers to the multiple layers of the health care system that interact to affect outcomes for patients with cancer and the quality of that care. The factors included in the care delivery system that potentially alter outcomes include social dynamics, financing systems, organizational structures and processes, health technologies, provider and individual behaviors. Because women's health care has its own unique challenges, the intersection between cancer care delivery and women's health is to be examined in this Frontiers in Oncology issue. The unique opportunities and challenges of improving the health care system for women with breast and gynecologic cancers are to be explored in depth. We will visit many topics of cancer care delivery with the unique perspective geared towards the care of women's malignancies.

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EDITORIAL
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Editorial: Cancer Care Delivery and Women's Health: Beyond the Patient and Provider Relationship

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Keywords: cancer care delivery, women's health, gynecologic cancer, breast cancer, health systems

Editorial on the Research Topic

Cancer Care Delivery and Women's Health: Beyond the Patient and Provider Relationship

The number of cancer patients and survivors worldwide continues to grow as a result of our growing and aging population. In 2013, an Institute of Medicine report detailed a crisis of the cancer care delivery system resulting in larger numbers of cancer patients combined with increasingly complex treatments and rising costs associated with health care (1). Since that time advances in genomics and a call for precision medicine have augmented these concerns and our expenditures on cancer care have continued to rise.

Multiple factors within the health-care system impact the experience of the cancer patient and oncology provider. Women with cancer are often the primary social support of their family creating unique social impediments for the families of patients. Additionally, part of a diagnosis of breast or gynecologic malignancy may include a perceived loss of "womanhood" and related body image concerns (2). Historical inequality, cultural perceptions, and attitudes and implicit bias impact the way that female cancer patients interact with the health-care system and may complicate shared decision-making and generate psychosocial barriers to quality care delivery. The multilevel interventions needed to advance the care and experience of the breast and gynecologic cancer patient are, therefore, distinct. In this issue of Frontiers in Oncology, Women's Health, we explore the specific challenges of the cancer care delivery system as it relates to the care of women with breast and gynecologic cancer.

Cancer care delivery refers to the multiple layers of the health-care system that interact to affect outcomes for patients diagnosed with malignancies and the quality of that care. These layers include but are not exclusive to the patient, her caregiver, the health-care team, the clinic or hospital, the health insurance system, pharmaceutical companies, and the government. Whereas cancer care of the 20th century primarily revolved around the oncologist–patient relationship, the scope of care for the cancer patient and survivor has grown significantly. Oncologic outcomes can be negatively impacted by the stress of navigating the complex structures of the health-care system (3, 4). The network of cancer care now includes multiple additional practitioners that the patient is in direct contact with (physical therapists, nutritionist, wound care nurse, etc.); practitioners that patient will never see (radiologists, pathologists, etc.); and countless ancillary staff members (tumor registrar, health insurance specialists, electronic medical records information technologist, etc). New subfields related to oncology (supportive care, onco-dermatology, etc.) have flourished. This intricate web of consultants has expanded to the point that patient navigators are now routinely employed within large cancer centers to ensure that the patient is able to find her way through the cancer care experience. Special populations such as the poor, the elderly, and minority women are at particular risk of getting lost within the system. Despite all this complexity, simple, inexpensive therapies such as collecting patient-reported outcomes or

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integrating palliative care into standard oncology practice that have demonstrated, statistically significant, clinical benefits are underutilized in clinical practice (5, 6).

Interdisciplinary teamwork is essential for all of these moving parts to function seamlessly, but teamwork and inter-team cooperation is not always incentivized by the health-care system (7). Shared decision-making becomes challenging when overlapping teams participate in the care of an individual patient without coordination and clear lines of communication. Novel oncology payment models, including accountable care organizations and pay for performance are being studied to improve a more collaborative approach to cancer care. The goal of innovative reimbursement strategies is to encourage all parts of this multifaceted system to work together while controlling cost (8).

Working toward a goal of a seamless patient experience within a system where all the moving parts work toward a common goal of best cancer care has spurred a new field of research—Cancer Care Delivery Research—which is defined by the National Cancer Institute as "how social factors, financing systems, organizational structures and processes, health technologies, and health-care provider, and individual behaviors affect cancer outcomes, access to and quality of care, cancer care costs, and the health and well-being of cancer patients and survivors." This field of research extends upon quality improvement and focuses on multilevel interventions to improve and inform cancer care through modifications of the structures and processes of cancer care delivery to enhance the patient experience and optimize value (9). Standard measures of care quality are needed outcomes to be accurately reported. Big data—electronic health sets so large and complex that they are difficult to manage with traditional software—are essential to this charge (10). Big data have the potential to transform the way health-care systems use technologies to provide feedback to practitioners and expand the evidence base for quality care in near real time.

Ultimately reducing fragmentation, increasing coordination and accurately measuring outcomes within the cancer care delivery system has enormous potential to improve oncologic care for women with breast and gynecologic cancers by minimizing under- and over-treatment, reducing health-care disparities and improving the experience of cancer care for patients and caregivers.

AUTHOR CONTRIBUTIONS

The author is responsible for the design of this article, the research, and the writing.

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REVIEW
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Payment Reform: Unprecedented and Evolving Impact on Gynecologic Oncology

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With the signing of the Medicare Access and CHIP Reauthorization Act in April 2015, the Centers for Medicare and Medicaid Services (CMS) is now positioned to drive the development and implementation of sweeping changes to how physicians and hospitals are paid for the provision of oncology-related services. These changes will have a long-lasting impact on the sub-specialty of gynecologic oncology, regardless of practice structure, physician employment and compensation model, or local insurance market. Recently, commercial payers have piloted various models of payment reform via oncology-specific clinical pathways, oncology medical homes, episode payment arrangements, and accountable care organizations. Despite the positive results of some pilot programs, adoption remains limited. The goals are to eliminate unnecessary variation in cancer treatment, provide coordinated patient-centered care, while controlling costs. Yet, meaningful payment reform in oncology remains elusive. As the largest payer for oncology services in the United States, CMS has the leverage to make cancer services more value based. Thus far, the focus has been around pricing of physician-administered drugs with recent work in the area of the Oncology Medical Home. Gynecologic oncology is a unique sub-specialty that blends surgical and medical oncology, with treatment that often involves radiation therapy. This forward-thinking, multidisciplinary model works to keep the patient at the center of the care continuum and emphasizes care coordination. Because of the breadth and depth of gynecologic oncology, this sub-specialty has both the potential to be disrupted by payment reform as well as potentially benefit from the aspects of reform that can align incentives appropriately to improve coordination. Although the precise future payment models are unknown at this time, focused engagement of gynecologic oncologists and the full care team is imperative to assure that the practice remains patient centered, embodies the highest quality in research and education, yet transforms into a sustainable and agile sub-specialty to pro-actively and effectively manage the immense and relentless financial pressures and regulatory expectations that will be faced over the next decade.

Keywords: physician payment reform, gynecologic oncology, MACRA, MIPS, alternative payment models

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INTRODUCTION

On April 16, 2015, President Barack Obama signed the Medicare Access and CHIP (Children's Health Insurance Program) Reauthorization Act (MACRA). This new legislation repealed the ineffective and maligned sustainable growth rate (SGR) mechanism of updating fees to the physician fee schedule (1, 2). As the policies within MACRA are implemented, they will significantly impact

reimbursement and care delivery for oncology services. Many payment reform models piloted thus far have primarily focused on primary care and hospital-based episodes of care with recent pilots in medical oncology. These models vary in the extent to which physician services are aggregated across providers and the degree to which payments are distributed across different settings. Examples include the use of a modified pay-for-performance or a fee for the use of disease specific oncology pathways, bundled payments, oncology patient-centered medical homes (PCMHs), episode payment for services, and accountable care organizations (ACOs). The sub-specialty of gynecologic oncology is unique; physicians frequently function as both the surgeon as well as the medical oncologist. They often coordinate other modalities of therapy, such as radiation, and frequently remain the primary coordinator of their patients' cancer care team throughout the trajectory of their disease. This includes those patients who transition to hospice. The nature of the training of gynecologic oncologists yields important efficiencies in terms of care coordination and potential reduction in unnecessary treatments or duplicative testing. Due to the breadth and depth of the subspecialty, physician payment reform will significantly impact the practice of gynecologic oncology. In this paper, we will first review some historic and current methods to achieve payment reform. Then we will review the preliminary details and implications of MACRA and discuss the possible profound and long-lasting effects on gynecologic oncology.

Historic and Current Components of Payment Reform

Currently, fee-for-service (FFS) is the most common reimbursement methodology in oncology despite efforts to implement alternative approaches. This form of payment can inadvertently incent high-volume, high-cost procedural services. FFS often undervalues or fails to reimburse evidence-based, cost efficient, effective services such as patient education, prevention, care coordination, or end-of-life discussions. As an unintended consequence, these perverse incentives can lead to fragmentation, inefficiency, and waste. Payment reform in the FFS system previously has consisted of pay-for-performance (P4P) programs that have usually been a variation of FFS payments with a bonus element added for achieving certain quality milestones. Historic quality contracts have generally been a P4P model with limited success.

The care of women with gynecologic malignancies in the United States has greatly improved over the last several decades. A recent study demonstrated an improvement in relative survival for all stages of ovarian cancer from 1975 to 2011 (3). Possible reasons for this beneficial trend include the recognition of the importance of surgical staging and cytoreductive procedures; platinum and taxane-based therapy; intra-peritoneal chemotherapy; and the development of other effective chemotherapeutic and biologic agents. A population-level analysis from 1983 to 2009 showed an improvement in relative survival for women with stages I–III cervical cancer (4). A recent study demonstrated an improvement in overall survival in patients with recurrent, persistent, or metastatic cervical cancer with the addition of bevacizumab to combination chemotherapy (5). There was no significant deterioration in health-related quality of life in patients receiving anti-angiogenic therapy (6). Such advancements in cancer survival and maintenance of quality of life are predicated on scientific research. Efforts in both academia and industry have yielded progress in the understanding of the mechanisms of cancer prevention and treatment, paving the way to novel therapies that translate into improved outcomes. Due in part to the success in cancer therapy, increasing demand, and the demographics of an aging population, cancer care will remain a major driver of escalating healthcare spending in the United States. In the United States, approximately 1.6 million people are diagnosed with cancer annually. A 2011 study projected total cancer spending to be approximately $157 billion in 2020 – a 27% increase from 2010 (7). "The distribution of total cancer care costs is 32% for chemotherapy drugs, administration, and radiation; 33% for inpatient and physician surgical claims; and 12% for other physician services. The remaining 22% is composed of evaluation and management, hospice, laboratory tests, imaging services, and inpatient stays without surgery" (8). Due to the broad range of services provided by many gynecologic oncologists, the sub-specialty contributes to numerous different categories contributing to the total cost of cancer care. Therefore, the impact of payment reform on gynecologic oncology could be significant.

Sustainable Growth Rate

The SGR was a method previously used by the Centers for Medicare and Medicaid Services (CMS) that was designed to control spending on physician services. Enacted by the Balanced Budget Act of 1997, the SGR was designed to ensure that the annual increase in the expense per Medicare beneficiary did not exceed the growth in the Gross Domestic Product. The SGR formula was responsible for determining the annual increases or decreases to the Medicare physician fee schedule. Under the SGR mechanism, if the growth in the volume of services exceeded the target growth rate, the yearly update to fees was to be reduced with a "conversion factor" to bring spending in line with the target. The short-term fixes imposed administrative burdens on CMS and clinicians and they created uncertainty for health care professionals and beneficiaries about uninterrupted access to care (9). The resulting instability and uncertainty led to 17 overrides of scheduled fee cuts. The repeal of the SGR now means that the temporary measures to override the growth rate formula will no longer dominate Medicare policy discussions, as they have for the last decade. The replacement of the SGR should also accelerate the movement away from unconstrained FFS payments and toward continued payment reforms.

Physician Quality Reporting System

The Physician Quality Reporting System (PQRS) is a voluntary quality reporting program established by CMS in 2007, which follows a P4P model – namely that physicians are paid a fraction of their FFS payments initially as a positive bonus on their overall reimbursable claims. The program was designed to encourage both individual providers as well as group practices to report quality of care data to Medicare (10). PQRS provides the opportunity to assess the quality of care provided by a physician or practice and quantify their performance on a particular metric. Beginning in 2015, if an eligible professional or group practice did not satisfactorily report

PQRS measures in 2013, they would receive a 1.5% payment penalty on their 2015 Medicare reimbursements. Providers and practices who report in a compliant manner for the 2015 program year will not receive the 2017 PQRS negative payment adjustment. The Society of Gynecologic Oncology (SGO) has published PQRS measures relevant to gynecologic oncology (11).

Electronic Health Records Incentive Programs ("Meaningful Use")

The electronic health record (EHR) incentive program was established as part of the American Recovery and Reinvestment Act of 2009 (ARRA). ARRA amended the Social Security Act by creating incentive payments to providers and hospitals "to promote the adoption and meaningful use (MU) of interoperable health information technology (HIT) and qualified EHRs. These incentive payments are part of a broader effort under the HITECH (Health Information Technology for Economic and Clinical Health) Act to accelerate the adoption of HIT and utilization of qualified EHRs" (12). "MU" has three stages that began in 2011. The objective of Stage 1 (2011–2012) was to promote basic EHR adoption, data capture, and sharing. For Stage 2 (2014), the objectives were to advance clinical processes and emphasize care coordination and the exchange of patient information. Stage 3 is expected to be implemented in 2016 with a goal to show that the quality of health care has been improved.

Physician Value-Based Payment Modifier

The Affordable Care Act (ACA) directs the Secretary of Health and Human Services (HHS) to develop and implement a budget-neutral process to financially reward physicians who provide health care that is high in quality and low in cost (13). This system, the physician value-based payment modifier (PVBM), will adjust the fee schedule payments based on the quality and cost of care delivered to Medicare beneficiaries. "The PVBM reward formula is a system in which performance is assessed in two dimensions (quality and cost), with payments accruing to physicians who have above-average performance along both dimensions. Physicians who perform worse than average or choose not to be involved will be paid less, while those with average performance will experience no change" (14). The maximum bonus is ~2% of Medicare fees and the maximum penalty is ~1%, based on the 2013 program year (13). Thus, the model is similar to a P4P-type program with the majority of payments in a traditional FFS setting and a smaller bonus or penalty based on performance. When defining PVBM, "CMS will use the PQRS quality measures reported by individual physicians and by groups under that program's reporting mechanism of which there are several options. Total per capita costs for Medicare beneficiaries will be used to calculate a cost composite score for the value-based payment modifier" (14).

MEDICARE ACCESS AND CHIP REAUTHORIZATION ACT OF 2015 ERA

When Congress passed the MACRA, it gave HHS the authority to move ahead with alternative payment models (APMs). MACRA introduced comprehensive changes to how Medicare pays physicians and hospitals for among many areas, oncology-related services. MACRA makes three important changes to how Medicare pays healthcare providers who care for Medicare beneficiaries. First, the new law repeals the SGR formula as a mechanism for determining Medicare payments for physicians' services and puts into place a predictable annual increase through 2019 before a complete transition to the new system described below. Second, MACRA establishes two payment options beginning in 2019, which create a new framework for rewarding providers for giving better care and not simply more care. One option is the merit-based incentive payment system (MIPS) that consolidates current programs and retains many elements of the current FFS structure with a new system for positive or negative adjustments to the fee schedule payments. Critics have argued that in many ways, it is largely a P4P-type model and many physicians who are either confused or intimidated by APMs will chose MIPS and potentially tolerate penalties and flat/negative payment adjustments in medicare. The second option, participation in an APM, is different from the current FFS system. Both choices move toward a valued-based system, with an overarching emphasis on quality, not volume, of healthcare services provided. Regardless of the pathway within MACRA, the new reimbursement system will likely require transformative changes to the structure of a medical practice. Both paths require practices to (1) report quality metrics, (2) demonstrate MU of EHRs and use resources responsibly, and/or (3) take on financial risk. Third, MACRA incentivizes practice transformation by combining the existing quality reporting programs into one new system. While many have hailed the repeal of the SGR mechanism, the passage of MACRA now raises new questions about where the United States health care system is headed in the post-SGR world of payment and delivery reform.

Merit-Based Incentive Payment System

The MIPS is a new payment system that consolidates existing P4P programs and accounts for quality, resource use, EHR utilization, and clinical practice improvement. MIPS combines parts of the PQRS, the PVBM, and the MU program – and adds a new category of clinical practice improvement activities – into a single program that will assess physicians on these categories. The MIPS Composite Score will include components for quality (approx. 30% based on PQRS by 2021), MU (initially 25%, then reduced to 15%), resource use (30% based on PVBM by 2021), and clinical practice improvement (25%). Clinical practice improvement activities are those that contribute to advancing care coordination, safety, and care. Examples include expanding access, care coordination, safety, and participation in registries. Although details on MIPS will be the subject of policymaking for several years, it is important to understand that some of the assessments made at the effective date of 2019 will be based upon 2017 data. For the 2015 and 2016 performance years, the PQRS, PVBM, and MU programs will continue as separate payment adjustment programs. MACRA provides physicians and other health care professionals with stable fee updates for 5 years (an update of 0.5% for the last 6 months of 2015 and an increase of 0.5% per year for 2016 through 2019). For 2015 to

2018, the current payment system remains unchanged. Under MIPS, the payment rates in 2019 will be maintained through 2025 but with positive and negative adjustments based on the composite performance score of each eligible physician or other health professional on a 0- to 100-point scale. The scores will be publicly reported on the CMS Physician – Compare website. The composite score will be reported for all providers, compared to peers, and will be available to consumers. The adjustments, however, are designed to be budget neutral so that there would be no effect on overall payments beyond an additional $500 million that would be made available each year from 2019 to 2024 to reward excellent performance (15). The MIPS payment adjustments can be significant (±9% adjustments) with top performers earning +27%.

Alternative Payment Models

The leadership at the Department of HHS aims "to have 30% of Medicare payments tied to quality or value through alternative payment models by the end of 2016 and 50% of payments by 2018" (16). Under the new legislation, clinicians who receive a substantial portion of their revenues from approved APMs will not be subject to MIPS. Instead, they will receive a 5% bonus each year from 2019 to 2024. To qualify, the APM must comprise 25% of provider revenue or patients between 2019 and 2020. By 2023, this increases to 75% of provider revenue or patients. In 2026, the payment rules for all clinicians change again, with payment rates under the APM increasing by 0.75% per year and rates for others increasing by 0.25% per year. MACRA incentivizes participation in APMs by establishing a system in which, beginning in 2019, qualifying healthcare providers may receive a lump sum for participation in a certified APM at a certain level. That incentive payment will be equal to 5% of the prior year's estimated aggregated expenditures under the fee schedule. Beginning in 2026, when the lump sum payment goes away, the baseline fee schedule payments will still be higher for qualifying APM participants than for other providers in the MIPS system. APMs must involve a downside risk and quality measurement. While, currently, there are not many APMs for oncology, the legislation encourages development and recognition of models available to medical specialists, such as oncologists. How an APM will be recognized for purposes of the program is still evolving, but may include existing models, such as ACOs, PCMHs, and bundled payment models. MACRA also introduces a new pathway to qualify APMs, called physician-focused payment models (PFPMs). While CMS will determine which PFPMs qualify as an APM under MACRA, the law mandates that qualifying PFPMs require the reporting of quality measures, the use of certified EHRs, and that the physician has "more than nominal financial risk" (with the exception of a PCMH, for which the risk requirement is waived). Stakeholders can submit proposals. A newly established Technical Advisory Committee will assess PFPM proposals from stakeholders and make recommendations to the HHS Secretary about which models to adopt as a qualifying APM and the Secretary will consider and release a list of available APMs. The Secretary must release criteria for a qualifying APM by November 1, 2016.

Approaches to the Design of Oncology-Focused APMs

Potential designs for APMs may be viewed along a continuum through greater bundling across either providers or payments. "APMs transition from volume- to case-based payments, reduce or limit the FFS component, and use performance measures to hold providers accountable. Providers gain flexibility by decoupling provider payments from the volume and intensity of specific services, but they also face greater accountability for lowering costs, and depending on the performance measures that affect payment, for better quality care and better results" (8). The ability of an APM to improve outcomes also depends on investments and support, such as the timely collection and analysis of validated data, systematic processes for data-driven learning, and deployment of user-friendly HIT systems. The success of more transformative APMs – including oncology PCMHs and oncology ACOs – will require greater investments in human resources, work flow changes, provider engagement, and other aspects of practice change, such as strategies to increase scale and deployment of sophisticated cost accounting tools. Successful implementation of a PCMH or an ACO will also impose a heavier administrative burden compared to clinical pathways or bundled payment models.

The specific type of APM implemented will also depend on the physician employment structure. The spectrum of an oncology provider's employment model spans from single-specialty private practice, multi-specialty independent group practice, to hospital-based employment in a comprehensive cancer center or large regional multi-hospital system. In each scenario, there will be variation in the extent of physician alignment and the ability to bundle professional and technical charges. Although smaller practices may be more agile to respond to change, large-scale operations can reduce costs via efficiency, controls, standardization, and supply chain management. A large-scale health care system, offering a broad range of services across the care continuum, may also be more adept at retaining a patient throughout their oncology journey. In addition to medical, surgical, and radiation oncology-related services, this could include emergency room visits, home health, palliative care, and other medical specialty services across a large geographic area. Therefore, factors, such as physician integration, scope of services offered, and the scale of the health care enterprise, will significantly impact the decision of which APM is most appropriate in any local market.

A recent paper provides an outline of four different APMs – clinical pathways, oncology PCMHs, bundled payments, and oncology ACOs – to show a continuum of payment incentives that can influence the extent to which care delivery changes limit or reduce costs (8). These APMs were selected "because they can support incremental to comprehensive clinical transformations, thereby accounting for the breadth and size of oncology practices, populations served, and payer types." These reforms, summarized in **Table 1**, can be viewed as building blocks along the spectrum of payment reforms.

Clinical Pathways

Oncology-specific clinical pathways are standardized, evidence-based, dynamic, cost-effective protocols for the treatment of

cancer patients. Although development, implementation, and assessment of compliance are challenges, pathways require comparatively limited structural changes to a practice or provider risk (30). This model is designed to encourage providers to adhere to disease-specific oncology pathways while reaching or exceeding quality benchmarks. An additional case management fee may be necessary to off-set the administrative burden of assessing pathway compliance and pathway maintenance. Early results show that pathway programs can decrease cost growth through diminished use of aggressive treatments that are not supported by clinical guidelines (31). Two papers demonstrate that pathways can reduce variation in chemotherapy use, while maintaining overall survival rates (32, 33). Reducing unnecessary clinical variation and providing more predictable costs is another goal of these reforms. Pathways alone, however, may not have a significant impact on care coordination or other aspects of personalized care. For some oncologists, pathways may represent an initial foray into practice standardization and assessment of compliance with evidence-based practice. Depending on the extent of physician integration and practice structure, proactive change management and a realistic assessment of local culture will be imperative to set the pace for pathway implementation and ultimately impact the likelihood of sustainable compliance.

Oncology Patient-Centered Medical Home

"The oncology PCMH is a practice-level approach that promotes care coordination and improvement through payments that are more extensively aligned with practice features expected to improve patient outcomes and patient-level performance measures" (8). Providers can use a per beneficiary per month fee in an oncology PCMH to support services that have traditionally not been reimbursed (i.e., access through expanded office hours, team-based care models, and advanced HIT) to encourage better patient education and care coordination and management (34). A successful implementation of an oncology PCMH would likely require an engaged and well-integrated group of oncology teams spanning a variety of sub-specialties beyond oncology. Improved care coordination combined with robust support for cost-effective services in the oncology PCMH model potentially reduces hospitalizations and emergency department (ED) visits, prevents overutilization of unnecessary high-cost drugs and services, and improves symptom management beyond the hospital setting (34, 35). Preliminary results from one oncology PCMH showed reductions in ED visits (68%), hospital admissions per patient treated with chemotherapy (51%), length of stay for admitted patients (21%), overall outpatient visits (22%), and outpatient visits in the chemotherapy population (12%) (34, 36). Although the increased administrative burden may erode margins, successful oncology PCMH models have reported significant net cost reductions via reduced ED visits and hospitalizations. One oncology PCMH reported aggregated savings of approximately $1 million per physician per year (37). Another program also saw substantial cost reductions from lower utilization of hospital admissions (34%), hospital days (44%), and ED visits (48%) (35). However, these savings have not been reproduced in all cases. The physician compensation model, practice structure, healthcare market, and local payer strategy may influence the level of adoption of an oncology PCMH. More evidence is required relevant to oncology PCMHs to determine specific factors of the payment and delivery reforms that may improve the likelihood of success.

Bundled Payment

A more comprehensive bundled payment methodology is possible, either within or outside an oncology PCMH. Providers are generally compensated with a one-time payment for a specific set of cancer services over a pre-determined treatment period or episode of care (32). "To the extent a broader range of services are bundled, providers can gain even more flexibility to redirect resources to cost-effective patient-centered activities that FFS does not reimburse" (8). The provider subsequently incurs greater accountability and more pressure to reduce the cost of care (38, 39). Recent results from one bundled payment pilot show a 34% reduction in total cost of care (40).

The extent of coverage of a bundled payment in oncology can vary based on how the bundle is designed. A bundle could be based on a timeframe; or within a pre-specified boundary on a pathway; or include technical and/or professional charges. Many other factors will need to be pre-determined. For example, how are costs allocated when care is delivered outside the scope of the agreement or in non-contracted facilities and labs? Most early pilots are limited bundles that included the administration of chemotherapy and supportive-care drugs (32, 39, 41, 42). More comprehensive bundles may include the drug acquisition costs, imaging and lab services, surgery, or radiation therapy. Bundled payments must be linked to performance benchmarks. To date, there are few prospective total cost bundles; there is a ground-breaking pilot program in head and neck cancer that bundles the total cost of care for 1 year in a prospective payment (24). The increased probability for cost variation per patient that accompanies more comprehensive bundles would imply that providers face more uncertainty about their net revenues. This likely explains why more comprehensive bundles have not been widely adopted to date. Another barrier to adoption is the challenge of cost accounting in a complex health care system. Factors such as physician integration and the ability of a hospital to fully cost expenses (i.e., labor, overhead, pharmacy, supplies, etc.) may vary widely. Therefore, there will likely be significant variation in the level readiness of oncologists and hospitals to move forward with bundled payments. At least initially, there may be significant variation in the scope and cost of a bundle based on local and regional factors. In the future, as more meaningful quality metrics become publically available, bundle payments may drive consumerism and competition.

Oncology-Specific Accountable Care Organization

The oncology ACO model partially links reimbursement to overall costs and quality of care for patients with cancer. In comparison, a "shared savings" oncology ACO would provide an incentive beyond the usual FFS payments, based on whether total spending for the relevant patients is below a benchmark and whether quality measures meet the pre-determined threshold. In an ACO environment, providers are accountable for the cost,

TABLE 1 | Comparison of oncology payment models by delivery, physician employment, and payment structure, and quality measurement.

Payment model		Clinical pathways	Oncology PCMH	Bundled payment	Oncology-specific ACO	Global payment
Delivery structure	Use of evidence-based pathways or guidelines	Yes	Yes	Yes	Yes	Yes
	Care coordination focus	No	Yes	Yes	Yes	Yes
	Requires major practice transformation	No	Yes	No (for the types of bundles currently in market)	Yes	Yes
Probability of implementation based on physician employment structure	Single-specialty group, private practice	Medium	Low	Low	Low	Low
	Multi-specialty group, private practice	Medium	Medium	Low	Low	Low
	Hospital employed, single general hospital	High	Medium	Medium	Low	Medium
	Hospital employed, comprehensive cancer center	High	High	Medium	Medium	Medium
	Hospital employed, multi-hospital system	High	High	High	High	High
Payment structure	Case-based payment component	Revenue neutral supplemental payment for pathways adherence	PMPM management fee	Episode-based prospective or retrospective payment for pre-determined defined bundle of service	Partial capitation	Total capitation
	Transition from P4P to value-driven care	P4P	P4P	Value driven	Value driven	Value driven
	Potential for global or capitated payment	No	No	Partially based on boundary of bundle (i.e., inpatient, imaging, ancillary service, etc.)	Yes	Yes
	Payment majority linked to quality and financial performance outcomes	No	No	Yes	Yes	Yes
Quality measurement	Incentives for continuous quality improvement activities	No	Yes	Yes	Yes	Yes
Pilot programs		Alabama Health Improvement Initiative, Oncology Clinical Pathways Pilot (17) and The WellPoint Cancer Care Quality Program (18)	New Mexico Cancer Center (19) and Wilshire Oncology Medical Group (20), Cancer & Hematology Centers of Western Michigan (21), Consultants in Medical Oncology and Hematology (22), and COME HOME, Moffitt Cancer Center and Aetna Oncology Medical Home Collaboration (23)	MD Anderson and UnitedHealthcare pilot in Head & Neck Cancer (24), Mobile Surgery International and BCBS of Florida (25), and Humana and 21st Century Oncology (26)	Florida Blue and Moffitt Cancer Center (27) and Baptist Health South Florida, Florida Blue and Advance Medical Specialities (28)	All-Payer Innovation Model in State of Maryland (29)

Adapted from KP's original work (8).

Patient-centered medical home (PCMH), accountable care organization (ACO), pay for performance (P4P), per member per month (PMPM).

quality, and overall care for a population in exchange for the opportunity to share savings with the payer. Therefore, the ACO construct encourages proactive management to deliver efficient, coordinated, and cost-effective cancer care. The increased accountability places critical importance on the administrative component of the ACO to manage and coordinate care thoughtfully. For this reason, some practices will require a significant transformation of practice and additional resources to participate as an oncology ACO.

Given the increasingly personalized, costly, and highly variable nature of oncology care, traditional ACOs have taken a measured approach toward oncology-specific reforms. Despite these challenges, there are several pilots of oncology-specific ACO arrangements and oncology-focused arrangements within population wide ACOs. These models link payment to performance metrics (**Table 1**). "Such oncology ACOs may also be partially or fully capitated, with some or all of the FFS payments related to oncology shifted into a fixed, risk-adjusted payment per patient that is contingent on meeting performance benchmarks. The extent to which an oncology ACO model resembles a global payment depends on the size and scope of the shift from FFS to a fully bundled capitation payment and whether other specialties

are included" (8). The oncology ACOs remain in the early phase of development, but they are on a path of increasing clinical and financial risk (27, 43). To date, there is one global payment pilot (29) in which the case-based payment is totally capitated. In this innovative model, Maryland and CMS will evaluate an all-payer system for hospital payment. Payment will be based on Medicare per capita total hospital cost growth. In exchange, Maryland will be accountable to generate a pre-determined cost savings while achieving quality targets in the domains of readmission, hospital acquired conditions, and population health. Oncology services would be included in this pilot.

MEDICARE ONCOLOGY CARE MODEL

Centers for Medicare and Medicaid Services is developing novel payment and care models with the goal of improving the effectiveness and efficiency of specialty care. In February 2015, CMS's Center for Medicare and Medicaid Innovation (CMMI) introduced a new payment and practice reform model, the oncology care model (OCM). The OCM is an innovative model for physician practices administering chemotherapy. Under the OCM, practices will enter into payment arrangements that include financial and performance accountability for episodes of care surrounding chemotherapy administration to cancer patients.

The goal of the OCM is to utilize appropriately aligned financial incentives to improve care coordination, appropriateness of care, and access to care for beneficiaries undergoing chemotherapy. The OCM encourages participating practices to improve care and lower costs through an episode-based payment model that financially incentivizes high-quality, coordinated care. Practitioners in an OCM are expected to rely on the most current medical evidence and shared decision-making. The OCM encourages commercial payers to participate in alignment with Medicare to create broader incentives for care transformation at the physician practice level. Other payers would also benefit from savings, better outcomes for their beneficiaries, and information gathered about care quality.

IMPACT ON GYNECOLOGIC ONCOLOGY

Much is still unknown in terms of the details of the MIPS and APMs and the subsequent impact on gynecologic oncology. The majority of current efforts to address new payment models focus heavily on medical oncology. In medical oncology, examples of pilot programs include CMMI's Oncology Care Model (44) and Regional Cancer Care Associates and Horizon BCBS (45). The latter pilot focuses on bundled payments for breast cancer patients treated with chemotherapy. There are a limited number of APMs for surgical oncologic procedures. Mobile Surgery International and BCBS of Florida have designed a bundled payment for radical prostatectomy for early-stage patients (25). In radiation oncology, 21st Century Oncology and Humana have developed a bundled payment for radiation therapy for 13 prevalent diagnoses, including breast, lung, and prostate cancers (26). On January 1, 2015, MD Anderson partnered with UnitedHealthcare in a pilot bundle in the treatment of head and neck cancers (24). This pilot program prospectively covers the total cost of care for head and neck cancer for 1 year. The sub-specialty of gynecologic oncology is unique, in that many gynecologic oncologists practice both surgical and medical oncology. In addition, the diseases managed by gynecologic oncologists frequently use radiation therapy, either in the primary, adjuvant, or palliative settings. For these reasons, the sub-specialty of gynecologic oncology is especially exposed to the unprecedented and evolving changes in physician payment reform. Due to the breadth of practice for many gynecologic oncologists, coupled with the heterogeneity of employment structure, APMs must be designed thoughtfully while embedding flexibility and equity. Due to the multitude of variables that require careful consideration and the variability in stakeholders, the optimal APMs will likely be designed locally.

In November 2015, the SGO submitted a request for information regarding the implementation of MIPS and the eligible APMs program as authorized under MACRA. The letter addressed numerous aspects of the MACRA law, and how the implementation should be done to positively impact the subspecialty of gynecologic oncology and those Medicare patients for whom SGO members provide care (46). SGO specifically commented on the following challenges to the implementation of MIPS: reporting mechanisms for quality performance; data stratification; barriers to successful quality performance; data accuracy; resource use performance; Clinical Performance Improvement Activities (CPIA); development of performance standards; and defining and incorporating improvement and public reporting.

"The forthcoming regulations should establish an easy pathway for PFPM [Physician-Focused Payment Models] proposals to be adopted as qualified APMs. CMS should clearly outline the criteria that will be used to evaluate PFPM proposals. CMS and the [Physician Focused Payment Model Technical Advisory Committee] PTAC should work collaboratively with medical societies and other organizations developing proposals, provide feedback on drafts, and provide data up-front to help in modeling impacts. These regulations should also make it clear that PFPMs recommended by the PTAC will be accepted by CMS. SGO is working very hard on its endometrial cancer APM with the intent of having it accepted as a PFPM" (46).

The SGO has endorsed disease site-specific quality indicators for ovarian, endometrial, and cervical cancers (47). In December 2015, CMS selected for consideration nine of the 15 process measures specific for gynecologic oncology (48). These quality measures were submitted for possible inclusion in the PQRS for 2017, which will be the first reporting year for MIPS. Should SGO's measures be accepted, they will be published in the CY 2017 Proposed Medicare Physician Fee Schedule Rule and will again be open for comment.

DISCUSSION

The payment reforms underway are intended to drive the improvement of patient-centered, high-quality, and efficient care that is consistent with the Institute of Medicine's six aims (49). The future of payment reform centers on legislation that incentives participation in an APM, while creating an environment

where FFS is less tenable. However, a successful transition from the current state to an APM assumes that the new paradigm will be clearly defined, equitable, and flexible enough to accommodate the necessary variation and heterogeneous environments in which oncology is practiced today. Medical societies and engaged physicians will certainly be critical in creating meaningful, actionable, and measurable quality metrics that will be important components of MIPS. The SGO has taken critical steps to develop and implement a Clinical Outcomes Registry (50). This subspecialty-specific registry was designed to be a tool to measure quality, compare outcomes, and could function as a platform for quality improvement and outcomes research.

Depending on a particular current state, moving into an APM will require a variable level of practice and culture transformation. For example, although dynamic gynecologic oncology-specific pathways have been developed, assessment of compliance is currently a resource intense process. Technology solutions, such as clinical decision support, may improve pathway monitoring but must also allow for necessary variation unique to cancer patients. Transforming practices into APMs beyond pathways will require local solutions that demand insight of the practice environment and strategic decisions that must account for many factors. Such critical factors include degree of physician integration; scope of oncology services provided; scale of health care system; financial health of the involved practice(s), hospital(s), and payer(s); competitive landscape of local market; and risk tolerance of the enterprise(s). Each practice environment will face unique challenges to adaptation. For example, smaller single-specialty practices may need to vie for scale or develop strategic partnerships to optimize care coordination. Larger academic practices with research and education components to their mission may be stressed as margins tighten. It will be incumbent on gynecologic oncologists and academic institutions to structure APMs such that gynecologic cancer research and education can be sustainable and continue to advance the field into the future.

Gynecologic oncologists function in a very wide array of practice settings. Therefore, the design of APMs will require flexibility. APMs impose both an administrative burden and financial risk that is likely to accelerate the existing trend toward practice consolidation. Independent, physician-owned practices may lack the resources, scope, and scale required to achieve and sustain compliance with the added administrative burdens involved in APM participation. Smaller practices are also less likely to be able to absorb the potential losses in a model that involves downside financial risk. Even gynecologic oncologists who are already employed or part of a large physician group will be affected. The hospitals or practices that employ gynecologic oncologists may further consolidate to achieve scale, which may further affect the employed physicians. No doubt, multi-specialty oncology practices and hospitals will be developing APMs for a wide range of disease sites, which may make cross-comparisons of gynecologic cancer APMs difficult between different geographic regions. The transformation of current models into a value-driven framework may require solutions devised at the local level. That is, how the new APM is developed and deployed may vary widely depending on the specific practice environment of a gynecologic oncologist. As these changes unfold, it will be critical that gynecologic cancer care remains patient-centered and of the highest quality.

The upside to the provision of high-quality, accountable, patient-centered care is clear. However, there are increasing resource-intensive administrative components to practice which must be considered as innovative payment models are designed. Some of these requirements divert time and resources away from direct patient care. According to a recent commentary (51), "the quality-measurement enterprise in U.S. health care is troubled." Some physicians, hospitals, and health plans view measurement as burdensome, expensive, inaccurate, and indifferent to the complexity of care delivery. Although P4P programs are among the oldest APMs, the success of these models is impeded by serious gaps in the current quality measurement system. According to a 2014 RAND report (52) that looked at 49 studies examining the effect of P4P on process and intermediate outcome measures, the overall results of the studies were mixed, and any identified effects were relatively small. A basic flaw in the design of existing P4P models is the reality that meaningful oncology-specific patient-centered outcome measures remain elusive. Although the pursuit of better value in cancer care is a necessary goal, simply establishing timelines is inadequate. Even with the repeal of the SGR, there are major challenges to achieving value-driven cancer care, including the lack of an agreed-upon, patient-centered definition of value; a shortage of meaningful and actionable performance metrics; and a deficiency of accounting systems capable of reflecting the true total cost of delivering cancer care.

CONCLUSION

Substantive payment reform in oncology is timely because there is great opportunity to align payments with the triple aim of better health and better care at a lower cost. The models described represent potential ways to address deficiencies in the current system, such as high and variable spending, fragmented and uncoordinated care, and insufficient reimbursement for services that often make a difference for patients and their families. APMs vary in the size, scope, and degree to which they shift away from FFS, but they increase provider accountability and support for innovative care delivery components.

While unprecedented payment reform activity is taking place in oncology, results are limited, and more evidence is needed to fully understand the implications of MACRA, MIPS, and APMs. To date, there are anecdotal examples of APM pilots around the country, but widespread adoption of new APMs by multiple payers is essential to build the evidence in support of a model. Although surgical oncology and radiation oncology pilots exist, most APMs to date have focused predominantly on medical oncology. Cancer care is far more interdisciplinary, and the most forward-thinking APMs must aim to incorporate the totality of care for the cancer patient. Given the range of services provided by gynecologic oncologists, payment reform has the potential to disrupt this sub-specialty disproportionately. Analysis and reporting of the initial experiences will be important to learn and make iterative improvements. While striving for breakthrough innovation, the path forward may require some degree of experimentation and tolerance for failure by

all parties involved. Preliminary experience indicates that savings can be achieved by payment reforms that support increased care coordination and the greater use of physician-led care teams. For example, such initiatives can reduce hospital readmissions, complications, and unnecessary imaging. Therefore, a critical priority is to develop further evidence of how new payment systems in oncology can better align physician reimbursement with care transformations to improve care coordination, quality of care, population health, and the patient experience. Engagement in payment reform is a unique opportunity to positively impact the future state of gynecologic oncology. In addition to fiscally responsible high-quality patient care, efforts in reform must protect research and education as margins tighten. Although much remains unknown, focused attention of gynecologic oncologists on payment reform is imperative to assure that the practice remains patient centered, embodies the highest quality, yet transforms into a sustainable and agile subspecialty to pro-actively and effectively manage the immense and relentless financial pressures and regulatory expectations to come.

AUTHOR CONTRIBUTIONS

SA was the primary author of the manuscript, including planning, research, writing, and review. KP provided expert review and feedback.

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PERSPECTIVE
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Electronic Records, Registries, and the Development of "Big Data": Crowd-Sourcing Quality toward Knowledge

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Despite many perceived advances in treatment over the past few decades, cancer continues to present a significant health burden, particularly to the aging US population. Forces including shrinking funding mechanisms, cost and quality concerns, as well as disappointing clinical outcomes have driven a surge of recent efforts into utilizing the technological innovation that has permeated other industries by leveraging large and complex data sets, so called "big data." In this review, we will review some of the history of oncology data collection, including the earliest data registries, as well as explore the future directions of this new brand of research while highlighting some of the more recent and promising efforts to harness the power of the electronic health record and the multitude of data co-located there, in an effort to improve individualized cancer-related outcomes in rapid real time.

Keywords: big data, cancer registry, crowd-sourcing, registries, quality measures

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Both the Institute of Medicine and the American Society of Clinical Oncology (ASCO) have called for a "national quality reporting program for cancer care as part of a learning health care system" (1). Furthermore, the current Presidential administration has made cancer one of its priorities, announcing its intentions to allocate additional funds for a "moonshot" to a cure. Cancer is a major public health issue, as it is the second leading cause of death in the US and is projected to surpass/exceed heart disease in the upcoming years. The lifetime risk of developing some form of cancer for men is 42% (1 in 2) and for women 38% (1 in 3). By 2030, the incidence of cancer will rise to 2.3 million cases per year as a result of the aging US population (2).

Recent cancer research budgets have been declining; however, the current climate is much more favorable. We find ourselves at crossroads of information technology, increased funding, and increased pressure for both quality care and cures.

In pursuit of these goals, and with the atmosphere of information technology, "big data" is an unchartered area in cancer. "Big data" is the term used for data sets that are so large or complex that traditional data sets processing applications are inadequate. The formation and management of these datasets can be exploited for real-time answers both in the efficacy of treatments in the real world as well as quality of care. As payers for health care in the United States and worldwide grapple with the movement away from fee for service-based reimbursement and toward payments for quality, information gleaned from large dataset may provide feedback that is crucial for improvements in the system. Additionally, "big data" compiled for research purposes provides a real-world laboratory for innovative treatments and interventions that may, in some places, fill in gaps where randomized prospective trials are impractical or cost prohibitive.

Population-based, cancer incidence data in the United States have been collected by the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program since 1973 and by the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) since 1995 (2). The North American Association of Central Cancer Registries compiles and reports incidence data from 1995 onward for cancer registries that participate in the SEER program and/or the NPCR. These data approach 100% coverage of the US population in the most recent time period and were the source for the projected new cancer cases in 2016 (2). These databases have provided an invaluable resource in tracking, categorizing, and noting trends of cancer as a public health issue. However, these existing systems fail to track the quality of the care for cancer patients.

We are currently in the midst of an explosion of the information industry. However, the information technology revolution has yet to mature in the medical field, despite near-universal penetrance of the electronic medical record. Many cancer patients experience highly fragmented care, with a combination of their records on paper, different electronic health record (EHR) systems, and physical disks for imaging, each housed in multiple locations. These uncoordinated and unconnected pieces of information impair the ability of oncologists to make an impact on the population scan and more difficult for the individual patient. Research based on an EHR is limited by the complexity of data collected and the context under which the data were collected. However, the EHR has unlocked the potential to turn individual level data into datasets that can provide information about the population and the efficacy of our interventions.

To repurpose the individual electronic pieces of a patient's electronic chart into "big data," data models must be created using clinical, administrative, and claims data. One such dataset is the HMO Research Network Virtual Data Warehouse (VDW)—a public, non-proprietary, research-focused data model that currently consists of 17 sites that together cover 13 million individuals; in total, the VDW has over 185 million person-years of data (3). Using this VDW, Kaiser Permanente has developed clinical research networks that include a colorectal cancer cohort, a severe congenital heart disease cohort and an obesity cohort (4). It is important to establish that "big data" is different than conventional large databases, one is a system that purely collects data, whereas "big data" is harvesting the data and analyzing in a fashion that gives us real-time feedback that could help providers make decisions in patient care. This could be a turning point in our care of oncology patients if this were to be successful. The goal of "big data" is the capability to extract value from large amounts of data, not just collect it.

Over the past two decades, additional organizations have attempted to fill that quality void and establish guidelines for evidence-based cancer care. For example, the National Comprehensive Cancer Network was started in 1995 to establish practice guidelines for clinicians taking care of cancer patients. This has become an invaluable resource for clinicians. In addition, the American College of Surgeons and the American Cancer Society jointly sponsor the National Cancer Database (NCDB), which is a database that covers approximately 1,500 facilities and approximately 70% of new cancer diagnosis in the US. They have over 30 million records to date (5). In addition to the NCDB, the Commission on Cancer, which is part of the American College of Surgeons, started to use the NCDB data to establish whether institutions were meeting certain quality measures. This started with a few disease sites and now covers nine, with continued plans to broaden.

Once established, registries such as those as listed above provide insight to the epidemiology of cancer, but now with improved informational technology, we have the potential to harvest more complex and important data points. We are starting to establish quality measures and analyze them compared to recognized national benchmarks that were not available or present before. Rapid advances in health information technology have created unprecedented opportunities to learn from real-world data.

Many cancer organizations are making this a priority, including ASCO, which has included "Big Data" as one of three major visions for cancer care (6). ASCO's CancerLinQ initiative, aims to collate data from every cancer patient in the US and make it available for analysis in the hope that it will lead to new insights. Their goals not only want to impact on a population basis but for the individual patient and provider. They propose real-time feedback to the oncologist to help them choose certain therapies and make clinical decisions. They are using a global software company, to create a big data platform. Many such software vendors are now commercially available. In the private sector, Flatiron Health has created the OncologyCloud–a big data program that aims to collect data from the medical records, doctors' notes, and billing information, to give real-time feedback to providers about treatments and outcomes. For example, part of their analytics can analyze cost of individual patient care, identify potential clinical trial candidates, which all streamlines with their specific EMR. Another example of "big data" harvesting is the Genomic Data Commons, this was developed and is housed at the University of Chicago, and here, they are using a "big data" approach to analyze cancer genomics. They are creating a cancer research community through a unified data repository promoting precision medicine, which is sponsored by the NCI.

We are in a transition time, as technology continues to exponentially improve, soon we will be able to extract all the data and quality measures that we need directly from the EHR. The goal of big data would be to not only link current registry databases but gather all data on all cancer patients and then use to analyze outcomes, which has never been done before. But ultimately the goal of "big data" is bigger and aspirational, it not only improved quality of care but also actual answers to cancer, and improved outcomes. For example, many of the chemotherapy regimens we use today have been adopted because they demonstrated a benefit of survival in a clinical trial. Over decades, pharmaceutical trials and cooperative groups have labored through the model of expensive, lengthy trials to get answers on which chemotherapy to use in which setting. This has been the standard of how we prove drug A is better than drug B. However, this paradigm represents only a small fraction of the total number of patients

with cancer (<5%). The advent of precision medicine has subdivided even common malignancies into increasing small subtypes making large prospective trials increasingly burdensome. "Big data" offers the potential to harness all of the data from all of our cancer patients. We could collect, harness, and analyze patients' clinical information and link it to molecular data and treatment outcomes to find answers to many of cancer's most elusive questions in real time.

The importance of health information technology in our pursuit of quality and cure cannot be underestimated. New, innovative, and affordable approaches to quality assessment and improvement as well as treatment efficacy will depend on our ability to create and maintain "big data."

AUTHOR CONTRIBUTIONS

Both SD and JL wrote and edited this Perspective.

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REVIEW
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Optimizing Cancer Care Delivery through Implementation Science

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The 2013 Institute of Medicine report investigating cancer care concluded that the cancer care delivery system is in crisis due to an increased demand for care, increasing complexity of treatment, decreasing work force, and rising costs. Engaging patients and incorporating evidence-based care into routine clinical practice are essential components of a high-quality cancer delivery system. However, a gap currently exists between the identification of beneficial research findings and the application in clinical practice. Implementation research strives to address this gap. In this review, we discuss key components of high-quality implementation research. We then apply these concepts to a current cancer care delivery challenge in women's health, specifically the implementation of a surgery decision aid for women newly diagnosed with breast cancer.

Keywords: implementation science, dissemination and implementation research, cancer care delivery, breast cancer, knowledge-to-action, decision aid

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INTRODUCTION

The 2013 Institute of Medicine report investigating cancer care concluded that the cancer care delivery system is in crisis due to an increased demand for care, increasing complexity of treatment, decreasing work force, and rising costs (1). The proposed conceptual framework for a high-quality cancer delivery system highlights the importance of engaging patients and their families, providing evidence-based care, and translating the evidence into routine clinical care. In the current system, translating beneficial research findings to the real world health-care setting is often slow and haphazard despite the proven benefits (2, 3). It has been suggested that an average of 17 years elapses before 14% of original research is integrated into routine physician practice (**Figure 1**) (4). This gap between the identification of beneficial research findings and the application in clinical practice has led to an increased focus on the processes for implementing new knowledge and the rapidly growing field of dissemination and implementation (D&I) science (5–9). Eccles and Mittman defined implementation research as "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice" (10). Implementation research spans *implementation* ("the use of strategies to adopt and integrate evidence-based health interventions and change practice patterns within specific settings") and *dissemination* ("the targeted distribution of information and intervention materials to a specific public health or clinical practice audience") (11). From past experiences, it is clear that those traditional, passive modes of implementing and disseminating evidence-based practices, such as publication in journals and development of consensus statements, are generally ineffective in sustainably integrating research findings into routine practice (5, 12). Therefore, systematic efforts to identify active, theory-driven implementation strategies are essential (4, 13–17).

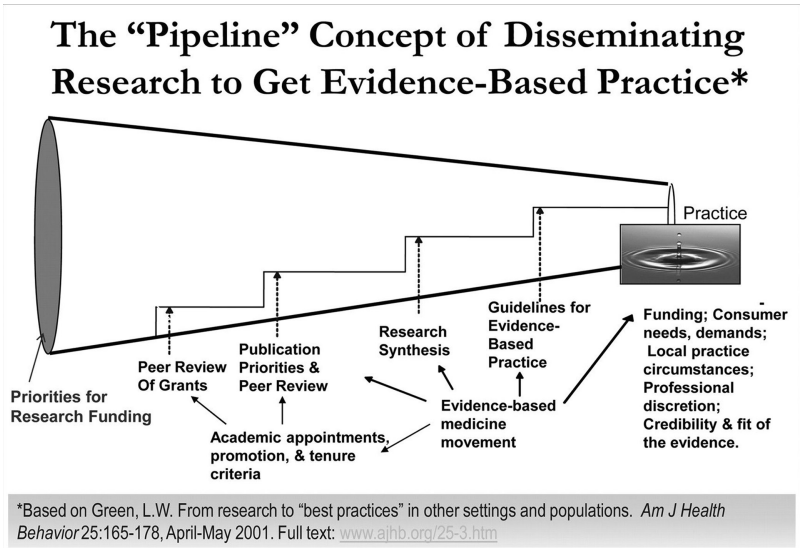

FIGURE 1 | The pipeline of production and translation of knowledge generated from research into routine clinical practice includes a series of successive screens designed to assure that high-quality research products are delivered to end users. However, this process results in only 14% of original research being integrated into routine clinical practice and does little to assure that the research products are relevant and/or useful to end users. From Green (5) with permission.

THEORETICAL FRAMEWORKS

Early implementation research was largely "trial and error" with only a minority (10%) of studies providing a theoretical rationale for their approach (18). The absence of a theoretical framework supporting early implementation efforts combined with lack of common terminology to describe processes made it difficult to predict the success of an implementation approach or for others to reproduce the process in other settings (19). A theory-driven approach to implementation that explores explicitly the link between an intervention and an outcome, and systematically strives to explain why the intervention worked or failed in a particular setting is critical to understand and operationalize the key implementation steps (7, 18, 19). In addition to facilitating the implementation for a specific intervention, this type of systematic approach will lead to the creation of generalizable knowledge surrounding methods for the sustainable implementation of an intervention across studies and settings. Theoretical models that broadly inform implementation research are multidisciplinary, pulling from the fields of medicine, public health, psychology, marketing, political science, and even agriculture. In 2011, more than 60 models to support D&I research had been utilized in the literature (20). Considerable effort has been made to consolidate these theories and models to provide researchers with a guide in identifying conceptual models that would best support their work. For example, Tabak et al categorized the theories and models relevant to D&I research according to their focus on dissemination and/or implementation activities and the socio-ecological level to which they are applicable (20). They also rated the flexibility of the model constructs, ranging from a score of 1 (very loose construct definition allowing researchers maximal flexibility in applying the model) to 5 (more defined constructs providing researchers with a more operational, step-by-step approach to D&I research activities). Examples of these categorizations for some commonly used models are presented in **Table 1**.

Two often used frameworks to guide implementation efforts include the consolidated framework for implementation research (CFIR) (21) and the RE-AIM framework (8). The CFIR focuses primarily on implementation. It synthesizes existing constructs from multiple published implementation theories into an overarching typology that can be used to conduct a diagnostic assessment of the implementation and context, track the progress of implementation, and explain the success (or lack of success) of an implementation strategy (21). Included constructs focus on the *characteristics of the intervention*, such as its source, complexity, or cost; *the outer setting*, such as relevant governmental policies and regulations or external pressure from competing organizations; *the inner setting*, such as structural characteristics of an organization, organizational culture, and organization readiness for implementation; the *characteristics of involved individuals*, such as their knowledge and beliefs about an intervention and their belief in their ability to implement the intervention; and *the process of implementation*, including planning the implementation, engaging key individuals, and evaluating the implementation efforts. Researchers can select relevant constructs from this framework to guide assessment of their intervention and monitor implementation progress. By contrast, the RE-AIM framework is an evaluation framework with an equal focus on implementation and dissemination (8). It guides evaluation of the *R*each of an intervention (is the intervention getting to the target population), *E*ffectiveness (is

TABLE 1 | Categorization of commonly used dissemination and implementation models [adapted from Tabak et al. (20)].

	Dissemination and/or implementation	Construct flexibility: loosely defined to highly structured constructs (scale 1–5)	Socio-ecological level				
			System	Community	Organization	Individual	Policy
RE-AIM (8)	D = I	4		X	X	X	
Consolidated framework for implementation research (21)	I-only	4		X	X		
Framework for knowledge translation (22)	D-only	5		X	X	X	
Normalization process theory (23)	I-only	3	X	X	X	X	
Health promotion research center framework (24)	D > I	4		X	X	X	X
The precede–proceed model (25)	D = I	5		X	X	X	
Replicating effective programs plus framework (26)	I-only	4		X	X		

D, dissemination; I, implementation.

the intervention effective in the real world setting), *A*doption (are target groups adopting the intervention), *I*mplementation [what is the fidelity, i.e., the degree to which the intervention is implemented as originally intended (9)], and *M*aintenance or sustainability (are the effects of the intervention maintained over time) (8). This type of evaluation framework can then facilitate comparisons between different interventions and methods of implementation and can inform both the choice of intervention and the needed implementation strategies.

SELECTION OF IMPLEMENTATION STRATEGIES

Dissemination and implementation theoretical models provide a systematic approach to developing and evaluating the implementation of interventions. Within these frameworks, specific implementation strategies can be selected that match the needs of a clinical program or practice (16, 17). These strategies vary in nature and complexity from a single component (such as reminders, educational meetings) to multifaceted designs, which include multiple discrete or interwoven strategies (5, 16, 17). Compilations of strategies and specific definitions of each strategy have been created to provide researchers with a mechanism for the identification of important and feasible options to meet the needs of their study. Using concept mapping in a multi-stage project known as the expert recommendations for implementing change (ERIC), Waltz et al. grouped 73 implementation strategies into 9 main clusters with similar conceptual backgrounds (**Table 2**) (17). The importance and feasibility of each strategy were then rated by experts in the field of implementation science. This type of compilation allows researchers to compare and prioritize different strategies most likely to be successful in their clinical context. Although further work must be done to examine the validity of these groupings, this represents an important resource for researchers developing and implementing interventions.

When considering implementation strategies, it is critical to consider the context in which an intervention will be implemented.

TABLE 2 | Implementation strategies organized by cluster by Waltz et al. showing mean importance and feasibility ratings provided by a panel of implementation science and clinical experts.

Implementation strategy cluster	Importance	Feasibility	Example of a strategy rated as both important and feasible
Use evaluative and iterative strategies	4.19	4.01	Provide audit and feedback
Provide interactive assistance	3.67	3.29	Facilitation
Adapt and tailor to context	3.59	3.30	Tailor implementation strategies
Develop stakeholder interrelationships	3.47	3.64	Inform local opinion leaders
Train and educate stakeholders	3.43	3.93	Conduct educational meetings
Support clinicians	3.23	3.06	Facilitate relay of clinical data to providers
Engage consumers	3.25	2.95	Involve patients/ consumers and family members
Utilize financial strategies	2.86	2.09	[a]
Change infrastructure	2.40	2.01	[a]

The importance rating scale ranged from 1 (relatively unimportant) to 5 (extremely important), and the feasibility scale ranged from 1 (not at all feasible) to 5 (extremely feasible).

[a]*No implementation strategies in these clusters were rated to be both important and feasible.*

The real world clinical environment is subjected to contextual factors, unlike the controlled research settings in which evidence-based interventions are often designed and tested (27–30). Contextual factors influence the success of implementation and strategies may need to be modified or additional strategies added to address the unique needs of local sites. These factors are recognized at different levels of the implementation process, such as the individual level, including team interactions and individual skill

sets, and the organizational level, where available resources and degree of managerial support for a particular intervention may vary between sites (29). Utilizing active, multifaceted implementation strategies in a manner that considers the local context and aligns with organizational priorities increases the potential of efforts being successful.

REPORTING INTERVENTION IMPLEMENTATION

To ensure adequate description of intervention implementation, a number of guidelines for specifying and reporting details of interventions and the implementation processes used have been created (**Table 3**) (19, 31–38). The goal of these initiatives was to increase the ability of others to deliver an intervention as originally intended, resulting in better fidelity and potentially leading to improved outcomes. Included as a requirement in many of these guidelines are details of not only the intervention itself but also the implementation process such as descriptions of who administered the intervention, the mode of intervention delivery, how the intervention's implementation may have been adapted to the local context, and how fidelity to the original intervention was maintained (31–33, 36–38). It is important to also describe the context in which an intervention was implemented. While utilizing this type of systematic approach to intervention development is necessary, extending its use in reporting both successful and unsuccessful interventions is critical to creating generalizable knowledge which will lead to improved care delivery.

Using theoretical models to guide intervention development, identifying active implementation strategies perceived to be feasible and important, and considering the local context in which an intervention will be implemented increase the likelihood that an intervention will be successfully implemented and sustained. To highlight further how these concepts can be applied to a contemporary clinical problem relevant to women's health, we discuss challenges and potential solutions to the implementation and dissemination of patient decision aids, focusing specifically on a breast cancer surgery decision aid.

BREAST CANCER SURGERY DECISION AIDS

Decision aids are a form of decisional support designed for use as an adjunct to clinical consultation and can facilitate patient-driven decision-making by clarifying and contextualizing the medical and psychological issues associated with the decision (39, 40). The Affordable Care Act promotes the routine use of decision aids to improve shared decision-making and decrease unwarranted variation in care and cost (41). Many decisions for cancer treatment require patients to consider the risks and benefits of various treatments in the context of their personal values, making them especially appropriate for application of a decision aid. Consider breast cancer surgery: as survival is equivalent for both breast conservation and mastectomy, women must weigh the increased risk of recurrence associated with breast conservation against the greater impact on body image associated with mastectomy in order to make a decision that matches their personal values. Active patient participation in this decision is essential, as it is associated with less decisional regret, more satisfaction with care, improved post-operative body image, and greater long-term quality of life (42–44). Breast cancer surgery decision aids effectively support this decision-making process by improving knowledge, decreasing decisional conflict, and facilitating communication between patients and surgeons (44–47). Unfortunately, despite their proven effectiveness and perceived ease of use, only a minority of women diagnosed annually with breast cancer receive one during the course of their care (48, 49). The current limited reach of evidence-based decision aids into the everyday care of cancer patients represents an ideal example where the application of implementation science can lead to improved delivery of cancer care.

TABLE 3 | Overview of available reporting guidelines for the implementation of interventions.

Reporting guideline	Method of development	Goal of guideline
Workgroup for intervention development and evaluation research (WIDER) group recommendations (31)	Expert recommendations to journal editors	Describes extensions to the CONSORT guidelines that will facilitate better communication of behavioral change interventions
Template for intervention description and replication (TIDieR) checklist (32)	Created through expansion of CONSORT criteria using a modified Delphi consensus approach	Describes a 12 item checklist to improve the completeness of reporting of interventions to improve replicability
Criteria for reporting the development and evaluation of complex interventions in health care (CReDECI2) (33)	Created through a systematic literature review and expert review	Describes a criteria list of 16 items pertaining to the reporting of the (1) development, (2) feasibility and pilot testing, and (3) introduction of an intervention and evaluation
Intervention taxonomy (ITAX) (34)	Researcher review of intervention study protocols to capture key elements of the interventions important to subsequent replication	Describes a taxonomy/catalog of key features of an intervention to consider in design, execution, and reporting
Strengthening the reporting g of observation studies in epidemiology (STROBE) statement (35)	Created during a 2-day workshop with methodologists, researchers, and journal editors	Describes a checklist of 22 items to guide reporting of observational research
Standards for quality improvement reporting excellence (SQUIRE 2.0) (36, 37)	Created with input from an expert panel with public feedback	Outlines a checklist of items to consider when reporting quality improvement studies
Standards for reporting implementation studies of complex interventions (StaRI) (38)	Created by multidisciplinary panel using an e-Delphi approach	Describes standards for reporting of implementation studies

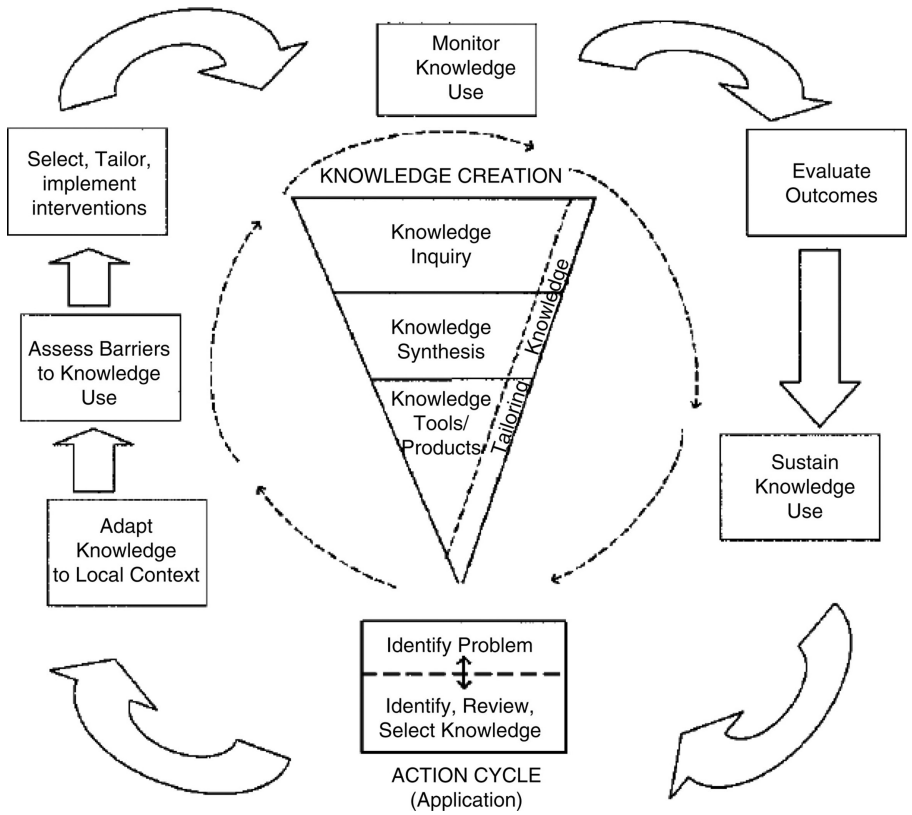

FIGURE 2 | Knowledge-to-action cycle. From Graham et al. (50) with permission. Copyright © 2006 The Alliance for Continuing Medical Education, the Society for Medical Education, the Society for Academic Continuing Medical Education, and the Council on CME, Association for Hospital Medical Education.

A number of theoretical models could be appropriate to guide an assessment of the challenges associated with decision aid implementation and to identify a strategy for implementation that is likely to be successful. Given the wide number of available in the literature, it is more important to apply an appropriate model well, than to identify the "perfect" model. The model we will use as the example to guide our discussion surrounding the implementation of breast cancer surgery decision aids is the knowledge to action cycle (**Figure 2**) (50). In our example, the fundamental knowledge-to-action gap being addressed is the idea that "decision aids work, but are rarely used." The knowledge-to-action cycle then outlines key steps to address this gap, including considering and/or adapting the intervention to the local context, assessing barriers to routine use, and selecting implementation strategies to address specific barriers.

Adapt Knowledge to Local Context

The local context in which an intervention will be implemented has a significant influence on the success of implementation and should be considered early in the planning process (27–30). In some clinical settings, it may be advantageous to tailor the intervention or the implementation to make it more suitable for a particular population or improve the fit within an organization's capacity. In other settings, additional implementation strategies may need to be incorporated. Adapting the implementation of an intervention to fit the local context can be an important step toward improving the success and sustainability of implementation. However, while adaptation may be desirable to maximize reach of the intervention, it is important to ensure that fidelity to the original intervention is maintained. A key step to accomplishing this is the identification of the core elements of an intervention and/or its implementation that is responsible for its effectiveness in achieving the intended outcome (9, 26, 51). The core elements can be specific components of the intervention or the specific implementation strategies essential for successful delivery of the intervention. These core elements should remain unchanged during adaptation, with tailoring focusing instead on those elements thought to be modifiable (9, 26, 51).

In our case of decision aid implementation, relevant aspects of the local context could include factors, such as financial resources of the institution, level of staffing within the specific clinic, and patient mix. These factors must be considered when developing an implementation process to ensure that implementation will be successful and sustainable. After considering these factors, examples of aspects of implementation that we would consider to be core elements critical for success would include the systematic identification of eligible patients prior to the clinical encounter (as opposed to rely on clinician identification of appropriate patients)

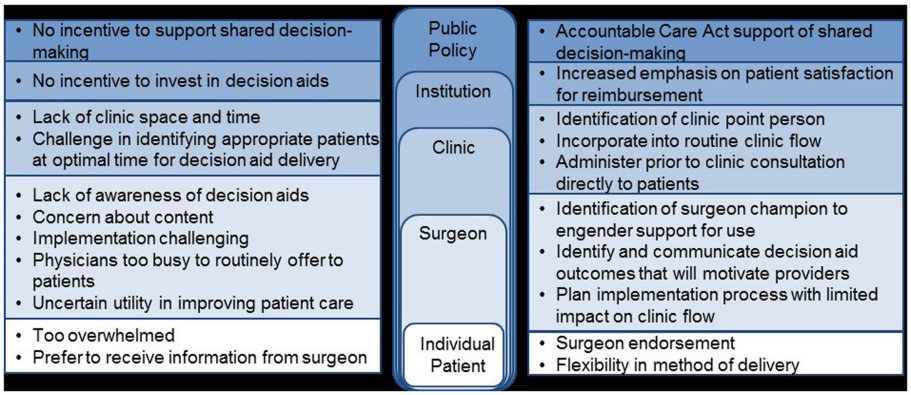

FIGURE 3 | Barriers and potential facilitators to use of a breast cancer surgery decision aid.

and administration of the decision aid outside of the surgery clinical setting (as opposed to ask the clinician to administer the decision aid themselves).

Select, Tailor, and Implement Interventions

Once the local context and barriers to use have been considered, implementation strategies must be selected to specifically address the known barriers. A useful tool for researchers in developing the package of implementation strategies needed is the compilation and categorization of strategies by Waltz et al. (17). In the case of decision aid implementation, we believe that "seamless" incorporation of the decision aid into routine clinical flow is critical for success. Specific challenges identified in our barrier assessment include limited clinic resources to administer decision aids, difficulty identifying appropriate patients in a timely manner, lack of surgeon buy-in, and patient preference to hear information from their surgeon (**Figure 3**). Although some clinics may be able to adjust their work flow to allow for decision aid administration, for many others, this is an insurmountable challenge and tailoring the logistics surrounding implementation will be necessary. One option to minimize the impact on the clinical workflow would be to utilize a decision aid administered directly to patients outside of the clinical encounter. Alternative decision aid formats, such as web-based decision aids, would be needed to accomplish this method of delivery efficiently and flexibility in method of deliver has been identified as a potential facilitator in one study (52–54). Challenges to identifying patients in a timely manner could be addressed by linking the identification of appropriate patients to scheduling of clinic visits or clinic intake calls; associating decision aid administration with a routine aspect of care already occurring will efficiently facilitate the systematic implementation of a decision aid (54). Utilization of a surgeon champion to engender support for the decision aid by other surgeons is critical for this type of intervention (54, 55). This individual can also be critical in preparing patients to be active participants in a decision aid intervention by endorsing the value of the decision aid as a way to enhance (and not subtract) from the future clinical encounter between patient and surgeon.

Monitor Knowledge Use and Evaluate Outcomes

As identified in the knowledge-to-action cycle, monitoring use and success of an intervention over time is an important step toward sustained use (50). Evaluation models, such as RE-AIM (8) and PRECEDE–PROCEEDE (25), provide a framework for identifying relevant constructs to judge success of an implementation process. In our case example of decision aid implementation, RE-AIM would be an appropriate evaluative model, focusing on constructs, such as the ability of the implementation to *R*each all appropriate patients without introducing a systematic bias through the exclusion of certain patient populations, the *E*ffectiveness of this method of decision aid delivery as a way to improve decision quality, and the acceptability of the intervention to patients and providers as a surrogate for future *A*doption. Additional evaluative endpoints could include implementation fidelity. CFIR could also be used to evaluate implementation and explain success or lack of success (21). The various CFIR constructs can help to categorize areas where interventions fail or where specific challenges exist, and help to then identify additional potential implementation strategies. For example, in the case of decision aid implementation, if limited commitment by surgeons is identified as a barrier (characteristics of individuals construct), strategies that more strongly incorporate opinion leaders and champions could be included. If the process to implement the decision aid is perceived to be too complex for the local setting (intervention characteristics construct), adapting the implementation process to the needs of the local setting (while keeping the core elements consistent) could be explored.

A critical component of the knowledge-to-action cycle is feeding back the outcomes of these evaluations to guide iterative improvements to the implementation process. Regardless of the method utilized in monitoring the performance of the intervention, it is necessary to solicit feedback from stakeholders and actively seek out opportunities for improvement. Early identification of lapses in the implementation process can allow a timely response and create generalizable knowledge, which

can inform the expansion of the intervention to other sites and clinical practices.

CONCLUSION

Decreasing the gap between the identification of beneficial interventions and the incorporation of these interventions into routine clinical care is an important step toward improving the quality of cancer care delivered. Successfully addressing this gap requires a systematic and theory-driven approach to the development and subsequent implementation of interventions. The growing field of implementation science has generated, and continues to generate, a broad base of generalizable knowledge surrounding how to successfully implement and sustain interventions. As we present in our clinical example, applying the concepts of implementation science to the unique challenges associated with cancer care for women can improve the quality of the cancer care we deliver.

AUTHOR CONTRIBUTIONS

HN and TA were responsible for concept development, literature review, and primary manuscript writing. CG participated in concept development and review of the manuscript.

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OPINION
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All Hands on Deck: Nurses and Cancer Care Delivery in Women's Health

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Access to expert gynecologic oncology care is hampered by geographic (1), racial (2), and socio-economic disparities (3). As cancer care grows in complexity and expense (4) with an aging and increasingly diverse population, the Institute of Medicine and others have called for improvements in cancer care delivery and research (5, 6). The growing workforce gap in supply of gynecologic oncologists – where demand is increasing, but number of providers remains stagnant (2) – highlights the need for fully utilizing the skills of all clinicians working across the cancer control continuum (prevention, screening, treatment, survivorship, and end of life). To that end, nurses can have an enormous impact on improving and expanding access to oncology care as clinicians, designers, and leaders of initiatives to improve care. Nurses comprise the largest group of health-care providers in the U.S. (7). In its 2010 report on the future of nursing, the Institute of Medicine called for all nurses to practice to the full extent of their nursing "education, training, and competencies" (5). We argue that promoting and expanding nurses' roles within innovative, multidisciplinary models of care in women's health is essential in order to improve growing gaps in cancer care.

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PREVENTION

Primary Prevention

Prevention of common women's cancers includes promotion of healthy lifestyles and vaccination, though the potential for widespread dissemination is hampered by ineffective implementation. For example, the prophylactic human papillomavirus (HPV) vaccine is a groundbreaking prevention tool which is now available to prevent cervical cancer. Uptake of the vaccine among youth in the U.S. is inadequate despite widespread insurance coverage and availability. In 2014, <40% of U.S. teenagers completed the three dose series before 18 years of age (8). Although physician recommendation has been shown to improve uptake of HPV vaccines (9), the recommendations of nurses could be equally or more effective in increasing HPV vaccine uptake in primary care, especially in rural and underserved areas (10). Gallagher et al.'s systematic review demonstrated that, despite challenges, school-based HPV vaccination programs in the U.S. and other countries have achieved higher levels of vaccine uptake when compared with those conducted at health-care facilities (11). School nurses are integral to such programs, where qualitative research by Boyce and Holmes demonstrated that they have the potential to promote vaccination of medically underserved children (12). In particular, school nurses often serve as opinion leaders in middle schools – where the target population for HPV vaccination is found – and can intervene with targeted education, follow-up, and tool kits to promote vaccination among students and parents (13, 14).

Health Education

Advanced practice nurses, such as nurse practitioners (NPs) and certified nurse midwives (CNMs), are often the only source of primary health care for women, especially in medically underserved areas (15). A major focus of NP and CNM practice is health education and promotion of healthy behaviors

(16, 17). NPs have led successful cardiovascular disease interventions in smoking cessation (18, 19) and obesity prevention (20) which would have crossover benefits for cancer prevention in the long term, and their contributions should be utilized to maximize prevention efforts for women.

SCREENING

Early Detection

Nurses have many opportunities to reduce the substantial gaps in access to gynecologic and breast cancer screening in the U.S., particularly for minority and underserved women (21). NPs and CNMs play important roles in providing primary care by performing cervical cancer screening, referring women for mammography and colon cancer screening, and then collaborating with or transferring care to specialist physicians as necessary (22). Despite their education, training, and evidence that their quality and patient satisfaction outcomes are equal or superior to that of physicians (7, 16, 23), NPs and CNMs are still underutilized in extending the reach of cervical and breast cancer screening in underserved communities (24, 25).

Navigation

Nurses may also work in a navigation role in primary care practice, helping patients understand the importance of cancer screening and follow-up after abnormal results. As an example, nurse navigation demonstrated an increase in women's follow-up colposcopy attendance after abnormal cytology screening (26). Utilizing all available nursing professionals in ambulatory settings would provide the comprehensive approach needed to improve cancer prevention care for women on a broad population level.

DIAGNOSIS AND TREATMENT

As integral members of the cancer care team during treatment, nurses' involvement in multidisciplinary cancer care treatment models can improve care post-diagnosis through management of treatment-related symptom toxicities, and improving adherence to treatment.

Symptom and Toxicities Management

Treatment-related symptom toxicities, particularly in novel therapies such as targeted agents and immune therapies, are often serious but difficult to recognize, and thus likely under reported (27). Nurses can play an integral role in the integration of patient-reported outcomes related to such therapies, particularly during assessment, patient education, and through communication *via* patient portals. The Oncology Nursing Society outlines competencies for certification of oncology nurses and NPs (28). Oncology Certified Nurses (OCN) are trained to provide specialized patient care that is validated by certification of knowledge in oncology nursing focusing on adults with cancer (29). Oncology NPs are specialists in symptom management (30) and discharge planning to improve quality of life long term.

In addition, nurses and NPs can offer support and education around discussions about sexual health (31) and fertility preservation (32). Nurses at the bedside or on research teams are essential for effective recruitment of women with gynecologic cancer to the clinical trials needed to improve cancer-related care (33) and have held leadership positions on gynecologic cancer treatment trials (34). Utilization of specially qualified nurses in many roles can enhance both the reporting and subsequent treatment of treatment-related symptoms and complications.

Adherence

Cancer centers increasingly utilize nurse navigators to assist women through complicated care regimens (35–37), resulting in increased adherence to treatment (38) and improved patient satisfaction with care (39). In addition, geographic differences can play a role in cancer treatment outcome disparities (1, 40). Oncology NPs can increase access to care for underserved areas through telemedicine and satellite clinics, addressing issues with access and facilitating appointment adherence (28). Innovative multiprovider visits, including medical and nursing staff, have been designed for women who are initiating ovarian cancer chemotherapy. Prescott et al. (41) described a shared medical visit model in which a multidisciplinary team, including the oncologist, NPs, nurses, and social workers, provided standardized education visits for gynecologic oncology patients planning to begin their series of platinum-based chemotherapy sessions. Nurses were integral in educating patients on expected side effects, coping tools, and the importance of shared decision-making throughout treatment. Nurse-led support groups can be important outlets for patients to support adherence through difficult treatment regimens.

Adjuvant hormone therapy, including tamoxifen and aromatase inhibitors, is a widely recognized and important component of breast cancer treatment for hormone receptor positive women. Despite the documented benefits, up to 50% of women who are recommended therapy do not initiate therapy or do not adhere to the regimen for the recommended 5–10 years, due in part to the myriad of side effects of hormonal treatment (42). In addition, as many cancer therapies move from intravenous to oral medications with complex home regimens, adherence becomes an increasingly important area where nurses can improve outcomes. Schneider et al. (43) described a small clinical trial ($N = 45$) of tailored nursing education intervention which improved both self- and pharmacy-reported adherence to oral chemotherapy (93% in intervention vs. 80% in controls at 2 months, no CI given). Nurses should play a key role in increasing patient knowledge of side effects and remedies, communicating benefits of treatment to prevent recurrence, and identifying coping strategies to resolve barriers to adherence.

SURVIVORSHIP

There is a growing need to address the many late and long-term effects that plague the growing number of gynecologic cancer survivors (44), and nurses at all levels are integral in this care.

Navigation Posttreatment

While appropriate utilization and implementation of survivorship care plans are still being explored (45, 46), nurse navigators

coordinate care as the cancer patient transitions back to primary care after active treatment. In addition, primary care, oncology, and advanced practice nurses educate the patient throughout treatment and into survivorship on managing the transition after a cancer diagnosis, including late and long-term effects, as well as the on importance of follow-up care after treatment to detect recurrence or secondary malignancies (47).

Clinical Care of Survivors

Models of care delivery for survivorship care include primary care, gynecologic oncologist-led, and survivorship clinics, offering multidisciplinary services. While there are differing opinions on the best setting for long-term follow-up and care of survivors, and this may differ based on cancer type and individual provider or institutions, there is emerging research that nurse-led survivorship clinics hold potential for this important care (48, 49). A technical report on models of survivorship care indicated that cancer survivors preferred follow-up from those with specialized training (50), and pointed to the need for more specialized survivorship training for oncology nurses and advanced practitioners. In addition, a systematic review comparing models of survivorship care for posttreatment follow-up of adult cancer survivors found no significant differences in quality of life or disease recurrence outcomes for nurse-led follow-up when compared with oncologist-led follow-up care. In fact, patient satisfaction was higher for nurse-led care in one study included in the review (51). Rosenberg and colleagues (52) explored the use of survivorship risk-adapted follow-up visits facilitated by an oncology nurse and involving discussion of survivorship care plans. The authors found that of the 1615 breast cancer survivors who participated in the intervention, most reported more confidence in understanding their diagnosis, treatment summary, and recommendations for posttreatment support. Overall, as nurse-led clinics are typically less costly to an organization, specialized nurses working in consultation with physicians could increase availability of oncology survivorship services.

END-OF-LIFE CARE

When a patient's prognosis changes and goals of curative treatment transition into advanced care planning, nurses can uniquely contribute in many areas. Advanced practice nurses in both oncology and primary care settings should be trained to effectively communicate conversations about worsening prognosis (53); however, application of this role is unclear in the literature; this represents a missed opportunity for improving an essential aspect of cancer care. Oncology nurses in both inpatient and outpatient settings establish strong relationships with patients through many hours of patient contact and can play a substantial role in helping patients and families consider their own goals and values as they relate to end-of-life care. Research indicates, however, that nurses experience ethical dilemmas surrounding these conversations, as their role is less defined and they are often hesitant to have these conversations with patients and families (54, 55). Inpatient nurses, who could be trained in end-of-life care, are able to function as "champions," for example, and act as a resource for their team (56). While physician–nurse teams are optimal for discussions surrounding end-of-life care, more education and training for nurses are important in order to optimize communication with advanced cancer patients as their prognosis worsens.

CONCLUSION

Women diagnosed with gynecologic cancers face difficult and complex treatment regimens with long-term health implications. Innovations and improvements in cancer care delivery in women's health must rely on all members of the health-care team. We argue that because the nursing workforce is vastly larger than that of gynecologic oncologists, and boasts breadth and depth of roles, training, and capabilities, it is essential to better utilize and integrate nurses within the multidisciplinary team to ensure comprehensive, woman-centered care before, during, and after cancer. It is time that women had equitable access to higher quality cancer care, and nursing is up to the challenge.

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JM and MM wrote early drafts and edited the final draft of the article.

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MINI REVIEW
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Alternate Service Delivery Models in Cancer Genetic Counseling: A Mini-Review

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Demand for cancer genetic counseling has grown rapidly in recent years as germline genomic information has become increasingly incorporated into cancer care, and the field has entered the public consciousness through high-profile celebrity publications. Increased demand and existing variability in the availability of trained cancer genetics clinicians place a priority on developing and evaluating alternate service delivery models for genetic counseling. This mini-review summarizes the state of science regarding service delivery models, such as telephone counseling, telegenetics, and group counseling. Research on comparative effectiveness of these models in traditional individual, in-person genetic counseling has been promising for improving access to care in a manner acceptable to patients. Yet, it has not fully evaluated the short- and long-term patient- and system-level outcomes that will help answer the question of whether these models achieve the same beneficial psychosocial and behavioral outcomes as traditional cancer genetic counseling. We propose a research agenda focused on comparative effectiveness of available service delivery models and how to match models to patients and practice settings. Only through this rigorous research can clinicians and systems find the optimal balance of clinical quality, ready and secure access to care, and financial sustainability. Such research will be integral to achieving the promise of genomic medicine in oncology.

Keywords: genetic counseling, telemedicine, access, cancer, comparative effectiveness

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INTRODUCTION

The world of cancer genetics has experienced exponential growth in diagnostic and treatment opportunities that use genomic sequencing information, as was most recently acknowledged by the national Precision Medicine Initiative (1). Even before the Precision Medicine Initiative, however, demand for cancer genetic counseling grew as germline genetic testing became increasingly incorporated into breast and ovarian cancer treatment decisions (2, 3), public coverage of celebrity *BRCA* mutation status (4) reached a wide segment of the U.S. population (5), and multi-gene panels for hereditary cancer susceptibility were introduced (6, 7). Due to these factors, cancer genetics clinicians across the U.S. noted an increase in referrals for hereditary cancer risk assessment (8).

Cancer genetic counseling has traditionally been practiced in person, with patients traveling to a health-care facility to meet with a genetics clinician (9). The counseling process has typically involved at least two in-person visits – an initial visit to perform risk assessment and, if applicable, informed consent for genetic testing ("pretest counseling") and for those who underwent

genetic testing, a posttest visit to disclose test results and discuss results' implications for cancer risk management in patient and family (10).

Pre- and posttest cancer genetic counseling is recognized to benefit individuals with cancer and their relatives. Counseling by clinicians trained in genetics has been associated with improved adherence to cancer risk management (11–14), better informed surgical decision making (2, 15), increased cancer genetics knowledge (16–19), high patient satisfaction (17, 20), and cost savings (21, 22). And, individuals who have undergone cancer genetic counseling, even those found to have a hereditary cancer syndrome, typically do not report long-term increased distress (18, 19, 23–30). Further, negative outcomes such as misinterpretation of test results, inappropriate medical management, and adverse psychosocial outcomes have been reported when genetic testing is performed without adequate genetic counseling (13, 21, 22, 31–34). In recognition of these benefits, pre- and posttest genetic counseling by qualified health professionals is recommended as standard-of-care by several professional organizations (35–39).

Yet, the confluence of new genomic sequencing techniques and greater public acceptance of cancer genetic counseling render the traditional in-person, multi-visit approach to genetic counseling insufficient to meet the demands of cancer genetics practice in the age of genomic medicine. Further, access to cancer genetics professionals varies widely across the U.S. (40–44). Rapid access to cancer genetic counselors is readily available in certain urban academic centers (45), but several groups, including rural residents, are underserved (9, 43, 44).

Alternate service delivery models for cancer genetic services have been proposed to improve access to care for individuals in underserved areas who are unable to travel to genetic counseling. The majority of genetic counselors report having used at least one alternate service delivery model (46). Here, we summarize the state of the science on alternate service delivery models for cancer genetic counseling and recommend future research on the effectiveness of these models. First, we present models in which genetics clinicians use alternate communication technologies to reach patients, followed by alternate visit models (group counseling and non-genetics clinician counseling) and direct-access testing models.

ALTERNATE TECHNOLOGY MODELS

Pretest Telephone Counseling

Telephone counseling refers to pretest genetic counseling that is provided remotely by telephone (47). It has been used by a substantial minority of cancer genetic counselors (9). Randomized trials comparing telephone with in-person cancer genetic counseling have shown that telephone counseling achieves short-term outcomes as well as in-person counseling. These trials have shown no difference by group on patients' knowledge (48, 49), psychosocial outcomes (e.g., distress, decisional conflict, and cancer worry) (48–50), satisfaction (50, 51), or patient-centered communication (49, 50). One study has shown cost savings to patients and institutions in telephone vs. in-person cancer genetic counseling (48). Among the outstanding research questions in telephone genetic counseling is whether telephone counseling facilitates psychosocial assessment and counseling to the same degree as in-person counseling, a concern raised in two studies (51, 52).

Pretest Telephone Counseling and Educational Materials, Posttest In-Person Counseling

A Dutch group has tested a model, termed "DNA-Direct," that uses a telephone consult plus mailed educational information for pretest counseling for hereditary breast and ovarian cancer syndrome, followed by in-person disclosure of genetic test results (53). In a non-randomized comparison of this model with traditional in-person pre- and posttest genetic counseling, the authors found favorable psychosocial outcomes in the DNA-Direct model, including lower distress and decisional conflict than in the traditional genetic counseling group (53, 54). Time to results disclosure was also lower in the DNA-Direct group.

Posttest Telephone Counseling

By far, the most commonly used alternate service delivery model in the U.S. is telephone disclosure of genetic test results (i.e., a posttest phone visit), which typically follows an in-person pretest visit (46). Although disclosure of test results *via* phone is widely used by cancer genetic counselors, a minority of cancer genetic counselors report using the phone as the primary model for results disclosure (46, 55, 56). Genetic counselors who disclose results by phone appreciate the convenience it provides to patients (56) and the medical benefits of disclosing results to patients more quickly than in-person disclosure, facilitating more timely cancer risk management (55, 56). Still, some genetic counselors have reported being uncomfortable returning certain genetic test results by phone (e.g., mutation positive results) (56).

Telephone disclosure of genetic testing results has been shown to be acceptable to patients. A randomized comparison of phone vs. in-person disclosure of results showed no difference by group in anxiety, distress, cancer genetics knowledge, or patient satisfaction (57). Further, this study found that a significantly higher proportion of participants in the in-person group would have preferred phone disclosure, compared with the proportion of phone disclosure participants who would have preferred in-person disclosure (57). Retrospective, non-randomized studies of method of results disclosure have found no difference by group (phone vs. in-person) on patient outcomes such as cancer worry, cancer risk perception, patient satisfaction, or cancer risk management behaviors (e.g., surveillance, prophylactic surgery) (55, 58). Of note, patient satisfaction with the model of results disclosure was significantly higher when patients were allowed to choose the model (55).

Telegenetics

Telegenetics is genetic counseling provided remotely by live videoconferencing, with visual and audio access (47). It has been most studied in the context of pretest cancer genetic counseling, but has been used for posttest counseling, too. Typically, the

approach consists of a genetics clinician at an urban health-care facility seeing a patient who has come to a different, often rural, healthcare facility. It has been used by a substantial minority of cancer genetic counselors (9, 46, 59), but is rarely the sole service delivery model used by a counselor (9). Patients have reported high satisfaction with telegenetics (60–65) due to convenience (63) and savings in cost and time (62).

However, comparative effectiveness research on telegenetics is limited. Our randomized trial of telegenetics vs. in-person cancer genetic counseling found that telegenetics is substantially cheaper for institutions than in-person counseling, with no difference in patient satisfaction by group (65). But, while early reports show that telegenetics may facilitate psychosocial assessment and counseling (64), neither behavioral outcomes (e.g., adherence to recommended cancer risk management) nor psychosocial outcomes of cancer telegenetics have been assessed in randomized trials (60). Further, data are mixed on whether telegenetics actually improves access to care (60). Cohen et al. found that telegenetics was used most for patients who lived more than 2 h away from the genetics center, but did not find that telegenetics was associated with shorter wait times to an appointment than in-person counseling (9). Finally, attendance of cancer genetic counseling was lower in the telegenetics than in-person group in our randomized trial, indicating that telegenetics may not be acceptable to all patients (65).

ALTERNATE VISIT MODELS

Group Counseling

Group counseling occurs when multiple individuals have pretest genetic counseling together, typically for the same indication (e.g., all have a family history of breast cancer) (47). Group counseling can be performed *via* multiple communication technologies, though it is typically performed in person. Depending on the study, patients may have the opportunity for individual discussions of personal issues with a genetics clinician immediately after the group session (16, 66) or *via* a subsequent telephone consult (67). Group genetic counseling has been used by up to 10% of cancer genetic counselors, but is rarely the sole service delivery model used by a counselor (9, 46).

Group genetic counseling has shown promise for increasing efficiency by decreasing per-patient time for genetics clinicians (16, 67). And, a randomized comparison of group vs. individual cancer genetic counseling showed no difference by group in cancer-specific distress or knowledge of breast cancer genetics (16). Similarly, a non-randomized comparison of group vs. individual cancer genetic counseling showed no difference in perceived personal control, cancer-specific distress, or patient satisfaction (66). However, questions remain about whether group counseling would be widely accepted by cancer genetic counseling patients. One study showed a high rate of declining group counseling, concerns about the effects of group dynamics on patients' privacy and decision making, and a preference for individual counseling over group counseling (67). A later, non-randomized study echoed this preference for individual counseling when patients were given the choice of service delivery model (66). This study also showed a lower rate of genetic testing uptake in the group counseling cohort than in the individual counseling cohort, though it is unclear whether this was due to a difference by cohort in the proportion of individuals for whom genetic testing was indicated or to a difference by cohort in the informed consent process (66). Further, it is not clear whether group genetic counseling improves access to care in underserved areas (9). And, as with other service delivery models, reimbursement for group counseling remains a challenge (9).

Non-Genetics Clinician Counseling

Several additional models in which a non-genetics clinician is the primary provider of genetic counseling have been described. These include models in which non-genetics clinicians provide pretest counseling and refer either all patients to a genetics clinician posttest or just patients considered complex; genetic counselors assist non-genetics clinicians in risk assessment and pre- and posttest counseling, and may see some complex cases themselves; and a genetic counselor educates a community of clinicians on pre- and posttest counseling and trains them to manage routine cases and refer complex cases (46). Although these models appear to be fairly widely used, with up to 36% of genetic counselors having been involved in one of these models (46), data on the comparative effectiveness of these models for improving access to care or facilitating the same beneficial behavioral and psychosocial outcomes as two-visit, in-person genetic counseling by trained genetics clinicians is lacking.

DIRECT-ACCESS GENETIC TESTING

Also known as direct-to-consumer testing, direct-access testing occurs when individuals order their own genetic testing from a commercial laboratory outside the context of a typical medical encounter and receive results and associated educational materials directly. Although much of the available direct-access testing focuses on genomic variants with a modest impact on cancer risk, some tests do report mutations in genes associated with hereditary cancer syndromes (e.g., *BRCA1/2*). It is also possible for patients to initiate testing for hereditary cancer syndromes through companies that coordinate with their physicians and provide access to genetic counseling. Data on patient outcomes of direct-access testing for hereditary cancer syndromes are limited, with case reports showing both benefits of this approach as a way to be tested without concern for genetic discrimination (68) and concerns about increased psychological stress when a *BRCA* mutation is detected incidentally *via* direct-access testing (69). Preliminary qualitative research suggests that initial negative psychological outcomes of direct-access identification of hereditary cancer risk may be temporary (70). As direct-access models grow in prevalence, comparative effectiveness studies with traditional genetic counseling models will become necessary.

DISCUSSION

Alternate service delivery models have the potential for improving access to cancer genetic counseling, which is of growing

importance as germline genomic information is increasingly incorporated into the care of individuals with cancer and their at-risk relatives. Such improved access may mitigate health disparities and help achieve the significant promise of genomic medicine (71). Telephone counseling, group counseling, and telegenetics have been well accepted by patients and may facilitate the patient-centered communication and psychosocial assessment that are the hallmark of cancer genetic counseling (16, 48, 51, 64, 65). Yet, considerable comparative effectiveness research is necessary to determine whether alternate service delivery models are as beneficial as in-person cancer genetic counseling. This holds true for alternate service delivery models provided by genetics and non-genetics clinicians. The latter is particularly important, given reports of negative outcomes of non-genetics clinicians providing cancer genetic counseling (13, 21, 22, 32–34).

Further studies are needed on the degree to which alternate service delivery models improve access to cancer genetic counseling. And here, we mean access broadly defined, not simply a patient's ability to be seen with limited disruption of their daily responsibilities, though this is important. Ideally, access would mean that patients can have cancer genetic counseling that is readily available, affordable, and comparable to in-person counseling on outcomes of import to patients, genetics clinicians, and referring clinicians. Determining whether an alternate service model (or suite of models) is comparable to in-person counseling will require rigorous methodology and a focus on patient-centered outcomes such as longer-term psychosocial outcomes and adherence to recommended cancer risk management (60, 65). Studies conducted with a cost analysis that includes real-world reimbursement of genetic counseling – a significant challenge to broad implementation of all alternate service delivery models (9, 72, 73) – will also be critical.

One additional lesson of comparisons of alternate service delivery models with traditional in-person cancer genetic counseling is that one size will not fit all. Uptake of cancer genetic counseling has differed by service delivery model (48, 53, 65–67), and patients may be most satisfied when they are allowed to choose the method in which they have genetic counseling (55). This suggests a pragmatic research agenda that helps match service delivery models to patients and practice settings. Such research should investigate the wide variety of patient characteristics that could impact their preference for a particular service delivery model [e.g., cancer status (affected vs. unaffected), demographic characteristics, comfort with technology, and distance to the nearest genetics facility]. Clinically, the lesson that one size will not fit all suggests that cancer genetic counseling patients will be best served by being presented with a variety of service delivery models and allowed to choose their preferred model.

Using alternate service delivery models to provide cancer genetic counseling involves balancing several factors thought to be important to the clinical experience, including patients' access to care and clinicians' perceptions of their own effectiveness to clearly explain potentially complex genetics concepts while assessing and responding to psychosocial cues. And, models ultimately need to strike this balance while maintaining patients' confidentiality, fitting into healthcare systems' work flows, and being financially viable. Telegenetics, which facilitates an educational and empathetic interaction quite similar to an in-person conversation (63), holds promise for meeting the clinical rigor genetics clinicians expect. And, several videoconferencing programs have the necessary security protocols to maintain confidentiality. But, studies of telegenetics to date have focused on a model in which patients must attend a local health-care facility, potentially limiting some patients' access and requiring staff at the remote clinic to facilitate patients' interaction with the genetics clinician. With U.S. Internet use approaching 90% (74) and the proliferation of smartphones (75), telegenetics sessions that meet patients where they are on their preferred device may provide an even better balance of rapid access and high-quality care that has a minimal impact on clinics' work flows. Whether such a model would be financially viable or help genetics clinicians meet growing demand for their services, however, remains to be seen.

AUTHOR CONTRIBUTIONS

AB: substantial contribution to conception of the work; drafting the work; final approval of version to be published; and agreement to be accountable for all aspects of the work. AR and JW: substantial contribution to conception of the work; revising the work for important intellectual content; final approval of version to be published; and agreement to be accountable for all aspects of the work.

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REVIEW
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Cancer Care Delivery and Women's Health: The Role of Patient Navigation

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Background: Patient navigation (PN) is a patient-centered health-care service delivery model that assists individuals, particularly the medically underserved, in overcoming barriers (e.g., personal, logistical, and system) to care across the cancer care continuum. In 2012, the American College of Surgeons Commission on Cancer (CoC) announced that health-care facilities seeking CoC-accreditation must have PN processes in place starting January 1, 2015. The CoC mandate, in light of the recent findings from centers within the Patient Navigation Research Program and the influx of PN interventions, warrants the present literature review.

Methods: PubMed and Medline were searched for studies published from January 2010 to October 2015, particularly those recent articles within the past 2 years, addressing PN for breast and gynecological cancers, and written in English. Search terms included patient navigation, navigation, navigator, cancer screening, clinical trials, cancer patient, cancer survivor, breast cancer, gynecological cancer, ovarian cancer, uterine cancer, vaginal cancer, and vulvar cancer.

Results: Consistent with prior reviews, PN was shown to be effective in helping women who receive cancer screenings, receive more timely diagnostic resolution after a breast and cervical cancer screening abnormality, initiate treatment sooner, receive proper treatment, and improve quality of life after cancer diagnosis. However, several limitations were observed. The majority of PN interventions focused on cancer screening and diagnostic resolution for breast cancer. As observed in prior reviews, methodological rigor (e.g., randomized controlled trial design) was lacking.

Conclusion: Future research opportunities include testing PN interventions in the post-treatment settings and among gynecological cancer patient populations, age-related barriers to effective PN, and collaborative efforts between community health workers and patient navigators as care goes across segments of the cancer control continuum. As PN programs continue to develop and become a standard of care, further research will be required to determine the effectiveness of cancer PN across the cancer care continuum, and in different patient populations.

Keywords: patient navigation, breast cancer, cervical cancer, gynecological cancers, women's health, cancer disparities

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INTRODUCTION

Profound advances in cancer screening, reductions in the prevalence of risk factors, and development of more effective treatments have positively contributed to increased longevity and quality of life among cancer survivors. Despite these improvements, disparities by race/ethnicity and socioeconomic status remain in cancer prevention, incidence, treatment, and mortality (1, 2). One approach to reduce cancer disparities is through patient navigation (PN). PN is a patient-centered, health-care service delivery model that assists individuals, particularly the medically underserved, in overcoming barriers to care (e.g., personal, logistical, system) across the cancer care continuum. PN is "navigation" in the health-care system compared to outreach, which is in the community and can use lay health advisors, community health workers (CHWs), etc. Typically, CHWs are trusted community members who provide information, support, and encouragement to receive screening tests (3). Previous intervention studies using CHWs to promote cancer screening have reported significantly increased screening rates for breast and cervical cancer (3, 4). CHWs and patient navigators differ in that CHWs work in the community, and their role ends when the patient enters the health-care facility. Patient navigators are typically housed in clinics; however, both the CHW and patient navigator complement each other in that they serve as a bridge between the health-care system and members of underserved communities.

Patient navigation began in 1990 by Harold Freeman who developed a PN program within a public hospital in Harlem, NY, USA to provide assistance to low-income women in need of breast cancer screening and timely follow-up to reduce diagnoses of late-stage breast cancer (5). Due to the promising results from Freeman's initial PN program and continued evidence of effectiveness, PN has grown nationally as a standard of care (6, 7). PN studies have demonstrated that PN can improve rates of cancer screening (8, 9), ensure follow-up rates after an abnormal screening test (10, 11), and improve cancer care outcomes (i.e., time to treatment, quality of life) (12, 13).

Several recent literature reviews including Robinson-White et al. (14), Paskett et al. (15), and Wells et al. (16) have described the evolution of PN as a model to address cancer disparities. In 2011, a literature review by Paskett et al. (15) provided an update to the 2008 review by Wells et al. (16) on the efficacy of PN for cancer care. Paskett et al. (15) found that within the 3-year window since Wells' review, the quantity of work in cancer PN literature was comparable to that of the previous years combined. In both reviews, most studies provided evidence for the effectiveness of increasing cancer screening rates including breast and gynecological cancers (15, 16). However, a paucity of research focusing on PN among cancer survivors during and after primary treatment and methodological limitations (i.e., lack of rigorous study design) of PN interventions were noted.

Since the 2011 literature review, many additional PN programs have been implemented especially those within the Patient Navigation Research Program (PNRP), funded by the National Cancer Institute (17) with support from the American Cancer Society (ACS). Active from 2005 to 2010, the PNRP provided funding to 10 institutions nationwide to develop and test interventions for follow-up and the initiation of treatment for four cancers for approved, validated screening tests: breast, cervical, prostate, and colorectal (18). Although any individual could benefit from PN, the PNRP focused efforts to identify and address barriers to care among populations experiencing cancer health disparities.

Breast and gynecological cancers are an optimal arena to use PN because of the known survival benefit of early detection through mammography and Pap tests with prompt follow-up of detected abnormalities. PN is particularly important in women's cancers because of documented racial and ethnic disparities in cancer care across disease trajectories. In 2015, cervical cancer incidence rates among Hispanic women were the highest of any racial/ethnic group, 50% higher than those among non-Hispanic whites (19). In addition, the death rate for cervical cancer in black women was double than that in non-Hispanic white women (2.0 vs. 4.2 per 100,000, respectively) (19). It is notable that although white women had the highest breast cancer incidence rate, black women had the highest breast cancer mortality rate (19, 20). Thus, PN may be a strategy to help reduce these documented disparities.

The purpose of this review is to: (a) provide a summary of the recent literature (2010–2015) on PN and breast and gynecologic cancers from screening through treatment along the cancer care continuum; and (b) highlight research challenges and opportunities of PN that impact women's health.

METHODS

PubMed and Medline were searched for studies published from January 2010 to October 2015, particularly those recent articles within the past 2 years, addressing PN for breast and gynecological cancers and written in English. Only original studies reporting quantitative, qualitative, or mixed methods results regarding PN that dealt with cancer screening, diagnosis, treatment, clinical trials, or survivorship were included in this review. Editorials, abstracts, anecdotal reports, literature reviews, and articles lacking data from original research were excluded, as were articles that included non-breast/non-gynecological cancers and/or men in the analyses. Search terms included patient navigation, navigation, navigator, cancer screening, clinical trials, cancer patient, cancer survivor, breast cancer, gynecological cancer, ovarian cancer, uterine cancer, vaginal cancer, and vulvar cancer.

A total of 209 articles referencing PN in women's cancers were found, of which 180 did not meet the inclusion criteria, resulting in 29 articles that met the criteria for inclusion in this review. Several notable PNRP articles were excluded because they included non-breast/non-gynecological cancer and men in their analyses (21–25). The 29 articles were then divided into categories along the cancer care continuum (screening, diagnostic resolution, and after primary diagnosis). The articles were reviewed and summarized by one study author (Jessica L. Krok-Schoen). Questions regarding inclusion were resolved by consensus among the other two authors (Jill M. Oliveri and Electra D. Paskett). Each article was reviewed, and the results presented are organized by placement along the cancer care continuum described above.

Table 1 comprises a summary of published cancer PN studies ($N = 29$).

RESULTS

PN for Cancer Screening

The literature on PN interventions to increase breast cancer screening included five studies (26–30), with two randomized controlled trials (RCTs) (27, 30). In a large RCT with 3,895 inner city women, Phillips et al. (30) found no statistical difference in mammography adherence between the control (usual care) and PN intervention groups at baseline. After the 9-month intervention, mammogram adherence was significantly higher in the PN intervention group compared to the control group (87 vs. 76%, respectively, $p < 0.001$). Marshall et al. (27) implemented a RCT to increase breast cancer screening among 1,905 older African American Medicare beneficiaries. Women in the intervention group who received educational materials and PN services had significantly higher odds of being within guidelines for mammography screening at the end of the 2-year follow-up period compared to women in the control group who received only educational material [odds ratio (OR) = 2.26, 95% confidence interval (CI) = 1.59–3.22].

The other three studies (26, 28, 29) examined the effectiveness of PN interventions to increase breast cancer screening among diverse populations, including African American, Latina, Native American (26), immigrant (28, 29), and refugee (28, 29) women. Burhansstipanov et al. (26) implemented an education-based PN intervention to facilitate mammography screening for African American, Latina, Native American, and poor white women in the Greater Denver Metropolitan area. Statistically significant associations were found between having received the PN intervention and reporting a mammogram screening for all racial/ethnic groups ($p < 0.05$). A study by Percac-Lima et al. (28) implemented an educational, language concordant PN program for Serbo-Croatian refugees and immigrants to overcome barriers to breast cancer screening and support them in scheduling a mammogram. They found that, at baseline, 44% of women had a mammogram within

TABLE 1 | Summary of published cancer patient navigation studies: 2010–2015.

Reference	Cancer	Design	Participants	Results
PATIENT NAVIGATION FOR CANCER SCREENINGS				
Burhansstipanov et al. (26)	Breast	Natural experiment then a quasi-control study	313 African American, Latina, Native American, and poor White women who had not received a mammography in more than 18 months enrolled in a navigation intervention	Navigation improved mammography among women for all racial/ethnic groups who received the navigation intervention compared to those women in the non-navigated group
Marshall et al. (27)	Breast	Randomized controlled trial	1,358 African American female Medicare beneficiaries who were ≥65 years of age randomized to receive either patient navigation and educational materials ($n = 638$) or educational materials only ($n = 720$)	Women in the intervention group had significantly higher odds of being up to date on mammography screening compared to women in the education only group (OR = 2.26, 95% CI = 1.59–3.22)
Percac-Lima et al. (28)	Breast	Quasi-experimental intervention	91 Serbo-Croatian speaking women overdue or never had a mammogram who received individually tailored interventions to encourage breast cancer screenings	At baseline, 44.0% of women had a mammogram within the previous year, with the proportion significantly increasing to 67.0% after 1 year ($p < 0.001$)
Percac-Lima et al. (29)	Breast	Quasi-experimental intervention	188 refugee women eligible for breast cancer screening at an urban community health center. The comparison group was English ($n = 2,072$) or Spanish-speaking ($n = 2,014$) women eligible for breast cancer screening	Patient navigation increased screening rates in both younger and older refugee women (64.1% before intervention, 81.2% after intervention) and were similar to the English (80.0%) and Spanish-speaking women (87.6%)
Phillips et al. (30)	Breast	Controlled cluster randomized trial	3,895 inner city women were randomized to a phone-based navigation intervention ($n = 1,817$) and usual care ($n = 2,078$) groups	At baseline, there was no difference in mammography adherence between the usual care and intervention groups. After the 9-month intervention, mammogram adherence was significantly higher in the intervention group (87.0%) compared with the usual care group (76.0%) ($p < 0.001$)
Wang et al. (31)	Cervical	Two-arm, quasi-experimental pilot study	Chinese women ($n = 134$) who has not had a Pap test within the previous 12 months assigned to either patient navigation (education and navigation services) ($n = 80$) and control (education only) ($n = 54$) groups	In the 12 months following the program, Pap screening rates were significantly higher in the intervention group (70.0%) compared to the control group (11.1%) ($p < 0.001$)
PATIENT NAVIGATION FOR DIAGNOSTIC RESOLUTION				
Basu et al. (32)	Breast	Pre-post design, quasi-experimental intervention	176 women diagnosed with breast cancer enrolled in a nurse navigation program to increase timeliness to diagnostic resolution and consultation	Navigation was found to significantly shorten time to consultation for women older than 60 years but not for women 31-60 years of age

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TABLE 1 | Continued

Reference	Cancer	Design	Participants	Results
Battaglia et al. (33)	Breast, cervical	Quasi-experimental intervention	Women with abnormal breast and cervical cancer screenings who were enrolled in the navigator intervention (n = 1,497) or usual care (n = 1,544) arm in the Boston Patient Navigation Research Program	There was a significant decrease in time to diagnostic resolution for navigated group compared with usual care group among those with a cervical screening abnormality (aHR = 1.46; 95% CI = 1.1–1.9); and among those with a breast cancer screening abnormality that resolved after 60 days (aHR = 1.40; 95% CI = 1.1–1.9). There was no difference before 60 days
Charlot et al. (34)	Breast, cervical	Quasi-experimental intervention	Women with a breast (n = 655) or cervical (n = 602) cancer screening abnormality enrolled in the Boston Patient Navigation Research Program	Language concordance was associated with timelier diagnostic resolution for all women of the cervical cancer screening abnormality group during the first 90 days (aHR = 1.46; 95% CI = 1.18–1.80), but not after 90 days. Race concordance was associated with significant decreases in time to diagnostic resolution for minority women with breast and cervical cancer abnormalities
Donelan et al. (35)	Breast	Group comparison study	72 women with abnormal mammography enrolled in a navigator program. 181 women with abnormal mammography were in the non-navigated group	There was no difference in timeliness of care, preparation for the visit to the breast center, ease of access, quality of care, provider communication, unmet needs, and patient satisfaction between groups
Dudley et al. (36)	Breast	Quasi-experimental intervention	460 low-income Hispanic women (260 navigated, 200 usual care) with an abnormal breast cancer screening result or untreated biopsy in the University of Texas Patient Navigation Research Program	The average days from definitive diagnosis to initiation of therapy was significantly reduced overall with navigation (navigation vs. usual care, 57 vs. 74 days, $p < 0.05$)
Freund et al. (37)	Breast	Meta analyses	3,083 women with abnormal breast cancer screening tests and 1,455 women with abnormal cervical cancer screening tests who participated in the Patient Navigation Research Program	One out of seven sites focused on abnormal breast cancer screening and two out of four sites focused on abnormal cervical cancer screening reported a significant benefit of PN on diagnostic resolution after cancer screening abnormality from 0 to 90 days Three out of seven sites focused on abnormal breast cancer screening and 2 out of four sites focused on abnormal cervical cancer screening reported a significant benefit of PN during 91–365 days
Hoffman et al. (38)	Breast	Prospective, pre-post study	2,601 women (1,047 navigated, 1,554 usual care) with abnormal breast cancer screening result/clinical abnormality enrolled in the DC City-wide Patient Navigation Research Program	The average number of days to diagnostic resolution was significantly shorter for navigated women than non-navigated women (25.1 vs. 42.1 days, respectively, $p < 0.001$), particularly among women who had a biopsy ($p < 0.001$)
Lee et al. (39)	Breast	Controlled cluster randomized trial design	1,039 (494 navigated, 545 usual care) women with abnormal breast cancer screening result/clinical abnormality enrolled in the Moffitt Patient Navigation Research Program	Patient navigation did not increase the timeliness of diagnostic resolution during the initial 3 months of follow-up but started to reduce time to diagnostic resolution after 3 months (aHR = 2.8, 95% CI = 1.30–6.13) and had a significant effect after 4.7 months ($p < 0.05$)
Luckett et al. (40)	Cervical, vulvar	Descriptive study	4,199 women at a tertiary care referral colposcopy center implementing a patient navigator program to reduce non-show rates	No-show rates declined from 49.7 to 29.5% after implementation of the patient navigator program
Markossian et al. (41)	Breast, cervical	Quasi-experimental intervention	Underserved women with abnormal breast or cervical screening test results were assigned to either patient navigation intervention (n = 355) (the Chicago Cancer Navigation Project) or usual care groups (n = 413)	Compared with the usual care group, the breast navigation group had shorter time to diagnostic resolution (aHR = 1.65, 95% CI = 1.20–2.28) and the cervical navigation group had shorter time to diagnostic resolution for those who resolved after 30 days (aHR = 2.31, 95% CI = 1.75–3.06), with no difference before 30 days
Paskett et al. (42)	Cervical	Meta-analysis	2,317 women with low and high-risk cervical abnormalities from four Patient Navigation Program centers who received patient navigation (n = 1332) or usual care (n = 985)	Low-risk women in the navigated group showed improvement in timely diagnostic follow-up in all racial groups, but significant effects were only observed in non-English speaking Hispanic women (OR = 5.88, 95% CI = 2.81–12.29). No effect was observed in high-risk women
Percac-Lima et al. (43)	Cervical	Quasi-experimental intervention	533 Latina women with an abnormal Pap smear requiring colposcopy received patient navigation. The comparison group was 253 non-navigated Latinas with an abnormal Pap smear requiring colposcopy	Navigated women had significantly fewer missed colposcopy appointments over time, with the average falling from 19.8 to 15.7% ($p < 0.05$), compared with an insignificant increase in the no-show rates from 18.6 to 20.6% in the comparison group
Raich et al. (44)	Breast	Randomized clinical trial	628 patients with abnormal breast screenings tests randomized to either intervention (n = 308) or usual care (n = 320) arms in the Denver Patient Navigation Research Program	For the abnormal breast screening group, 92% of the navigated patients reached diagnostic resolution of the initial abnormal test, as compared with 77% for the usual care patients ($p < 0.001$)

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TABLE 1 | Continued

Reference	Cancer	Design	Participants	Results
Ramirez et al. (45)	Breast	Prospective, pre-post study	425 Latina women with abnormal breast cancer screening results enrolled in either a patient navigator program (Six Cities Patient Navigation Study) (n = 217) or usual care (n = 208)	The time to diagnosis was shorter in the navigated group (mean, 32.5 vs. 44.6 days in the usual care group; HR = 1.32). Navigation significantly shortened the time to diagnosis among women who had BI-RADS-3 radiologic abnormalities (mean, 21.3 vs. 63.0 days; HR = 2.42); but not among those who had BI-RADS-4 or 5 (mean, 37.6 vs. 36.9 days; HR = 0.98)
PATIENT NAVIGATION AFTER PRIMARY DIAGNOSIS				
Chen et al. (46)	Breast	Pre-post design, quasi-experimental intervention	100 newly diagnosed women with breast cancer who were enrolled in a navigator program (n = 51) and non-navigated (n = 49)	Overall adherence to the quality indicators significantly improved from 69 to 86% ($p < 0.01$) with the use of patient navigators. Only one individual indicator, use of surveillance mammography, significantly improved (52–76%, $p < 0.05$) for the navigated women, not for the non-navigated women
Haideri and Moormeier (47)	Breast	Retrospective case series analysis	157 women who received navigation services and 103 women who received usual care after being diagnosed with breast cancer	There was no difference in the stage of presentation or the overall survival between the intervention and usual care groups. For the navigated women, there was a modest decrease (9 days) in the time between initial presentation and definitive therapy
Hendren et al. (48)	Breast	Randomized controlled trial	319 newly diagnosed breast cancer patients were randomized to receive a patient navigation intervention for improved quality of life (n = 141) or usual care (n = 129) in the University of Rochester Patient Navigation Project	There was no significant effect of patient navigation on disease-specific quality of life scores between navigated and usual care breast cancer patients undergoing primary cancer treatment
Ko et al. (49)	Breast	Multisite, quasi-experimental intervention	1,004 (navigated = 498, usual care = 506) women newly diagnosed with breast cancer enrolled in the Patient Navigation Research Program to improve receipt of recommended care	Among women eligible for antiestrogen therapy, navigated women had a significant higher likelihood of receiving antiestrogen therapy compared with non-navigated controls (OR = 1.73, $p < 0.01$). Among the women eligible for radiation therapy after lumpectomy, navigated women were no more likely to receive radiation than women in the usual care group (OR = 1.42, $p = 0.22$)
Madore et al. (50)	Breast	Quasi-experimental pilot study	20 medically underserved women recently diagnosed with breast cancer who were enrolled in the Breast CARES intervention to overcome treatment barriers	There was a decrease in depression and cancer-related distress and an increase in social support. Participation in the intervention helped the women overcome financial barriers (73.0%), transportation problems (60.0%), and communication barriers with medical staff (73.0%)
Raj et al. (51)	Breast	Retrospective, pre-post study	186 women with breast cancer from a disadvantaged minority community who participated in a patient navigator program to improve quality measures	Women who received navigation services received high-quality cancer care, as defined by concordance with ASCO/NCCN quality measures. These navigated women also had a favorable breast cancer stage distribution with >50% having *in situ* or stage 1 disease
Ramirez et al. (52)	Breast	Quasi-experimental intervention	480 Latinas with breast cancer enrolled in either a patient navigation program for timely diagnostic resolution (n = 251) or usual care (n = 229) in the Six Cities Study	A significantly higher percentage of navigated women initiated treatment within 30 days (69.0 vs. 46.3%, $p < 0.05$) and 60 days (97.6 vs. 73.1%, $p < 0.001$) compared to women in the usual care group. Time from cancer diagnosis to first treatment was significantly lower in the navigated group (22.22 days) than usual care group (48.30 days)
Ulloa et al. (53)	Breast	Prospective, pre-post study	130 low-income women from California enrolled in a patient navigation intervention to improve communication about survivorship care	The intervention significantly improved short-term recall of patient-specific breast cancer knowledge ($p = 0.05$) and reduced communication barriers (15.0% at week 1 to 6% at 3 months, $p < 0.05$)

the previous year, with the proportion increasing to 67% after 1-year ($p = 0.001$) of receiving the education-based PN intervention. Lastly, another study by Percac-Lima et al. (29) found that an education-based PN intervention to overcome barriers to breast cancer screening and information on how to obtain mammogram screening when needed among Somali, Arabic, or Serbo-Croatian refugee women improved mammography rates and significantly decreased disparities in screening rates between refugee and English- and Spanish-speaking women receiving care at the same health center.

One study in our review examined the impact of PN on screening rates for gynecological cancers. Wang et al. (31) found Chinese women in need of a Pap test reported significantly higher Pap test screening rates for those who received the PN intervention (education and PN services) compared to the control group (education only) (70 vs. 11.1%, respectively, $p < 0.001$).

PN for Diagnostic Resolution

Six studies (32, 35, 36, 38, 39, 45) were identified that focused on PN interventions to reduce time from abnormal breast cancer screening to diagnostic resolution. Of the six studies, one RCT by Lee et al. (39) examined the efficacy of PN among medically underserved populations in Tampa, FL, USA. Results showed a lagged effect of PN; PN did not increase the timeliness of diagnostic resolution during the initial 3 months of follow-up [adjusted hazard ratio (aHR) = 0.85, 95% CI = 0.64–1.13], but reduced the time to diagnostic resolution after 3 months

(aHR = 2.8395% CI = 1.30–6.13) and had a significant effect ($p < 0.05$) after 4.7 months. Several quasi-experimental studies (32, 36, 38, 45) on PN and diagnostic resolution for abnormal breast cancer screening reported that PN significantly shortened time to diagnostic resolution compared to women who did not receive PN. One cohort study (35) exploring patient perspectives of clinical care and PN in follow-up of abnormal mammography reported no differences in the timeliness of care, preparation for the visit to the breast center, ease of access, quality of care, provider communication, unmet needs, and patient satisfaction between navigated and non-navigated groups.

Three studies, a meta-analysis (42), descriptive study (40), and quasi-experimental study (43), were published during the time period reviewed that examined PN for diagnostic resolution of an abnormal cervical cancer screening result. A recent meta-analysis by Paskett et al. (42) examined the effectiveness of PN for diagnostic resolution of an abnormal cervical cancer screening among four PNRP centers. Within these centers, low-risk women in the navigated group showed improvement in timely diagnostic follow-up in all racial groups, but statistically significant effects were only observed in non-English speaking Hispanic women (OR = 5.88, 95% CI = 2.81–12.29). No effect was observed in high-risk women. A pre-post study (40) implemented a PN program to reduce no-show rates at a colposcopy center. After implementation, no-show rates for abnormal Pap test follow-up declined from 49.7 to 29.5% ($p < 0.0001$). In another quasi-experimental study (43) focused on Latinas in need of abnormal Pap test follow-up, navigated women had significantly fewer missed colposcopy appointments over time (i.e., reduction from 19.8 to 15.7%; $p = 0.02$) compared with an insignificant increase in no-show rates from 18.6 to 20.6% in the comparison group.

Three studies (33, 34, 41) explored PN interventions with regard to diagnostic resolution after an abnormal breast or cervical cancer screening test. A study by Markossian et al. (41) reported PN for abnormal breast cancer screening was associated with shorter time to diagnostic resolution (aHR = 1.65, 95% CI = 1.20–2.28, $p = 0.002$). However, there was a lag in the effectiveness of PN regarding diagnostic resolution for abnormal cervical cancer screening. In the first 30 days, the difference between those in the PN arm vs. those in the comparison group was not significant. But, from days 31 to 365, women in the PN group experienced a shorter time to diagnostic resolution compared with those women who received usual care (aHR = 2.31, 95% CI = 1.75–3.06, $p < 0.001$). A similar trend was noted by Battaglia et al. (33) among participants with an abnormal breast and cervical cancer screening test. Conversely, Charlot et al. (34) found a language concordance PN intervention was associated with timelier resolution for the cervical cancer screening abnormalities group during the first 90 days (aHR = 1.46, 95% CI = 1.18–1.80), but not after 90 days. No significant difference was found between the navigated and non-navigated breast cancer screening abnormality groups throughout the course of the study.

The PNRP studies included other cancers (colorectal and prostate), but the majority of the cancers were breast and cervical. A meta-analysis by Freund et al. (37) assessed the timeliness of diagnostic resolution for an abnormal breast and cervical cancer screening result across the PNRP. The results of the meta-analysis found little benefit during the first 90 days of care as only one of the seven sites focusing on breast cancer screening and two of the four sites focusing on cervical cancer screening observed a positive effect of PN on time to diagnostic resolution ($p < 0.05$). Greater benefit from navigation was seen from 91 to 365 days for diagnostic resolution among three of the seven sites focused on breast cancer screening and two of the four sites focused on cervical cancer screening ($p < 0.05$). Meta-regression revealed that navigation had its greatest benefits within centers with the greatest delays in follow-up under usual care.

One study (44) reported on the difference in time to diagnostic resolution between those in the PN intervention vs. control groups. A RCT from the Denver PNRP center evaluated the effectiveness of PN programs for increasing rates of diagnostic resolution for abnormal breast cancer screening. Raich et al. (44) found PN shortened time to resolution in the navigated group ($p < 0.001$) compared to the usual care group. Specifically, PN improved diagnostic resolution for patients presenting with mammographic BIRADS 0 and 3, but not BIRADS 4/5 or abnormal breast examinations.

PN after Diagnosis

The results of the literature review for PN after cancer diagnosis resulted in eight studies (46–53), including one RCT (48), reporting effects on various outcomes among cancer patients including start of treatment, receipt of recommended care, completion of treatment, quality of life and depressive symptoms, communication with physicians, and quality measures. Hendren et al. (48) found no significant effect of PN on disease-specific quality of life scores between navigated and usual care breast cancer patients from baseline to 3 months. Other studies suggest that PN had no effect on time to completion of primary cancer treatment, satisfaction with cancer-related care, or psychological distress, and they attributed the non-significant findings to the open eligibility criteria (all patients) instead of targeting those with shown need, as seen in other effective interventions (49, 51, 52).

A study by Ramirez et al. (52) sought to examine the effectiveness of PN in reducing time from breast cancer diagnosis to initiation of treatment among Hispanic/Latino women. Compared to control patients, there was a significantly higher percentage of navigated women who initiated treatment within 30 days (69.0 vs. 46.3%, $p < 0.05$, intervention vs. control, respectively) and 60 days (97.6 vs. 73.1%, $p < 0.001$, intervention vs. control, respectively) from diagnosis. Also, time from breast cancer diagnosis to first treatment was significantly lower in the navigated group (22.22 days) than among women in the control group (48.30 days).

In a large, multisite study, Ko et al. (49) sought to improve the receipt of recommended care for newly diagnosed breast cancer patients, and the findings varied based on the type of treatment received by the patients. Among women eligible for antiestrogen therapy, navigated participants were more likely to receive antiestrogen therapy compared with usual care participants (OR = 1.73, $p = 0.004$). Among women eligible for radiation therapy after lumpectomy, navigated participants were

no more likely to receive radiation than usual care participants (OR = 1.42, $p = 0.22$).

Barriers to Care and PN

Several studies have conducted secondary analyses to understand the association between barriers to care and clinical outcomes, particularly within the PNRP. A 2015 study by Ramachandran et al. (54) explored the association among number of barriers to care, type of barriers, and timeliness of diagnostic resolution among women with abnormal cancer screening results. They found that 74% of breast cancer screening participants and 55% of cervical cancer screening participants reported at least one barrier to diagnostic resolution. Navigated women with barriers resolved cancer screening abnormalities at a slower rate compared with navigated women with no barriers. Another study by Ramachandran et al. (55) using Boston PNRP data, found the odds of timely diagnostic resolution reduced as the number of barriers increased (one barrier, aHR = 0.81, 95% CI = 0.56–1.17, $p = 0.26$; two barriers, aHR = 0.55, 95% CI = 0.37–0.81, $p = 0.0025$; three or more barriers, aHR = 0.31, 95% CI = 0.21–0.46, $p < 0.0001$). Lastly, Katz et al. (56) examined the effect of having barriers to diagnostic resolution and time to resolution among participants in the PN intervention arm with a breast or cervical cancer abnormality in the PNRP. They found that 63.7% of breast abnormality and 46.6% of cervical abnormality participants had at least one barrier resulting in longer time to diagnostic resolution among breast (aHR = 0.74, 95% CI = 0.67–0.83, $p < 0.01$) and cervical (aHR = 0.79, 95% CI = 0.70–0.90, $p < 0.01$) participants vs. those with no reported barriers.

Specific types of barriers patients report were described by several studies (57–59). Korber et al. (57) found the most common barriers to cancer treatment were patient-provider communication and knowledge of patient resources. Other studies found location of health-care facility (59), transportation problems (58), not speaking English (55), no insurance (56), financial concerns (58, 60), lack of social/practical support (58, 59), and lack of information about the abnormality (57) as the most prevalent barriers to cancer care among patients enrolled in PN interventions.

Some studies have attempted to determine which variables are associated with having a barrier to cancer care to identify women most in need of PN. Several studies (55, 60–62) found that women with barriers to cancer care were more likely to be racial and ethnic minorities (55, 60), unmarried (62), part-time employed/unemployed (60, 62), non-English language speakers (55, 61), and have public/no health insurance (55, 60) compared to women without any barriers to care.

DISCUSSION

As evidenced in this literature review, PN has been shown to help women receive cancer screenings, receive more timely diagnostic resolution after a breast and cervical cancer screening abnormality, initiate treatment sooner, receive proper treatment, and improve quality of life among cancer patients. Also, it was shown that PN eliminates barriers to care. PNRP demonstrated: (1) who has barriers; (2) that barriers delay the receipt of care; and (3) types of numbers of barriers that impact time to treatment (54–56).

Several trends emerged from this review. PN programs have been implemented among diverse populations specifically focused on reducing health disparities in racial and ethnic minorities and/or underserved populations. It is important to note that each study population and setting was unique, thus generalizability of these findings may be limited. Another trend noted was the limited effectiveness for certain groups receiving PN, alluding to the possibility that PN is not equally effective for all groups. Results found significant differences in PN effectiveness with regard to age (32), ethnicity (42), location of care (37), type of screening test (38), and type of treatment (49). Although relevant for all populations, use of a "one-size-fits all" approach to PN may not be the best approach. The original intent of PN is to improve the experience of care among patients with the greatest needs by tailoring actions to an individual's barriers to care (63). If implementation across the patient population is too demanding on resources, especially due to the fact that the American College of Surgeons Commission on Cancer (CoC)'s accreditation mandates are currently unfunded, targeting PN implementation may be a possible solution. By identifying those most likely to need PN, scarce resources can be diverted to women in most need and most likely to delay or not receive prompt, appropriate care (64).

Finally, although there is evidence of the potential of PN to improve outcomes related to cancer screening and diagnostic resolution, many studies have utilized less robust designs (i.e., quasi-experimental and descriptive studies), as mentioned by previous reviews (14–16). A notable difference between this review and the prior reviews is an increase in the number of studies evaluating PN on cancer screening and treatment outcomes. Another difference between this and previous reviews was inclusion of studies that evaluated the association of PN with reported outcomes during cancer treatment and post-treatment. Yet, there was great heterogeneity among the studied outcomes (e.g., quality of life, proper treatment), and therefore, cumulative evidence, as seen in PN interventions on cancer screening and diagnostic resolution, is lacking.

Research Opportunities in PN and Women's Health

Due to the increased prevalence of PN in health-care systems, there are growing research opportunities in PN and women's health. One area that is ripe for researchers is PN in cancer survivorship, particularly among post-treatment cancer survivors. Increases in the number of individuals diagnosed with cancer each year, as well as improving survival rates, have led to an ever-increasing number of cancer survivors (20). As evidenced by this review, implementation of PN interventions among post-treatment cancer survivors is lacking. Future research should not only explore adherence to post-treatment surveillance behaviors but also treatment outcomes that can affect the physical and psychological well-being of women.

The PN literature on women's cancers is growing; however, it is limited in that researchers have primarily focused on breast cancer (as seen in the literature on PN after diagnosis). Although

cervical cancer incidence and mortality rates have steadily decreased, it is estimated that in 2015, 12,900 new cases of invasive cervical cancer occurred and 4,100 died from this disease (19). There is a wide racial and socioeconomic disparity in the incidence and mortality rates from cervical cancer. Underlying these disparities are often education, language, geographic, and trust factors (65). As evidenced by this review, the few studies that have explored PN in gynecological cancers showed promising results. Thus, researchers should make gynecological cancers a focus for their PN interventions to maximize the positive impact on this survivor population. Important yet understudied subpopulations, such as women with increased genetic risk, should be considered. PN can provide education, support, and guidance within the clinical setting for these women to receive appropriate screenings, genetic testing and counseling, prompt diagnosis, and proper treatment.

Women may also benefit from PN during cancer care that is tailored to specific family-related barriers, such as child care and transportation. Women often assume the role of caregivers and income-earners and may need more assistance in caregiving for others while receiving cancer care for themselves. PN can link them to resources that offer emotional (i.e., support groups) and tangible support (i.e., house cleaning, child care) and has the potential to improve quality of life and psychosocial outcomes for both women with cancer and women who are caregivers.

Navigators should consider the age of the female patient and their stage in life during PN interventions. For example, younger women often face very different challenges and complications than older women, including concerns about becoming a mother; caring for children when faced with a life-threatening illness; premature menopause leading to loss of fertility; sudden onset of vasomotor symptoms; long-term consequences of early ovarian decline; body image and sexuality; and career and work concerns related to productivity and job security (66). For older adults, age-related concerns may include spousal caregiving; lack of social support; quality vs. quantity of life; comorbidities; risk of polypharmacy; mobility challenges; housing and transportation needs; and declining cognitive function and information processing (67, 68). Navigators from the PNRP used a standardized, structured list and an open-ended approach that captured barriers to care identified by participants. Future studies should utilize this approach to collect information on barriers to care and explore age-related differences in reported barriers to address individual needs accordingly.

The similarity of patient navigators to the participants is important for the success of PN interventions. For example, patient navigator race and language concordance improved the timeliness of care in a minority population (34). Likeness to the patient population is already a typical characteristic of CHWs, who work within a target community to improve community awareness and adherence to cancer screenings, and thus, this successful strategy should be extended to navigators. Since the CHWs' role is to connect underserved populations from the community with screening services, PN programs should work with CHWs to assist women across the entire cancer care spectrum from cancer prevention to post-treatment. Future research should explore the effect of a combined CHW and PN intervention to increase community engagement, improve access to preventive health services, facilitate timely diagnosis and treatment, and ultimately improve the health of women in underserved areas.

AUTHOR CONTRIBUTIONS

JK-S was responsible for the planning, literature review, writing, editing, and submitting the manuscript. JO was responsible for the planning, literature review, writing, and editing the manuscript. EP was responsible for the planning, writing, and editing the manuscript.

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OPINION
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Clinical Trial Accrual: Obstacles and Opportunities

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Keywords: clinical trial accrual, gynecologic oncology, accrual, participation, enrollment

Less than 2% of patients diagnosed with cancer participate in a clinical trial in the United States (1). Gynecologic oncology patients do not appear to participate in trials with any more frequently than other cancer types. While gains in progression free survival have continued to improve overall life span for women with advanced gynecologic cancers, more cures have not been realized. Clinical trials, defined by the National Institute of Health as "a research study in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" (2), are the primary focus for enrollment of most patients with an active malignancy. Clinical research studies such as tissue banks and longitudinal cohort studies provide invaluable data for researchers but require a consenting population and may be overlooked when the focus is on therapeutic intent. Lack of accrual to clinical trials leads to early closure of studies and a waste of critical resources as well as extended periods of enrollment, which can hinder the ability to interpret the results. Stensland et al. reported that 1 in 4 cancer clinical trials were stopped early with 1 in 10 being stopped for poor accrual (3). A panel of experts convened by the NCI and ASCO to discuss barriers to clinical trial enrollment in 2013 (4) cited barriers in three areas as most significant: (1) patient/community, (2) physician/provider level, and (3) site/organizational. Physician/provider level barriers include willingness to refer a patient for study, lack of knowledge about available clinical trials, and concern regarding a patient's ability to participate (4–6). Patient/community barriers have been noted to include being unaware of trial opportunities and complexity and stringency of the protocol (7).

But really, in this time of internet and social media, of immediate and total access to seemingly endless information, *why* are adult patients not enrolling on clinical trials? A large single institution review of clinical trial enrollment noted a dramatic difference in the proportion of pediatric cancer patients enrolled in clinical trials compared to adult (22 vs. 6%) (8). Is this because parents of children with cancer and young adults with cancer are so much better at searching the internet for clinical trial opportunities? Unlikely, this high rate of participation in the pediatric population preceded the internet age. I believe there are two vital differences between the adult and pediatric cancer communities. First, centralization of treatment in pediatric cancer results in high volume centers. The rarity of pediatric cancer forced pediatric oncologists to band together in universities and research centers. The vast majority of children and young adults are treated in these centers today. Data from several areas suggest that treatment in high volume centers results in improved pediatric oncology outcomes (8, 9). Still, most pediatric cancers are exceptionally rare. Even at high volume centers, collaboration with other sites must be done to gather enough similar cases for research.

Second, and perhaps most importantly, there is a pervasive culture in pediatric oncology that "clinical trials are standard practice in cancer treatment for children, adolescents, and young adults" (https://www.childrensoncologygroup.org/index.php/what-is-a-clinical-trial). The pediatric oncology community has remained faithful to the charge that cure is the goal (10). In addition, the research structure embraces that the cancers in this space are inherently rare and as such designed studies that use the available patient volume. These elements seem to combine to provide a complete package of physician motivation, patient engagement, and available studies for the vast majority of patients despite the low numbers.

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In gynecologic oncology, there are no data to suggest that female gynecologic cancer patients participate in clinical trials at a higher rate. However, a recent large retrospective study by Cliby et al. suggests that treatment for ovarian cancer at high volume centers improves outcomes (11). The authors of this study suggest that a national effort be made to provide access to women to centers with expertise in ovarian cancer. It remains to be seen if these data will move patients from community settings into centers where participation in clinical trials is more common.

The National Comprehensive Cancer Network states on their website that "without clinical trials, cancer care can't improve." This group compiles clinical practice guidelines from the data produced by clinical trials to help guide the care for patients treated off study. Access to this resource is simple and available to both patients and providers. It is updated regularly and carefully curated.

This is in sharp contrast to information about open clinical trials. The main resource for clinical trials information is the national registry of clinical trials, which is available online at www.clinicaltrials.gov. The goal of the registry was to require the registration of all clinical trials in the US and to provide a resource for clinicians and patients to find open studies. The site is searchable by location and disease but is often woefully out of date. Studies that have closed months ago are often still listed as actively recruiting, studies that have published data are not listed as published, and studies that are open will often have incorrect listings of site information. This lack of timely and correct information results in the inability for interested patients and clinicians to find open and appropriate trials.

The barriers for women with cancer to participate in clinical trials are numerous but they are not insurmountable. Dramatic and sweeping cultural change is necessary to bring about rates of adult enrollment that rival the pediatric population. A profound commitment to the provision of timely data to the national clinical trials registry by sponsors and the timely curating of the website is required for better clinical trial information. A commitment to providing access to high volume centers with experience in gynecologic cancer is required for improving outcomes with the current available strategies. Lastly, physicians and patients need to fully commit themselves to a belief that clinical trial participation can really bring about better treatments and better drugs and most importantly, better lives.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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Disparities in Gynecological Malignancies

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Objectives: Health disparities and inequalities in access to care among different socioeconomic, ethnic, and racial groups have been well documented in the U.S. healthcare system. In this review, we aimed to provide an overview of barriers to care contributing to health disparities in gynecological oncology management and to describe site-specific disparities in gynecologic care for endometrial, ovarian, and cervical cancer.

Methods: We performed a literature review of peer-reviewed academic and governmental publications focusing on disparities in gynecological care in the United States by searching PubMed and Google Scholar electronic databases.

Results: There are multiple important underlying issues that may contribute to the disparities in gynecological oncology management in the United States, namely geographic access and hospital-based discrepancies, research-based discrepancies, influence of socioeconomic and health insurance status, and finally the influence of race and biological factors. Despite the reduction in overall cancer-related deaths since the 1990s, the 5-year survival for Black women is significantly lower than for White women for each gynecologic cancer type and each stage of diagnosis. For ovarian and endometrial cancer, black patients are less likely to receive treatment consistent with evidence-based guidelines and have worse survival outcomes even after accounting for stage and comorbidities. For cervical and endometrial cancer, the mortality rate for black women remains twice that of White women.

Conclusion: Health care disparities in the incidence and outcome of gynecologic cancers are complex and involve biologic factors as well as racial, socioeconomic, and geographic barriers that influence treatment and survival. These barriers must be addressed to provide optimal care to women in the U.S. with gynecologic cancer.

Keywords: heath disparities, gynecologic malignancies, race, socioeconomic factors, barriers to health

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INTRODUCTION

The Institute of Medicine released a landmark report in 2003 titled "Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care," which demonstrated disparities in the U.S. health care system between treatment of racial and ethnic minorities and Whites, subsequently resulting in poorer health outcomes for millions of Americans (1).

Since that time, the National Cancer Institute (NCI) through the Center to Reduce Cancer Health Disparities (CRCHD), the American Cancer Society, the American Society of Clinical Oncology, and the Society of Gynecologic Oncology has committed to the goals of eliminating disparities in cancer-related outcomes (2–4). The NCI defines cancer health disparities as "differences in the incidence, prevalence, mortality, and burden of cancer and adverse related conditions that exist among specific population groups in the United States (2)."

The etiology of disparities in cancer treatment and outcomes has been linked to the complex interplay of race/ethnicity, cultural, socioeconomic, and educational factors. Geographic variability in provider and hospital standards and biological differences between ethnic groups must also be considered (1, 4, 5). Finally, variation from evidenced-based treatment guidelines has been indicated as a modifiable factor that can result in poorer survival outcomes (6).

This review aims to describe some of the important underlying issues that may contribute to the disparities in gynecological oncology management in the United States, namely geographic access and hospital-based discrepancies, research-based discrepancies, influence of socioeconomic and health insurance status, and finally the influence of race. This review continues with detailing site-specific disparities in gynecologic care for endometrial, ovarian, and cervical cancer.

GEOGRAPHIC ACCESS AND HOSPITAL-BASED DISCREPANCIES

A growing body of evidence has demonstrated the importance of access to high-volume hospitals and providers for optimal management and outcomes related to gynecologic malignancies. Several studies have demonstrated worse survival outcomes associated with low volume hospital centers and providers (6–9). A recent analysis of 96,000 patients with ovarian cancer identified by the National Cancer Data Base demonstrated 56% of patients were not receiving the standard of care as designated by the National Comprehensive Cancer Network (NCCN) guidelines. The study also demonstrated that 25% of women received care at very low volume institutions, defined as those treating one to seven cases of ovarian cancer annually. The authors concluded that deviation from NCCN guidelines and treatment at very low volume institutions were both independent predictors of worse disease-specific overall survival (hazard ratio 1.33, 95% CI 1.26–1.41 and HR 1.08, 95% CI 1.01–1.16, respectively) (6, 7). A prior study had also demonstrated that lower volume centers were less likely to provide recommended comprehensive surgical staging procedures (10). An analysis of Surveillance, Epidemiology, End Results (SEER) database demonstrated that chemotherapeutic treatments also varied depending on geography and available oncological providers (11, 12). Per the US Census Bureau, 81% of people live in cities or suburbs with 19% living in rural areas. Shalowitz et al. recently reported that an estimate 7663 women with gynecological malignancies (9% of the total cases of gynecological cancers per year) live in low-access counties in the US located 50 miles from the nearest gynecologic oncologist. These counties were more likely be rural, have residents with lower median incomes, and have more White and Hispanic patients than counties in closer proximity to gynecologic oncologists (13). Although this study did not include outcomes data, prior studies have reported that treatment by a trained gynecological oncologist with increased operative volume yields favorable survival outcomes (14–17). Other studies also associated increasing distance from a gynecological oncologist with increased cervical and endometrial cancer mortality (18). It is therefore important to consider geographic and hospital system-related disparities which influence both access to care and adherence to evidence-based treatment guidelines.

RESEARCH-BASED DISCREPANCIES

Given varied survival outcomes among minority patients, there has been increased focus on attempting to recruit minorities for clinical trials to elucidate inherent differences in tumor biology, response to therapy, and survival in clinical situations where treatment regimens are controlled between groups. The National Institutes of Health (NIH) Revitalization Act of 1993 specifically addressed this issue encouraging enrollment of women and minorities to NIH-sponsored research. However, upon analysis of the four most common NCI-funded clinical trials (breast, prostate, colorectal, and lung cancers) from 1996 through 2002, investigators found that although clinical trial enrollment rate increased by almost 50% during this time period, the proportion of trial participants who were non-White actually declined – Hispanic patients from 3.7% of trial participants to 3.0% and Black patients from 11.0% of trial participants to 7.9% (19). It is not surprising that decreased minority enrollment in clinical trial also exists for gynecologic cancers. Scalici et al. recently published their paper on minority participation in 170 Gynecologic Oncology Group (GOG) trials from 1994 to 2013. They reported that of a total of 45,259 patients were included in GOG trials with 83% being White, 8% Black, and 9% other ($p < 0.01$). They also used Center for Disease Control (CDC) age-adjusted incidence to determine that observed enrollment of Black patients was 15 times lower than expected for ovarian cancer trials, 10 times lower than expected for endometrial cancer trials, 4.5 times lower than expected for cervical cancer trials, and 5.2 times lower than expected for sarcoma trials ($p < 0.001$) irrespective of the type of study or year published (20). Scalici et al. also found that African American participation in clinical trials actually decreased from 16% from 1994 to 2002 to 6% from 2009 to 2013. A recent review utilizing qualitative interviews concluded that the key barriers to minority recruitment to clinical trials were lack of opportunities to participate and lack of encouragement to enroll (21). Additionally, language barriers and logistical issues such as cost of travel may play a role in the recruitment of some minority populations (22). Prior studies have implicated a reduced acceptance to enrollment due to minority skepticism as a factor for reduced involvement in clinical trials (21, 23, 24). However, a study evaluating clinical trial consent rates by race demonstrated no difference in the willingness of Blacks and Hispanics to participate in health research compared to non-Hispanic Whites when offered clinical trial enrollment (25). To fully understand and optimize treatment for

minority patients, it is imperative that these issues be addressed. The NRG Oncology Accrual Workshop recently held a meeting to increase minority recruitment for clinical trials (26).

SOCIOECONOMIC STATUS AND HEALTH INSURANCE STATUS

Individuals with lower socioeconomic status have disproportionately higher cancer incidence rates and death rates than those with higher socioeconomic status, regardless of demographic factors such as race/ethnicity (27). According to the US Census Bureau's report on Income and Poverty for 2014, the median household income in the US was $53,657 with significant variation by race, with Asians the highest at $74,297, and Blacks the lowest at $35,398 (28). The official poverty rate was 14.8%, accounting for 46.7 million people. In 2014, women made an average 79% of what men earned with a median income of $39,621 compared to $50,383 earned by men. Sixteen percent of women were below the poverty line, compared to 13.4% of males. Gender differences in poverty rates were more pronounced for those aged 65 and older (12.1% for women vs. 7.4% for men). Ten percent of non-Hispanic Whites, 12.0% of Asians, 26.2% of Blacks, and 23.6% of Hispanics lived below the poverty level (29). The US Census Bureau's report of Health Insurance Coverage in the US reported the percentage of people without health insurance coverage decreased by 10.4%, or 33.0 million in 2013, compared to the number of uninsured in 2013. Despite these great strides in providing health insurance in the US, Blacks and Hispanics still have a higher rate of uninsured individuals compared to Asians and non-Hispanic Whites (11.8 and 19.9% vs. 9.3 and 7.6%, respectively). Additionally, 16.6% of uninsured individuals earned <$25,000 per year (30). Individuals in lower socioeconomic groups often present with advanced stage disease and are less likely to receive standard regimens of treatment (31).

A recent study by Bristow et al. evaluating the SEER-Medicare database for advanced ovarian cancer found poorer adherence to NCCN treatment guidelines associated with low socioeconomic status [OR 1.32, 95% CI (1.14–1.52)] and worse survival when accounting for the effects of other variables [HR 1.25, 95% CI (1.17–1.34)] despite equivalent Medicare insurance status (32). Additionally, insurance status seems to affect the type of care provided. Goff et al. demonstrated that payer status (private insurance vs. Medicaid) significantly impacted the chance of undergoing optimal surgical management in ovarian cancer (14). Esselen et al. demonstrated that Black women and uninsured women/women with Medicaid were less likely to undergo minimally invasive hysterectomies for uterine or cervical cancer after analysis of 46,450 women identified by the National Inpatient Sample (33). In a previous study by Harlan et al. examining 11 different cancer types, investigators noted significantly lower adherence to treatment guidelines for Black patients with Medicaid compared to Black patients with Medicare or private insurance (27). The same investigators found lack of private insurance a barrier to guideline based treatment for Black and Hispanic women with ovarian cancer, suggesting health insurance status may serve as proxy for other socioeconomic factors (34). Similarly, another analysis of adherence to NCCN guidelines in patients with ovarian cancer identified through the National Cancer Data Base demonstrated median household income of less than $35,000 was associated with non-adherence to evidence-based guidelines (OR 1.26, 95% CI 1.21–1.32) and worse survival (HR 1.06, 95% CI 1.02–1.1) (35). These findings were consistent with prior studies that have linked poverty level and low socioeconomic status to poorer adherence to evidence-based treatments and worse ovarian cancer survival (36–38). In addition to treatment administration, a recent evaluation of 8211 elderly patients with ovarian cancer identified from the SEER database demonstrated a decreased chance of hospice referral associated with non-White race [OR 1.44; 95% CI (1.26–1.65), $p < 0.001$], the lowest income group [OR 1.17; 95% CI (1.04–1.32), $p = 0.01$], and Medicare fee-for-service (vs. managed care) [OR 1.39; 95% CI (1.24–1.56), $p < 0.001$] (39).

RACE

Per the US Census Bureau, as of 2015, there are 321,729,000 people living in the United States with approximately 63.7% of the population described as Non-Hispanic White, 16.4% of the population described as Hispanic or Latino, 12.2% of the population described as African American, 4.7% Asian, and 0.9% Native American, Hawaiian, or Alaskan Native. Black men and women are more likely to die from cancer than any racial or ethnic group (31). Despite the reduction in overall cancer-related deaths since the 1990s, the 5-year survival for Black women is significantly lower than for White women at each stage of diagnosis, with the gap in survival actually increasing over the past few decades (40). Although the incidence of a new cancer diagnosis per 100,000 individuals is lower for Black women than White women (391.7 vs. 418.3, OR 0.94, $p < 0.05$), the death rate per 100,000 individuals is higher (180.6 for Blacks vs. 155.0 for Whites, OR 1.17, $p < 0.05$) (40). Interestingly, for all cancer sites, Hispanic women had a lower incidence of cancer relative to non-Hispanic White women [333.2 per 100,000 individuals compared to 433.9 per 100,000 (RR 0.8, $p < 0.05$)]. Additionally, for all cancer sites, Hispanic women had a favorable prognosis compared to non-Hispanic women with a mortality rate of 100.5 per 100,000 compared to 154.7 per 100,000 (RR 0.6, $p < 0.05$) (41). A notable exception is cervical cancer, where the incidence per 100,000 individuals for Hispanics was 11.8, compared to 7.2 for non-Hispanic Whites (RR 1.6, $p < 0.05$) and the mortality rate was 3.0 per 100,000 for Hispanics and 2.1 per 100,000 non-Hispanic Whites (RR 1.5, $p < 0.05$) (41). In general, Asian women had lower incidence and mortality rates than non-Hispanic White women across all cancer types (42–44). Among all Asians, the incidence of cancer per 100,000 is 314.9 with a mortality rate of 115.5 per 100,000, which is notably lower than that for non-Hispanic Whites (477.5 and 190.7, RR 0.7 and RR 0.6, $p < 0.05$, respectively) (45).

OVARIAN CANCER

Epithelial ovarian cancer (EOC) is the fifth cause of cancer death among women in the United States, accounting for an estimated 21,290 new cases and 14,180 cancer deaths in the US in 2015

(31). With aggressive surgical and chemotherapeutic management, overall survival has improved from 36% during the period of 1975–1977 to 45% during the period 2004–2010 ($p < 0.05$). However, the survival rate over the same time period for Black women has actually decreased from 42 to 36% (46). From 2002 to 2011, the mortality rate associated with ovarian cancer decreased significantly by 2% per year among White women, 1.4% per year among Hispanic women, but remained unchanged among Black women (47).

Several studies have demonstrated that worse survival outcomes among the Black population results from barriers that impede access to quality care and standardized evidence-based surgical and adjuvant treatment (32, 36, 48). Although the incidence of ovarian cancer is higher among White women (12.8 new cases per 100,000) compared to Black women (9.8 new cases per 100,0000), Black women tend to present with more advanced stage ovarian cancer compared to White women (49, 50). Black women have a higher incidence of medical comorbidities compared to White women that may influence treatment decisions (51, 52). However, several studies evaluating large nationally representative databases have demonstrated that Black patients are less likely to receive treatment consistent with evidence-based guidelines and have worse survival outcomes even after accounting for stage and comorbidities (32, 36, 37, 53). Parham et al. found that Black patients were less likely to receive combined surgery and chemotherapy treatment (48). In an analysis of a state specific database, Bristow et al. found that compared to White patients, Black race was associated with a statistically significant and independent lower likelihood of hysterectomy, lymphadenectomy, bowel resection, and surgery by a high-volume surgeon (54). Goff et al. also found that Black and Hispanic patients were also less likely to receive comprehensive staging compared to White patients (14). A SEER analysis by Wright et al. demonstrated delayed administration of adjuvant chemotherapy in Black patients, which was associated with an increased mortality rate (55). Importantly, the difference in survival outcomes among races is reduced or eliminated after accounting for access issues, socioeconomic status, stage, and treatment (4). The similarity in survival outcomes is highlighted in several GOG clinical trials where Black and White women receive similar treatments (56, 57). After review of available literature, it appears that equal treatment yields equivalent survival outcomes for both Black and White patients with ovarian cancer (4).

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic cancer in the US accounting for 54,870 new cases and 10,170 deaths in 2015 (31). For all stages, the 5-year survival rate is 82%, 95% for local disease, 68% for regional disease, and 18% for distant metastatic disease (31). White women had the highest incidence of endometrial cancer compared to other ethnic groups (24.8 per 100,000); however, the mortality rate is twice as high for Black women (7.3 per 100,000 vs. 3.9 per 100,000) (58). The 5-year survival for White women from 2004 to 2010 was 85% compared to 65% for Black women over the same time period (46). Similar to ovarian cancer, several studies have attributed this difference in survival to inequalities in access to care, adherence to evidence-based treatment guidelines, and socioeconomic barriers (59, 60). Unlike ovarian cancer, there may be inherent differences in tumor biology between White and Black patients with endometrial cancer as equal treatment has not correlated with equal outcomes (4). Black patients tend to be diagnosed at higher stages, with higher grade lesions, and high-risk histologies (61–65). Although worse tumor characteristics are associated with worse overall survival, after accounting for all histopathologic and sociodemographic factors, several large database analyses demonstrated worse survival associated with Black race (66–70). Black patients are less likely to be treated for advanced disease and less likely to undergo surgery (62, 71–73). However, Black women are more likely to be treated at high volume institutions with high volume specialized surgeons (74). When staging lymphadenectomy was performed, there were similar rates between Blacks and Whites (64). Other studies have demonstrated similar use of adjuvant chemotherapy and radiotherapy (73). Despite similar treatment, worse overall survival persists among Black women with endometrial cancer. In a GOG randomized clinical trial for advanced and recurrent endometrial cancer, Black women had a 26% greater chance of death compared to White women despite similar surgical and chemotherapeutic treatments after controlling for prognostic factors (75). Several studies have evaluated molecular differences in tumors from Black and White women in effort to identify why Black women have poorer prognosis relative to White women. These studies have primarily focused on p53 mutations, HER2/neu expression, and PTEN mutations. Mutations in tumor suppressor gene p53 have been associated with non-endometrioid histology, high grade tumors, advanced stage at presentation, and poorer overall survival (76). Clifford et al. demonstrated that Black women with stage I tumors were three times more likely to overexpress mutant p53, associated with worse survival and higher recurrence rates (77). Santin et al. demonstrated threefold higher HER2/neu expression in Black patients with serous endometrial cancer than in White patients with the same histology. The investigators concluded that overexpression of Her2/neu was an independent variable associated with poorer survival outcomes (78). Maxwell et al. demonstrated fewer PTEN mutations, associated with better outcomes and endometrioid histology, among Black patients compared to White patients (79). Further genetic and molecular studies need to be performed to further elucidate the causes of worse overall prognosis of Black patients with endometrial cancer.

CERVICAL CANCER

Cervical cancer is the fourth most common cancer in the world. In the US, with the success of cervical cancer screening, the annual incidence is 12,900 with 4,100 deaths in 2015 (31). In 2015, the incidence of cervical cancer for Blacks was 11.4 per 100,000, 13.8 per 100,000 for Hispanics, and 8.5 per 100,000 for non-Hispanic Whites. The mortality rate was 4.9 per 100,000 for Blacks, 3.3 per 100,000 for Hispanics, and 2.3 per 100,000 non-Hispanic Whites (80). The overall 5-year survival for cervical cancer from 2004 to

2010 among White women was 71% compared to 62% in Black women (31). Interestingly, although the mortality rate is higher for Hispanics compared to non-Hispanic Whites, the 5-year survival for cervical cancer is 75% among Hispanic women compared to 71% for non-Hispanic Whites (41). Disparities in cervical cancer incidence and mortality are a direct reflection of unequal access to prevention, screening, and ultimate treatment. Data from the National Immunization Survey demonstrated a lower rate of HPV vaccination among Black and Hispanic adolescent girls compared to White adolescent girls (81). Although Black adolescents were more likely to initiate HPV immunization, they were less likely to complete the three-dose injection series (82, 83). Congress passed the Breast and Cervical Cancer Mortality Prevention Act of 1990, which allowed low-income, uninsured, and underinsured women to gain access to breast and cervical cancer screening and diagnostic services. Overall, 83% of women who have not had hysterectomies reported having a Pap smear in the prior 3 years, including 85% of Black women, 83.5% of White women, and 79% of Hispanic women (84). Despite the relative success with initiating screening, differences in follow-up from abnormal cervical cytology remains an issue, with Black women the most likely to be lost to follow-up (85). Consequently, Black women were more likely to present with more advanced disease than White women (31).

Additionally, treatment differences related to race have been shown to play a role in outcome disparities. Black women were less likely to receive a radical hysterectomy than White women for early stage cervical cancer (86) and were less likely to receive intra-cavity radiation therapy for locally advanced disease (87). Farley et al. demonstrated that in an equal access environment with identical treatment for cervical cancer between White and Black patients, there was equivalent 5- and 10-year survival data between races, reinforcing the idea that equal care results in equal survival outcomes in cervical cancer (88).

CONCLUSION

Health care disparities in the incidence and outcome of gynecologic cancers persist and, in some cases, are worsening. The explanation for these disparities is complex and involves racial, economic, geographic, and biologic factors that influence treatment and survival. Much of the information available outlining these disparities have focused on disparities between Black and White women, with limited studies available regarding other minority populations. Additionally, as most of the studies investigating health disparities evaluated large nationally representative databases with limited detailed clinical information, it is not possible to account for other confounding factors that may have influenced treatment decisions or deviations from evidence-based guidelines. Despite diagnostic and therapeutic advances that have resulted in improved survival among American women in general, significant barriers exist in providing optimal care to millions of women in the US with gynecologic cancer. While not all factors involved in healthcare disparities are modifiable, identification and elimination of those that are must be a considered a top priority in a country that considers access to quality healthcare a basic human right.

AUTHOR CONTRIBUTIONS

SC was responsible for conducting the literature search and formulating the content of the manuscript. DG, TC, and KH were responsible for editing and adjusting content within the manuscript.

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Preventing Cervical Cancer in the United States: Barriers and Resolutions for HPV Vaccination

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Human papillomavirus (HPV) vaccination rates for preadolescent and adolescent girls in the United States are far behind those of other developed nations. These rates differ substantially by region and state, socioeconomic status, and insurance status. In parents and young women, a lack of awareness and a misperception of the risk of this vaccine drive low vaccination rates. In physicians, lack of comfort with discussion of sexuality and the perception that the vaccine should be delayed to a later age contribute to low vaccination rates. Patient- and physician-targeted educational campaigns, systems-based interventions, and school-based vaccine clinics offer a variety of ways to address the barriers to HPV vaccination. A diverse and culturally appropriate approach to promoting vaccine uptake has the potential to significantly improve vaccination rates in order to reach the Healthy People 2020 goal of over 80% vaccination in adolescent girls. This article reviews the disparities in HPV vaccination rates in girls in the United States, the influences of patients', physicians', and parents' attitudes on vaccine uptake, and the proposed interventions that may help the United States reach its goal for vaccine coverage.

Keywords: HPV, vaccination, cervical cancer, disparities, health policy

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INTRODUCTION

Nearly 13,000 American women will be diagnosed with cervical cancer in 2015, and over 4,000 women will die from cervical cancer (1). With the introduction of regular Papanicolaou (Pap) smear screening in the 1950s, cervical cancer incidence rates dropped over 80% (2). While this represents a huge public health success, there is potential for even greater impact on this disease with the human papillomavirus (HPV) vaccination. HPV is the known necessary cause for cervical cancer, and in 2006, the first vaccine targeting HPV was approved in the United States for prevention of both cervical cancer and genital warts. This four-valent vaccine (trade name Gardasil, Merck & Co., Inc.) is active against HPV genotypes 6, 11, 16, and 18, which are responsible for approximately 66% of cervical cancers and 90% of genital warts. It is administered as three injections over 6 months (3). In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended HPV vaccination as a routine vaccine for girls aged 11–12 and approved it for all women up to the age of 26 (4). In 2009, a bivalent vaccine, targeting oncogenic HPV genotypes 16 and 18 was also approved (trade name Cervarix, GalaxoSmithKline) (4), which was found to be similarly efficacious against cervical cancers caused by these HPV genotypes (3). More recently, in December 2014, the Food and Drug Administration (FDA) approved a nine-valent vaccine (trade

name Gardasil 9, Merck & Co., Inc.) that covers five additional HPV genotypes (31, 33, 45, 52, and 58), which are responsible for an additional 15–20% of cervical cancer cases (5). Soon after, in February 2015, the ACIP incorporated the nine-valent vaccine into its recommendations for routine recommendation as an alternative to the four- and bivalent HPV vaccines (6). Phase III trials of the newest vaccine show over 95% efficacy against the additional HPV genotypes (5); therefore, vaccinating the next generation of young women has the potential to prevent almost 90% of cervical cancer cases.

The development of a vaccine against HPV was a major breakthrough in science, but its potential public health success heavily depends upon the acceptance and uptake in any given population. Compared to other developed nations, the United States has been slow to vaccinate. In the first year after the vaccine was approved, only 11.6% of American girls aged 13–17 received at least one dose (7), in contrast to over 80% of girls aged 13–17 who initiated vaccination in Australia (8). One of the key differences between these two countries is the way in which Australia approached the public health need: a successful nationwide, school-based, government-funded HPV vaccination campaign was launched in 2007 (8). While it is too early to show reductions in cervical cancer rates in those vaccinated, the prevalence of genital warts in Australian women under 21 years of age has dropped over 90% in the last 5 years, compared to no change in the rates for women over the age of 30, who did not receive vaccine (9).

Since 2007, vaccine uptake rates have improved in the United States. However, they are still well below goal. Two recent national surveys estimated that between 34 and 60% of eligible girls of ages 11–26 years have received at least one dose of the vaccine (i.e., vaccine uptake), and fewer than half complete the entire three dose regimen (i.e., vaccine completion) (7, 10). Healthy People 2020 has set a goal to reach 80% vaccine completion in girls aged 13–15 by the year 2020 (11). In order to achieve this, vaccination rates will need to more than double in the next 5 years. Understanding the country-specific factors behind the low vaccination rates will help inform interventions to improve uptake in the United States.

In this review, we will evaluate the recent research in disparities in vaccine uptake in the United States, examine key stakeholders' attitudes toward the vaccine, and consider potential interventions that may help improve vaccination uptake rates in the United States. While this vaccine has been approved and is recommended for boys as well (4), this review will focus on the available research for vaccination in girls.

NOTABLE DISPARITIES IN HPV VACCINATION

In the United States, cervical cancer disproportionately affects women of low socioeconomic status, minority populations, and those with limited access to the health-care system (12, 13). The racial disparities may be even more pronounced than previously thought (14). Differences in HPV vaccination initially paralleled these same racial and socioeconomic disparities, but recent data suggest that racial and socioeconomic disparities have decreased significantly (15). However, differences in vaccine uptake are still pervasive by region, insurance status, and sexual orientation (16–19).

Regional Differences

Human papillomavirus vaccination rates vary widely by state. In 2009, HPV vaccination initiation was highest for the Northeast and Midwest regions of the United States and lowest in the Southeast (20). Additionally, family physicians located in the South less routinely offer the vaccine when compared to family physicians in the Northeast, Midwest, and West regions of the United States. These differences were not seen among pediatricians, who have high rates of vaccine delivery nationwide. This may be due to pediatricians' emphasis on immunization in their education and scope of practice, as pediatricians were also more likely to participate in the Vaccines for Children Program, a federally funded immunization program. Family physicians are also historically slower to incorporate any vaccine recommendation compared to pediatricians (21). The National Immunization Survey-Teen (NIS-Teen), an annual survey used by the Center for Disease Control (CDC) to monitor vaccination coverage in adolescents, surveyed over 20,000 adolescents in all 50 states and the District of Colombia (DC) in 2014 and found that Kansas has the lowest state-level HPV vaccine uptake rate: only 38.3% of girls aged 13–17 had initiated vaccination, while Rhode Island has the highest: 76% of girls aged 13–17 had initiated vaccination (10). Unfortunately, the states with the highest cervical cancer rates also have some of the lowest HPV vaccination rates (22). **Figure 1** demonstrates the vast state-wide differences in HPV vaccination initiation and completion in girls aged 13–17 during 2014 according to the NIS-Teen survey data. These regional differences may reflect how much each state's government has chosen to encourage the vaccination. Washington, DC, USA, for example, puts resources into both educational interventions and mandates the vaccine; likely as a result, the percentage of girls receiving at least one dose rose from 38.7% in 2008 to 75.2% in 2014, second only to Rhode Island (15, 23).

Ethnic/Racial Disparities

Minority populations – black women and Hispanic women specifically – are more likely to be diagnosed with cervical cancer (14). HPV also appears to be more prevalent in black women compared to all other racial and ethnic groups in the United States (25). In the first several years after the HPV vaccine was made available, studies reported that young black women were less likely to initiate vaccination, and if they did initiate vaccination, they were less likely to complete the vaccination series than other racial groups (16, 26, 27). Fisher et al. performed a meta-analysis of the available data from vaccine inception to March 2012 and confirmed this finding [OR 0.89 comparing vaccine initiation in non-Hispanic black women to non-Hispanic white women, 95% confidence interval (CI): 0.82–0.97] (19).

However, in the more recent literature, estimates of vaccine uptake by racial category demonstrate positive change and may reflect a rapidly changing landscape of vaccine acceptability and accessibility. Data from the 2014 NIS-Teen survey show that more non-Hispanic black adolescents received at least one

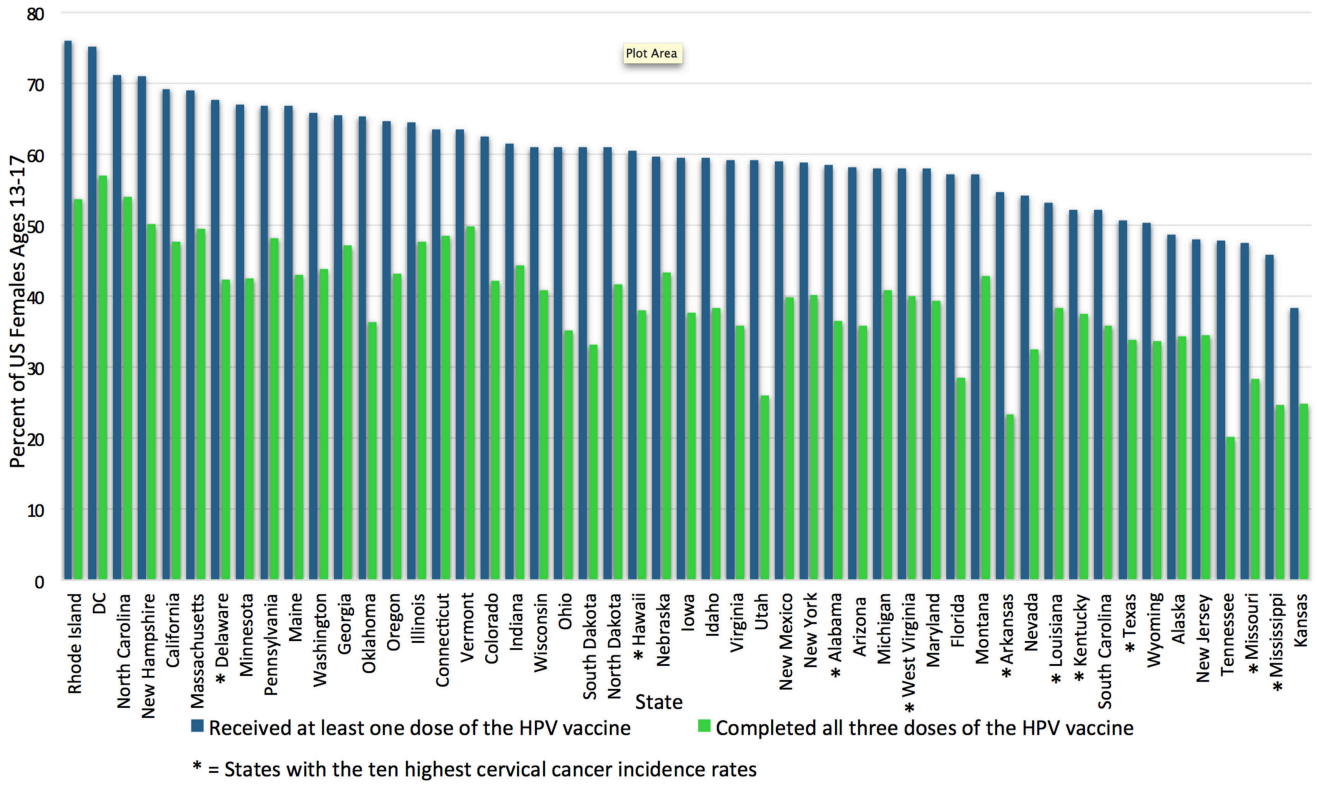

FIGURE 1 | Uptake and completion rates of HPV vaccination by state. This graph shows the percentage of female adolescents aged 13–17 who initiated and completed the HPV vaccination series in the United States in 2014, by state. HPV vaccination uptake ranges from 76% in Rhode Island to 38.3% in Kansas (15). The 10 states with the highest cervical cancer incidence rates according to the CDC in 2012 are marked with *; most are among those with the lowest HPV vaccination rates (24). HPV vaccination rates adapted from the NIS-Teen survey data reported in Reagan-Steiner et al., (15). DC, District of Columbia; HPV, human papillomavirus.

dose of the HPV vaccine than their white counterparts (66.4 vs. 56.2%, $p < 0.05$). Compared to NIS-Teen data from 2008, where vaccine uptake rates of both races was around 35%, these rates show improvements in uptake for both groups over time (23). However, rates of receipt of all three doses remain low for both groups (39 vs. 37.5% non-Hispanic black vs. non-Hispanic white women, p-value not given) (15).

It is unclear whether vaccination rates among Hispanic and Asian women differ from rates in non-Hispanic white women. A systematic review of the studies comparing vaccine rates among these groups was inconclusive (19). In the 2014 NIS-Teen survey, Hispanic adolescents were both more likely to initiate vaccination compared to non-Hispanic whites (66.3 vs. 56.1%, $p < 0.05$) and more likely to have received three doses (46.9 vs. 37.5%, $p < 0.05$) (15). While these data are encouraging and demonstrate a closing gap in racial and ethnic disparities, the fact that fewer than half of all groups complete the series indicates that there is significant room for improvement (21).

Sexual Orientation

While the HPV virus is prevalent in women who have sex with women (28), this group of women is less likely to report appropriate Pap screening (29). Gay, lesbian, and bisexual women or "sexual minority adults" are also more likely to smoke than their "non-minority" counterparts (30). Smoking increases the chances of HPV-related cervical changes, persistence of HPV (31), and progression from cervical dysplasia to invasive cancer (32). Therefore, regardless of sexual orientation, national screening and vaccination recommendations apply and may be even more important. However, an analysis of the 2006–2010 National Survey of Family Growth (NSFG) found that lesbian women are less likely to have initiated HPV vaccination than their heterosexual counterparts (8.5 vs. 28.5%, $p = 0.007$). In this study, there were no differences between bisexual women and heterosexual women in vaccine initiation. These percentages should be interpreted with caution, as the sample sizes for these subgroups of women were small ($n = 62$ for lesbian women and $n = 235$ for bisexual women); however, the differences among these different groups remain concerning (17). A national online survey targeted at the lesbian, gay, and bisexual community, which included 543 gay and bisexual women aged 18–26 found more encouraging results: 45% reportedly had initiated the HPV vaccine (18). While the NSFG survey may be an underestimation due to its small numbers, the online survey may be an overestimation as those volunteering to participate in online health surveys may be more likely to have received health care and vaccination, and they

failed to differentiate between lesbian and bisexual women. Due to the small number of other studies addressing vaccine uptake in gay and bisexual women, the true percentage of vaccine initiators in this group is not known. Given the available data, however, vaccine uptake among sexual minority adults appears lower than the average of 60% for all American female adolescents aged 13–17 (10).

Socioeconomic and Insurance Status

In the United States, cost is frequently cited as a barrier to HPV vaccination initiation and completion (18, 21, 27, 33). Historically, women of lower socioeconomic status were less likely to initiate and complete the HPV vaccine series (16, 19, 27). In 2008, pediatricians and family practice physicians reported that financial concerns were the most frequently cited reasons for not vaccinating (21). Much of this, however, may be explained by insurance status. Women with any insurance in the United States are much more likely to have been counseled about the HPV vaccine, are more likely to intend to get vaccinated, and are more likely to have initiated vaccination than uninsured women (16, 19, 33, 34). A meta-analysis demonstrated that lack of health insurance, rather than income itself, was one of the most important factors associated with failure to initiate HPV vaccination (19). This finding is very important from a public health perspective, as this plays a critical role in determining strategies that could improve vaccination initiation and completion.

The passage of the Affordable Care Act (ACA) in 2010 is one major public health change that is expected to improve HPV vaccination. Under the ACA, any person with insurance can receive the HPV vaccine without any additional cost sharing (i.e., they do not have to pay a copay) when they go to an in-network provider (35). If the cost of vaccination is truly a pivotal barrier, a rise in vaccine uptake should be seen after the passage of the ACA.

STAKEHOLDERS' KNOWLEDGE AND ATTITUDES TOWARD HPV VACCINATION

An understanding of the various stakeholders' knowledge and attitudes about the HPV vaccine is critical to understand why vaccination has not been more widely accepted and to help inform strategies to improve its uptake.

Parents' Knowledge and Attitudes

Generally, parents' knowledge of HPV in the United States is poor. In a subset of the National Health Interview Survey 2010, 4 years after the four-valent vaccine was approved, only 63% of 5,735 parents of children aged 8–17 had even heard of the HPV vaccine (36). Another survey 3 years later failed to show any meaningful improvement: 68% of American adults had heard of the HPV vaccine (37). Parents who lack knowledge frequently cite concerns about side effects and vaccine efficacy as reasons not to vaccinate their daughters (21, 38, 39). Some of this lack of knowledge may be related to lack of education, which may result in failure to vaccinate: mothers with lower education level are less likely to have their daughters vaccinated than mothers with higher education level (26).

Parents' attitudes toward their children and the vaccine also influence vaccination rates. Parents who perceive their daughter to be at low risk of sexual activity often fail to vaccinate their daughters (39). Parents are more likely to refuse or delay vaccination for girls who are 11–12 years old than for girls who are 13–15 years old, and concerns about sexual activity, including the unfounded concern that receipt of the vaccine will result in risky sexual behavior, are associated with these delays (21, 40). Open discussion with the physician may help to alleviate these fears and change parents' attitudes regarding vaccination, as parents who did not feel they could discuss their concerns with their physician were more likely to not vaccinate their child (38). Additionally, a mother's own health practices influence her decisions about her daughter: mothers with more exposure to a primary care physician who regularly receive preventive care (e.g., Pap smears, mammograms) are more likely to agree to vaccinate their daughters, perhaps reflecting the value they place in preventive medicine (41, 42).

Patients' Preferences

While over 80% of young women (ages 15–25) have heard of the HPV vaccine (17), young women express similar concerns as their parents with regards to adverse effects and efficacy (18, 43). On the one hand, many girls and women who do not intend to get vaccinated cite a perceived low risk for HPV as their reason against vaccination. On the other hand, young women who report that they do intend to get vaccinated are more likely to have already had sex, when the timing of the vaccination is less ideal (34). Additionally, college-age women are influenced by their peers and are more likely to get vaccinated if it is perceived as the social norm (44). Most of the studies conducted on patients' attitudes toward the HPV vaccine focused in adolescents and adults but few explore the attitudes of 11- to 12-year-old girls who would ideally receive the vaccine. One small study did evaluate the attitudes of this population and found that 11- to 12-year-old girls are interested in information about vaccine efficacy and side effects, but a discussion of sexual health was less important to both the girls and their mothers (45).

Physician Influence

The ACIP recommends HPV vaccine to be given to girls of ages between 11 and 12, at the same time as the tetanus–diphtheria–acellular pertussis (Tdap) vaccine and the four-valent meningococcal vaccine (46). However, parents and their daughters often rely on the physician to communicate these recommendations (45), and lack of physician recommendation is one of the most frequently cited reasons for not vaccinating preadolescent and adolescent women (38, 43). In a longitudinal study of 388 vaccine-eligible girls, only 37% received an HPV vaccine recommendation by the physician over the course of a year (47). The reason for this extraordinarily low rate of physician recommendation is only partially understood. Providers with low self-reported vaccination rates report delaying the vaccine in patients who they perceive to be at low risk for sexual activity. Thus, the ignorance and misconception from the health-care provider ultimately drive low vaccination initiation rates. This even goes so far that parents of these children report that their

doctor supported or even suggested delaying the vaccine (40). In contrast, a positive physician recommendation has been shown to significantly increase intent to vaccinate (48). In a survey of over 17,000 parents of girls of ages 12–17, parents who had been counseled by a physician were 23 times more likely to have initiated vaccination and 14 times more likely to complete the series. In fact, differences in physician counseling practices may largely explain the differences in interstate vaccination rates (16).

The language used in communication also likely has a large influence on patients' decision to vaccinate; approximately 25% of family practice physicians and pediatricians reported that they do not strongly endorse the vaccine themselves. Therefore, these physicians may not recommend vaccination to their patients at all, or if they do, the authors of the study suggest that they may appear ambivalent and, therefore, their recommendation is less likely to be pursued (49). Both pediatricians and family physicians often delay vaccination: they are both almost twice as likely to strongly recommend the vaccine to girls aged 13–15 vs. 11–12 (21). The sensitive nature of the vaccine, as it relates to sexual activity, also influences physician comfort discussing the vaccine. One study found that almost half of those surveyed felt that it was necessary to discuss sexuality before recommending the vaccine (21), and vaccine recommendation rates are lower in physicians who feel uncomfortable discussing sexuality (49).

INTERVENTIONS TO IMPROVE DELIVERY OF THE HPV VACCINE

There are two key themes to the barriers to HPV vaccination in the United States, which have been reviewed so far, and which much be addressed for any intervention to significantly impact uptake rates. First, misinformation and lack of education is prevalent among parents, physicians, and young women. Second, there has historically been a lack of access to care, either due to the cost of the vaccine for those with insurance or under- or uninsured status. The ACA created the "Prevention and Public Health Fund" which funds "Immunization Grants" provided by the CDC to programs, which are designed to improve vaccination rates (50). There are several different strategies, including education-based, systems-based, and region-based interventions that have been studied to determine, which might best address the current known barriers to vaccination.

Educational Interventions

Many of the barriers to vaccination which have been described above highlight the need for education of all stakeholders: the parents, young women, and physicians. However, a recent systematic review of educational interventions to improve HPV vaccination rates concluded that the widespread implementation of educational interventions would be unsuccessful (51). This is likely due to the fact that different interventions are necessary to reach different communities, and each must be tailored to a specific audience. Gargano et al. (52) demonstrated the importance of understanding and targeting the audience in an intervention designed to increase adolescent awareness and interest in HPV vaccination. Their first step was a focus group to determine how best to reach the target community. They also incorporated the HPV education into the already-existent structure of the school through the use of the science teacher. By engaging the target community, they were able to significantly increase middle and high school students' interest in vaccination through education (52). A study targeting Hispanic women first administered a survey to ensure the educational material was tailored toward the target population's baseline knowledge and was able to demonstrate significant increase in intention to vaccinate (53). While these two studies were successful in increasing interest in vaccination and willingness to vaccinate, other attempts have been less successful. An online intervention called "MeFirst" incorporated college students' baseline knowledge of HPV in order to design a tailored educational intervention; however, 3 months after the intervention, those randomized to the tailored education were no more likely to have initiated the vaccine series than those who had just read the CDC information face-sheet (54). Of note, few studies evaluate actual vaccination uptake outcomes, and most rely on changes in reported intention to vaccinate as a surrogate, which may over-estimate the impact of education on vaccination rates. Given the variability in results of these studies, it is unclear what impact educational interventions alone would ultimately have on HPV vaccination initiation and completion.

Clinic-Based Interventions

Interventions with a systems-based approach have also been studied and are encouraged by the CDC as a mechanism to reach the Healthy People 2020 goal (10). One type of systems-based approach focuses upon intervention at the level of the practice and/or clinic. Standing orders, which authorize non-physician health-care personnel to administer a vaccine to an individual through a protocol approved by an authorized practitioner, are one evidenced-based method, which increases vaccination rates and is endorsed by the U.S. Preventive Services Task Force (55). A survey of young women attending a gynecology clinic found that standing orders for the HPV vaccine were generally acceptable to this population, particularly for the series completion (56).

Automatic reminders or recall-based interventions also increase vaccination rates: a systematic review of seven studies demonstrated that reminder systems for the parents or patients, whether that be through telephone calls, letters, text messages, or outreach visits, are consistently effective in improving HPV vaccination overall (57). These interventions are also relatively easy to implement and may be particularly helpful with improvement of vaccine completion rates (58). However, as with the educational interventions described above, this type of intervention may not work in all groups and may not work if used alone. In one study of mostly Hispanic and black parents attending a pediatric clinic in Texas, reminder phone calls resulted in improvements in rates of receipt of the second and third doses of the HPV vaccine, but only in Hispanic populations (59). These results further highlight the need to understand the community and culture when initiating and evaluating an intervention. Furthermore, the above data support a diverse and multifaceted approach to increasing vaccine uptake.

Another systems-based intervention encouraged by the CDC targets the physician and combines education, reminders, audits, and feedback to help address the physician contribution to low

vaccination rates (10). In one cluster randomized controlled trial, clinics that received focused clinician education, electronic health record based alerts, and quarterly performance feedback for physicians had a modest, but statistically significant, increase in vaccine initiation compared to control clinics (58). Reminders for both parents and physicians can improve vaccination rates, and while alone, they will likely not get the United States to the Healthy People 2020 goal alone, they are a powerful adjunct to any vaccine promotion program.

School-Based Interventions

School-based interventions are another type of systems-based approach that has been successful in several countries where there is already a framework for government-funded universal vaccination, such as Australia (8). While many believe that the concept of a school-based vaccine clinic is also feasible in the United States, some studies suggest that key stakeholders are skeptical of this approach. Focus groups in New Mexico were conducted with key stakeholders: parents of adolescent girls and boys, adolescent girls, middle school nurses, and middle school administrators and highlighted their concerns with this type of intervention. Overall, parents were uncertain about a middle school-based program, and school administrators felt that they lacked the implementation authority (60). However, other studies suggest that this type of intervention can be successful in the United States. School-based vaccine clinics seem particularly more feasible with the passage of the ACA and no-cost-sharing insurance coverage of the vaccine. In a cluster randomized controlled trial in Denver (CO, USA) in 2011, 16 schools were randomly assigned to a school-based vaccine clinic ($n = 8$) or a control. Clinics were held three times a year to accommodate the HPV vaccination schedule. Consent and insurance information was collected from the parents prior to vaccine administration. Compared to controls, children in the intervention schools were more likely to receive the Tdap vaccine, the meningococcal vaccine, and the HPV vaccine. The biggest increase was seen in HPV vaccination rates, where students were 70% more likely to receive the vaccine. One of the issues raised in this study was that less than half of the vaccine clinic costs were recuperated through insurance claims, although this may be related to their study population (over 40% of students were uninsured and were not charged for vaccine administration) (61). Regardless, this randomized controlled trial provides important evidence that school-based vaccine clinics are feasible and can be effective in the United States. Additional government funding or partnership with local agencies could help cover costs and, coupled with education, stands to have the biggest impact on vaccination rates. Furthermore, just as with the other types of interventions discussed, adjusting approaches to fit each community or school may ultimately be needed in order to gain widespread acceptance.

State- and National-Level Interventions

Four of the six jurisdictions (Chicago, DC, Georgia, and Utah) which demonstrated improvements in HPV vaccine uptake from 2013 to 2014 had received funding through Prevention and Public Health Fund and had instituted a variety of interventions ranging from education to monetary support for vaccine programs (15). In addition to funding, state mandates may also have the potential to improve vaccination rates. Until recently, only two states had instituted a mandate for HPV vaccination. In 2008, Virginia passed a mandate for all girls entering the sixth grade to have at least one HPV vaccine, and in 2009, Washington, DC, USA, passed a similar mandate (15). Both included the ability to "opt-out" at parental discretion. These two states now have widely disparate rates of vaccine initiation, demonstrating the variability in the effectiveness of mandates. On the one hand, Washington, DC, USA, ranks number 2 for vaccine initiation in girls aged 13–17, and as previously mentioned was one of the only six jurisdictions to show improvement in vaccination rates from 2013 to 2014. On the other hand, Virginia still ranks 28th for vaccine initiation (see **Figure 1**) (15). Focus groups conducted in Virginia revealed that its public generally was not ready for the mandate: parents felt the government did not have the right to provide parental consent, they felt they did not have enough information about the new vaccine before the mandate was launched, they distrusted the motivations of Merck, and they wanted more education about the vaccine before having to make a decision (62).

State mandates may, therefore, be appropriate for some states, but not for others. In fact, a total of 24 states have previously tried to introduce a mandate into their legislatures, and only Virginia, DC, and Rhode Island have been successful in passing it into viable law (63). Rhode Island's state mandate recently went into effect on August 1, 2015; it requires both girls and boys to have at least one dose of the vaccine to enter seventh grade this year, two doses to enter eighth grade by 2016, and three doses to enter ninth grade by 2017. In contrast to the DC and Virginia mandates, exceptions to vaccination are only made for physician-documented medical reasons or if it is against the parents' religious beliefs (64). It remains to be seen if this mandate will be acceptable to the Rhode Island population, but the state currently ranks number 1 for vaccine uptake, which may reflect a positive attitude and predict acceptance of the vaccine in this population. Further research on the effectiveness of these mandates and other state-based interventions is needed to understand why particular interventions work in some regions and not others. It is unlikely that state mandates alone will help the United States reach its vaccination goal; lessons from Virginia's mandate show us that education prior to mandate is the key.

Finding the Right Intervention

Table 1 provides a matrix demonstrating the various proposed interventions and the barriers which they have the potential to address. An analysis of 21 HPV vaccination programs implemented in low- and middle-income countries found that tailoring the intervention to meet the community's unique needs is an effective method of improving vaccination rates (24). This same principle can be applied in the United States, where it is unlikely that one intervention will achieve success in all regions and states. While education may help address physician, patient, and parent attitudes and beliefs, education alone has not been shown to improve the HPV vaccination rates enough to reach the 2020 goal. State mandates, if used alone, merely provide an incentive to vaccinate without addressing attitudes and lack of knowledge. Therefore, mandates can result in failure when education is

TABLE 1 | Addressing barriers through interventions: improving HPV vaccination rates.

			Barriers to HPV vaccination					
			Parent/patient lack of knowledge	Physician bias	Regional differences	Follow-up (vaccination completion)	Access to care	Cost
Interventions	Individual level	Parent/patient educational interventions	X					
		Physician educational interventions		X				
	Clinic level	Parent/patient reminders and recalls				X		
		Physician reminders and feedback		X		X		
	School level	School-based vaccine clinics		X	X	X	X	
		School-based vaccine clinics with education	X	X	X	X	X	
	State/national level	State-based mandates		X			X	
		National no cost-sharing coverage (ACA)			X		X	X

This matrix demonstrates potential HPV vaccination interventions at various levels, from individual to national, and the ways in which each intervention interacts with different barriers to vaccination. It is clear that there is not one intervention which alone can address all barriers, and a multipronged approach at the individual, clinic, state, and national levels will be necessary to reach the Healthy People 2020 goal of 80% vaccine completion in young women.
HPV, human papillomavirus.

lagging or not included. Reminder systems for physicians and patients, similarly, will not improve knowledge, but can help with vaccine completion rates. The ACA legislation has helped improve access but does not address knowledge or attitudes. Clearly, there is no intervention that will alone result in widespread uptake of the vaccine. From the available evidence, the optimal intervention would involve a school-based vaccine clinic combined with complementary parental and student education, addressing the majority of the barriers to vaccination. It is beyond the scope of this review to evaluate HPV vaccination uptake in males in the United States. However, similar interventions which increase vaccination rates in girls would likely work for both sexes if tailored toward improving knowledge, access, and acceptability in both populations. As vaccination coverage increases for both boys and girls, HPV vaccination will become more of a social norm, which will help perpetuate further vaccination of generations to come.

CONCLUSION

The United States has a long way to go to reach the Healthy People 2020 goal of HPV vaccine coverage in over 80% of girls aged 13–17. The release of the nine-valent vaccine at the time of increasing vaccine uptake represents a possible tipping point in the fight against cervical cancer and could be the first step in the eradication of the HPV-related disease. An understanding of the attitudes and points of view of the various stakeholders is the key to designing interventions that are tailored to the needs of various communities. While education is the key for all, it will likely not be enough. Efficient and effective use of the electronic health record to remind physicians and parents about when vaccines are due is a proven option. Additionally, school-based vaccination methods hold the greatest promise here in the United States and have proven effective in other developed countries. The CDC encourages state and local public health departments to help lead HPV vaccination campaigns, to reach out and educate and motivate both parents and clinicians on HPV vaccination, and to incorporate HPV vaccination into each jurisdiction's cancer control plans (10). State mandates are not enough. It is clear that a multifaceted approach is necessary to break down the barriers to HPV vaccination that is so prevalent in the United States.

AUTHOR CONTRIBUTIONS

Both authors certify that they contributed substantially to the conception, design, and analysis in this review, and both participated in drafting and revising the manuscript. Both authors approve of this review in its final form and take responsibility for its content.

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Ovarian Cancer: The Fallopian Tube as the Site of Origin and Opportunities for Prevention

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High-grade serous carcinoma (HGSC) is the most common and aggressive histotype of epithelial ovarian cancer (EOC), and it is the predominant histotype associated with hereditary breast and ovarian cancer syndrome (HBOC). Mutations in *BRCA1* and *BRCA2* are responsible for most of the known causes of HBOC, while mutations in mismatch repair genes and several genes of moderate penetrance are responsible for the remaining known hereditary risk. Women with a history of familial ovarian cancer or with known germline mutations in highly penetrant genes are offered the option of risk-reducing surgery that involves the removal of the ovaries and fallopian tubes (salpingo-oophorectomy). Growing evidence now supports the fallopian tube epithelia as an etiological site for the development of HGSC and consequently, salpingectomy alone is emerging as a prophylactic option. This review discusses the site of origin of EOC, the rationale for risk-reducing salpingectomy in the high-risk population, and opportunities for salpingectomy in the low-risk population.

Keywords: salpingectomy, BRCA1, BRCA2, ovarian cancers, fallopian tubes

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INTRODUCTION

In 2015, approximately 22,000 women in the United States were diagnosed with ovarian cancer and 14,000 died from this devastating disease (1). Ovarian cancer is a heterogeneous disease that can be divided into three main types: sex cord stromal tumors, germ cell tumors, and epithelial ovarian cancer (EOC). EOC accounts for the vast majority of ovarian cancers and consists of different subtypes, namely, mucinous, endometrioid, clear cell, low-grade serous, and high-grade serous carcinoma (HGSC) (2). The various histotypes differ in epidemiology, etiology, and treatment. High-grade serous ovarian carcinoma is not only the most common subtype of EOC, accounting for 75% of cases, but also the most aggressive. Most women present at advanced stages (stage III or IV) at diagnosis, at which point the 5-year survival rate ranges between 20 and 40%. However, for patients with stage I disease, the 5-year survival rate exceeds 90% (3). Molecular and genetic data indicate that HGSC of the ovary may have a similar origin to HGSC of the fallopian tube and peritoneum, and therefore, it has been suggested that all the three be described collectively as HGSC (4). Of the patients diagnosed with a HGSC, 15–20% will have a known germline mutation in the highly penetrant homologous repair pathway genes, *BRCA1* or *BRCA2*.

In the general population, the incidence of ovarian cancer is higher in white women than in women from other racial or ethnic groups, and survival rates at 12 years are better in Caucasian American women (38%) compared with African-American women (32%). Of interest, Hispanic

women (43%) and Asian women (52%) have higher survival rates. It is estimated that about 1 in 500 Americans have a mutation in *BRCA1* or *BRCA2*. The lifetime risk of developing ovarian cancer with germline mutations in *BRCA1* and *BRCA2* is 40–60 and 11–27%, respectively (5–9). The burden of hereditary breast and ovarian cancer syndrome (HBOC) was previously thought to be confined to white women, particularly those of Ashkenazi Jewish descent. However, recent studies of different immigrant populations in the United States and in their respective countries of origin have identified pockets of women who bare a similarly high genetic burden as the Ashkenazi Jewish population. Women of Bahamian heritage, for example, are estimated to have 27.1% of breast cancer cases due to *BRCA* mutations (10, 11). The ovarian cancer burden in these isolated high-risk populations is still unclear, but likely to be as high as those women of Ashkenazi descent. Other highly penetrant genes, such as *PTEN* and *TP53*, and moderately penetrant genes, such as *PALB2*, *BRIP1*, *CHEK2*, and *ATM* (12), are also associated with HBOC, albeit at lower frequencies than the prevalence of *BRCA1* and *BRCA2* mutations. Norquist et al. recently reported *RAD51C*, *RAD51D*, and *BARD1* as additional genes mutated in the germline of invasive serous ovarian cancer patients (12, 13). These data suggest that despite the growing list of genes involved in ovarian cancer predisposition, 70–85% of the women diagnosed with HGSC have "sporadic" disease.

Ovarian cancer incidence and mortality among US women has declined in those aged 35–59 years due to earlier detection methods or changes in risk (3). Conversely, in Southern and Eastern Europe, there is a corresponding rise in incidence (14) as women reduce breastfeeding and have fewer children (decrease in parity), which are both known risk factors. A similar trend of increasing incidence is expected in low–middle income countries (14).

Screening methods with CA-125 and transvaginal ultrasound have proved mostly ineffective in decreasing mortality for sporadic HGSC and ovarian cancer in general (15, 16). Early detection has been and continues to be a challenge in ovarian cancer because the disease is habitually asymptomatic before peritoneal spread (17). However, with the identification of pockets of the population at high risk for HBOC, there is an opportunity to reduce the burden of disease through increased and targeted genetic testing as well as screening and prevention measures for ovarian cancer risk reduction.

CELL OF ORIGIN OF SEROUS OVARIAN CANCER

Ovarian Surface Epithelia

Prior to the reported observation of *in situ* carcinoma in the distal end of the fallopian tube of women undergoing prophylactic surgery, the ovary was thought to be the etiological site of high-grade serous ovarian cancer. Now, there are two candidates for the cell of origin, namely, the fallopian tube epithelium (FTE) and the ovarian surface epithelium (OSE). Both share common mesodermal embryological origin and close anatomic proximity. The fallopian tube, along with the uterus, uterine endocervix, and superior aspect of the vagina are derived from an invagination of the celom known as the Mullerian or paramesonephric ducts. The OSE is derived from the mesothelial celomic epithelium that lines the primitive ovary (18).

The "incessant ovulation" hypothesis, proposed by Fathalla (19), suggested that continuous ovulatory cycles during the reproductive lifespan of a woman increase her risk of developing HGSC (19). He proposed that ovulation resulted in an increase in inflammation through which the secretion of cytokines, chemokines, bradykines, and hormones induce DNA damage *via* oxidative stress in the cortical inclusion cysts (CIC) observed in the ovary. These events, along with proliferation of the OSE, promote metaplastic changes leading to neoplastic transformation (2, 15, 19).

Xenografts of transformed OSE cell lines and genetic animal models have been used in an attempt to model HGSC in the absence of *in situ* pre-neoplastic lesions in the ovary. Genetic mouse models deleting *BRCA1*, *Rb1*, and *TP53* genes from the OSE resulted in leiomyosarcomas (20) and not HGSC. In contrast, targeted deletion of these genes in the fallopian tube epithelia of mice has led to the development of tumors genomically and pathologically similar to HGSC (21). The somatic mutational spectrum found in lesions associated with the ovary proper and neoplastic lesions have been shown to have *KRAS*, *BRAF*, *CTNNB1*, *ARID1A*, *PTEN, PPP2R1A*, and *PIK3CA* (22). These tumors rarely have *TP53* mutations, which suggest a distinct etiology and natural history of tumorigenesis from that of HGSC.

Fallopian Tube Epithelia

There is now substantial convincing clinical and molecular evidence in support of the FTE as the source of the cell of origin of low- and high-grade serous ovarian cancer (22). Experimental *in vitro* manipulation and transformation of human fallopian tube epithelial cells have demonstrated that these cells in a xenograft model can give rise to tumors, which resemble primary HGSC (23). Additionally, mouse models targeting *BRCA* and *TP53* in fallopian tube epithelia develop HGSC (21).

A series of transcriptional studies by Tone et al. and George et al. have shown that the phenotypically normal fallopian tube epithelia from *BRCA1* and *BRCA2* mutation carriers show transcriptional differences when compared to epithelial cells with a normal *BRCA* genotype. These differences have been shown to impact different molecular pathways. Consequently, these pathways are implicated in tumor initiation, progression, and recurrence (24–26). As a result of these studies, the authors proposed that chronic inflammatory states through cyclical ovulation in the presence of a mutated *BRCA* allele could predispose the normal FTE to undergo neoplastic transformation, which may lead to serous carcinoma. This would primarily occur through deregulation of DNA damage response genes and synergistically through upregulation of cytokines, proinflammatory and proliferation genes.

The *BRCA*-associated carcinomas share some common genomic features such as frequent mutations of *TP53* and copy number landscape features including *Cyclin-E1* amplification and deletion of *Rb1* (27). Altered BRCA function is not unique to hereditary HGSC but is prevalent *via* somatic mutations (6%) (28–31), promoter hypermethylation (13–31%) (28, 32–34), and

other genetic or epigenetic alterations, predominantly in the homologous recombination (HR) pathway in HGSC. This has led to determining the "BRCAness" profile in patients (35, 36). Overall, these differences in morphologically normal epithelia from *BRCA* mutation carriers have shed light into the effects of heterozygosity and predisposition to the development of HGSC and, importantly, potential features that might be manifested in the STIC.

Detailed histopathological examination of tubal epithelia in *BRCA* mutation carriers undergoing risk-reducing surgery led to the discovery of putative cancer precursor lesions in the fallopian tube referred to as serous tubal intraepithelial carcinoma (STIC) (37–40). STIC was first reported by Piek et al., who described dysplastic epithelial changes in the fallopian tubes of women with a *BRCA1* or *BRCA2* mutation, who underwent risk-reducing salpingo-oophorectomies (RRSO) (38, 41). These lesions have distinct morphological features such as loss of polarity, epithelial tufting, and pleomorphic nuclei, and in addition, there is abnormal p53 expression and a high-proliferative index (refer to Lheureux et al. for commentary) (2, 42).

Since the discovery of the STIC, three possible pre-neoplastic lesions have been described, including the p53-signature, low grade serous tubal intraepithelial lesions (STIL), and secretory cell outgrowths (SCOUTS) (43). These lesions share a combination of phenotypic and/or genomic alterations with the cancer cells in HGSC. *TP53* mutations, which are ubiquitous in HGSC, are usually concomitantly found in STIC and HGSC (2, 44). Over-expression of p16 has been documented in some STILS and over-expression of Pax8, Bcl-2, and loss of Pax2 expression has been observed in SCOUTS (45). However, none of these lesions are clinically actionable, as it is still unclear which of these lesions and/or combination of genomic alterations, has the pathogenic capacity to give rise to a carcinoma.

Many studies have now reported the incidence of non-invasive neoplastic lesions (STIC) in the distal end of the fallopian tube. It is estimated that occult invasive and STIC are identified in 0.9–8.5% of women undergoing RRSOs (2, 39, 40, 43, 46–63) (**Table 1**). The frequency of STIC lesions increases with age and is lower with oral contraceptive use (64). It is important to note that the large range in estimates of the prevalence of occult and STIC lesions is reflective of the variances in diagnostic methodologies used by different centers and study groups (42).

Powell and colleagues reported that in a long-term follow-up study of women diagnosed with non-invasive serous tubal epithelial carcinoma who underwent RRSO, 6% (1/17) recurred 43 months after risk-reducing surgery compared to 43% of women who had unsuspected invasive carcinoma at time of surgery (65). There is a continued need to understand the effects of inflammation and hormones on the fallopian tube epithelia, relating to latency and the preferential sites of seeding, are critical for addressing prevention and risk-reduction strategies in genetically high-risk populations.

TABLE 1 | Evidence of serous tubal intraepithelial carcinoma in risk-reducing salpingo-oophorectomy of asymptomatic women with known *BRCA1* or *BRCA2* mutations or strong family history of breast or ovarian cancer.

Reference	Number of RRSO cases	Incidence of STIC or occult carcinoma in the distal end of the fallopian tube
Colgan et al. (53)	60	5 (8.3%)
Piek et al. (41)	12	5 (41.6%)
Leeper et al. (55)	30	3 (10%)
Powell et al. (49)	67	4 (6%)
Carcangiu et al. (56)	50	4 (8%)
Finch, et al. (48)	159	7 (4.4%)
Callahan et al. (52)	122	7 (5.7%)
Shaw et al. (39)	176	15 (8%)
Hirst et al. (54)	45	4 (8.9%)
Powell et al. (59)	111	6 (5.4%)
Manchanda et al. (50)	117	10 (8.5%)
Mingels et al. (58)	226	16 (7.1%)
Reitsma et al. (60)	303	3 (0.99%)
Wethington et al. (62)	593	12 (2.0%)
Cass et al. (57)	78	9 (11.5%)
Sherman et al. (61)	966	25 (2.6%)

Opportunities for Ovarian Cancer Risk Reduction

Epidemiological data show that oral contraceptives, aspirin, and other non-steroidal anti-inflammatory drugs reduce the risk of ovarian cancer. In a meta-analysis as a primary prevention mechanism by Havrilesky et al., oral contraceptive pills use reduced ovarian cancer risk by 50% if used for more than 10 years (66). Recently, aspirin use was associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin (67). These observations highlight the relationship between ovulation and its inflammatory accompaniment with ovarian cancer development. Women identified at highest risk, that is, germline mutation carriers and/or strong family history of ovarian cancer, may benefit from use of these chemoprevention strategies.

Tubal ligation (tubal sterilization) has been shown to reduce ovarian cancer risk that theoretically is spread through retrograde menstrual flow (68–70). In particular, tubal ligation was associated with reduced risk of invasive ovarian cancer, with the greatest benefit seen in the endometrioid and clear cell subtypes (71). The mechanism of protection is through prevention of retrograde menstruation, and hence, a decrease in Fenton's reaction (generates reactive oxidative species) in the environment of the fallopian tube as well as prevention of endometrial cells implanting in the ovary. Although tubal ligation appears to be protective for all histotypes of ovarian cancer, it is least effective in reducing risk for the most lethal subtype, HGSC (71).

Salpingectomy

As early as 2002, Rebbeck et al. suggested that bilateral prophylactic oophorectomies reduced the risk of ovarian and breast cancer in women with *BRCA1* or *BRCA2* mutations by as much as 96% (72). Olivier et al. demonstrated that risk-reducing salpingo-oophorectomy reduced the risk of ovarian, fallopian tube, and peritoneal papillary serous carcinoma in *BRCA1* and *BRCA2* mutation carriers (some women still developed peritoneal disease) (73).

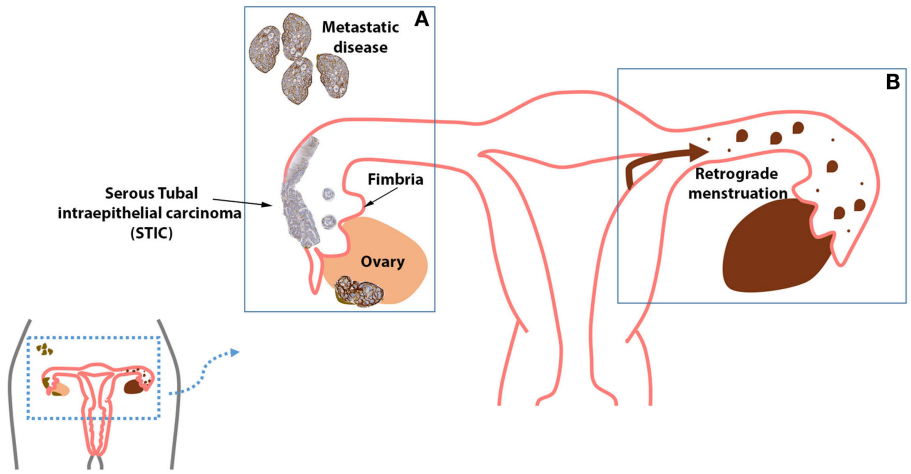

FIGURE 1 | **(A)** High-grade serous carcinoma (HGSC) is the most common histologic type of cancer seen in the ovaries, fallopian tube, and peritoneum. **(B)** The fallopian tubes may act as a possible conduit for retrograde menstrual flow, which is theorized to induce the malignant transformation of cells *via* oxidative stress, inflammation, and hyperestrogenism. Further, endometriosis has been strongly linked with endometrioid ovarian carcinoma and clear cell ovarian carcinoma.

As previously mentioned, there is clear evidence supporting the role of the fallopian tube as the etiological site of HGSC [and most likely low-grade serous carcinoma (22)]. For this reason, women with known risk for breast and ovarian cancer may undergo prophylactic surgical removal of the ovaries and fallopian tubes, a procedure known as RRSO. Current guidelines from the National Comprehensive Cancer Network and the Society of Gynecologic Oncologists suggest that RRSO to be completed by the post-child bearing period, the age of 35–40, or 10 years younger than a first-degree relative diagnosed with ovarian cancer (74). However, it is believed that the majority of these high-risk women do not undergo RRSO by age 40 (75). This modality of precision prevention involves risk stratification and risk reduction in patients carrying both highly penetrant (76) (*BRCA1* and *BRCA2*) and moderate to lower penetrant genes such as *PTEN*, *PALB2*, *CHEK2*, *ATM*, and *BRIP1*. The removal of the fallopian tubes alone is referred to as risk-reducing salpingectomy (RRS). In young women identified with a *BRCA1* or *BRCA2* mutation, RRS is performed in an effort to reduce ovarian cancer risk while maintaining adequate hormonal levels to avoid the effects of early menopause. This latter approach, however, is not restricted to women at high risk for serous ovarian cancer, as it will also have a beneficial impact on reducing the risk of development of endometriosis-associated clear cell and endometrioid ovarian cancer (**Figure 1**).

Opportunistic Salpingectomy

Opportunistic salpingectomy refers to removal of the fallopian tubes in women who are *not* at an increased risk of developing ovarian cancer. In 2010, a population-based and institution-wide study in British Columbia, Canada, was initiated whereby three recommendations to gynecological surgeons were made: (1) consider opportunistic salpingectomy during hysterectomy, (2) consider excisional bilateral salpingectomy rather than tubal ligation for sterilization, and (3) refer all HGSC patients for *BRCA1/2* germline testing (77). Interim results on surgical outcomes revealed that the rates of hysterectomy with bilateral salpingectomy increased 3.5-fold compared to hysterectomy alone, and the rates of tubal ligation as a mode of surgical sterility decreased from 99.7% in 2009 to 66.7% in 2011, while the rate of bilateral salpingectomy concomitantly increased 111-fold compared to 2009 rates (77). The authors also reported that the length of hospitalization post-hysterectomy and bilateral salpingectomy was not longer than for hysterectomy alone and that there was no significant difference in the rate of blood transfusion or hospital readmission among these two groups. In addition, there was no significant difference in length of hospitalization or rate of transfusion for bilateral salpingectomy compared to tubal ligation.

The caveat to opportunistic salpingectomy is that even if implemented on a large scale, the true impact of ovarian cancer reduction will take years to be realized (77). It is also important to note that salpingectomy alone, unlike oophorectomy, does not reduce the risk of breast cancer by modulating levels of estrogen.

There is categorical evidence that RRSO reduces ovarian and breast cancer death and all-cause mortality (78, 79). There is currently no evidence that points to the outcome and impact of ovarian cancer risk reduction for two-stage procedure of salpingectomy followed by oophorectomy. In the United States, MD Anderson is conducting a clinical trial assessing prophylactic salpingectomy with delayed oophorectomy (80). A report from the Nurses' Health Study concluded that compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy for benign disease was associated with a decreased risk of breast and ovarian cancer but an increased risk of all-cause mortality (81, 82); therefore, one can stipulate

that salpingectomy alone may be sufficient in the genetically "low-risk" population, while the overall benefit versus harm of these approaches requires close attention in the genetically high-risk population. Specifically, oophorectomy offers protection against breast cancer even after menopause and improves survival in those with breast cancer (83). As these prevention modalities are implemented, it is important that the goal of decreasing the incidence and burden of ovarian cancer is not at the expense of worsening the incidence and mortality of breast cancer in women who are at increased risk due to co-morbidities.

AUTHOR CONTRIBUTIONS

SG wrote and conceptualized. RG researched references and made figure. BS wrote and conceptualized.

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REVIEW
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Ovarian Cancer and *BRCA1/2* Testing: Opportunities to Improve Clinical Care and Disease Prevention

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Without prevention or screening options available, ovarian cancer is the most lethal malignancy of the female reproductive tract. High-grade serous ovarian cancer (HGSOC) is the most common histologic subtype, and the role of germline *BRCA1/2* mutation in predisposition and prognosis is established. Given the targeted treatment opportunities with PARP inhibitors, a predictive role for *BRCA1/2* mutation has emerged. Despite recommendations to provide *BRCA1/2* testing to all women with histologically confirmed HGSOC, uniform implementation remains challenging. The opportunity to review and revise genetic screening and testing practices will identify opportunities, where universal adoption of *BRCA1/2* mutation testing will impact and improve treatment of women with ovarian cancer. Improving education and awareness of genetic testing for women with cancer, as well as the broader general community, will help focus much-needed attention on opportunities to advance prevention and screening programs in ovarian cancer. This is imperative not only for women with cancer and those at risk of developing cancer but also for their first-degree relatives. In addition, *BRCA1/2* testing may have direct implications for patients with other types of cancers, many of which are now being found to have *BRCA1/2* involvement.

Keywords: ovarian cancer, *BRCA1/2*, testing, treatment, prevention

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INTRODUCTION

Over the last four decades, there has been modest progress in the 5-year overall survival rates of women diagnosed with ovarian cancer, despite enhanced surgical efforts and introduction of doublet platinum/taxane chemotherapy. Worldwide, newly diagnosed cases of ovarian cancer have reached 239,000, positioning this malignancy as the seventh most common cancer in all women, with the highest incidence in Europe and North America (1). Typically diagnosed at an advanced stage (III/IV), high mortality rates for ovarian cancer continue to persist with almost 152,000 deaths per year (**Figure 1**) (2).

The lifetime risk of spontaneously developing and dying from ovarian cancer are 1.39 and 1.04%, respectively; however, the incidence of developing ovarian cancer significantly increases in carriers of germline mutations, mainly with either the *breast cancer gene 1* (*BRCA1*) or *2* (*BRCA2*) genes. The lifetime risk of developing ovarian cancer is 40–60 and 11–27% for *BRCA1* and *BRCA2* mutation carriers, respectively (3). These particular mutations are implicated in 10–15% of all ovarian

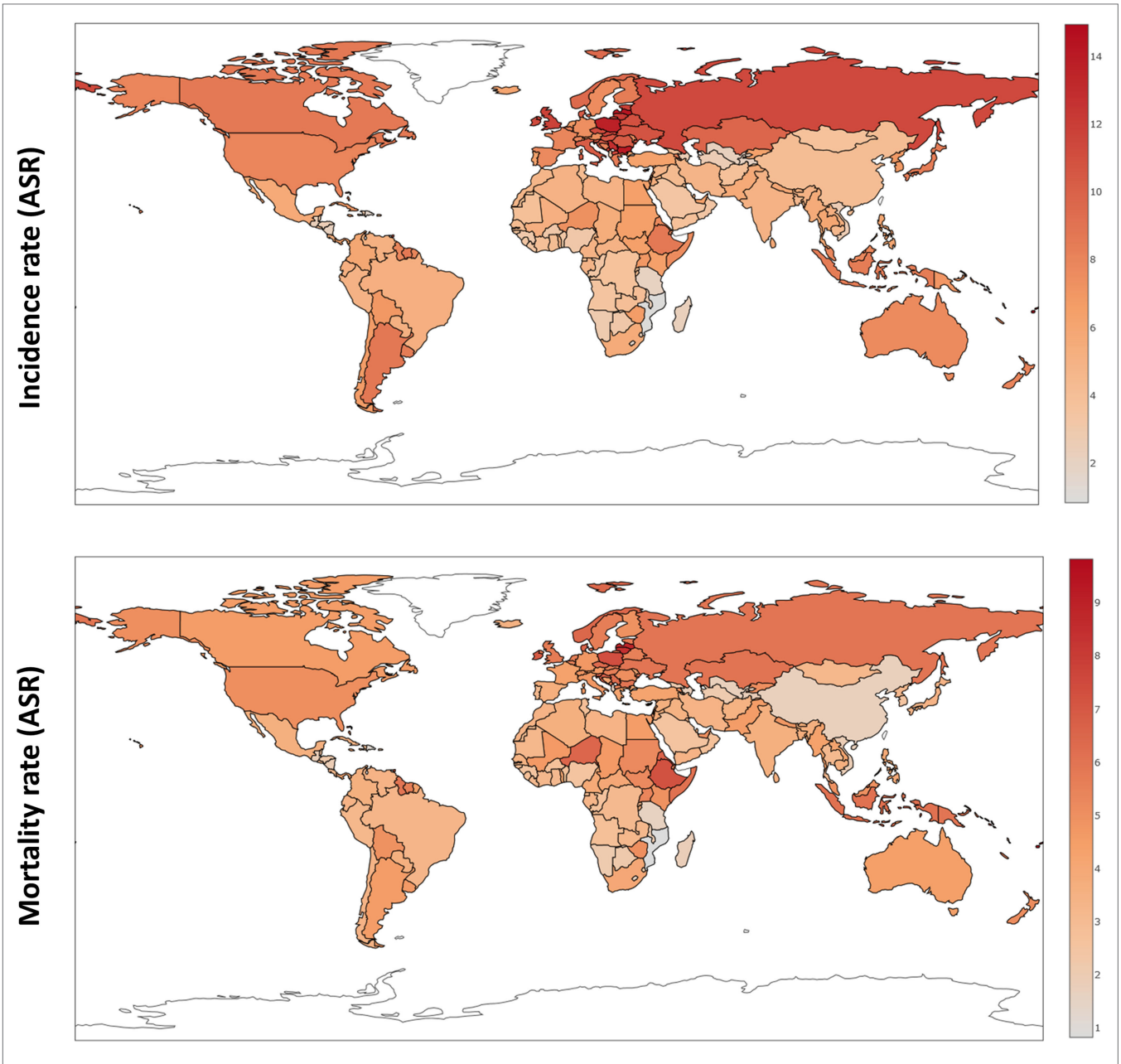

FIGURE 1 | **Ovarian cancer incidence and mortality rates worldwide (ASR) based on GloboCan data (1).**

cancer cases and almost 20% of high-grade serous histology [high-grade serous ovarian cancer (HGSOC)] (4), including in women without a family history of breast or ovarian cancer. Approximately, one-third of patients with hereditary ovarian cancer have no close relatives with cancer (3). Family history-based testing for *BRCA1/2* germline mutations has been shown to miss a significant proportion of women at risk for developing cancer (5), perhaps as a result of incomplete or incorrect family history reporting (6, 7) or potentially due to a lack of updating new family history information as it becomes available (8).

At present, a variety of selection criteria are used to determine the eligibility for *BRCA1/2* testing, including family history, age at onset, tumor clinicopathological features, and computational risk prediction models (BRCAPRO, BOADICEA, Myriad, and Manchester scoring system) (9). The clinical criteria for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancers in women are based on personal and family history factors that may contribute to the disease (10) and are related to the likelihood of testing positive above a common testing threshold of 10% (11). These models often underestimate the probability of finding a mutation (12–14). It has been shown that the current family history approach does not identify 60% of Ashkenazi Jewish *BRCA* mutation carriers (15), thus creating a critical gap in practice that affects clinical treatment strategy and

possibly patient outcome. As such, in light of advances in our understanding of *BRCA*-related breast and ovarian cancers – and the opportunity to directly impact therapeutic decision-making in these women – the recommendations to include universal germline *BRCA1/2* testing to all women diagnosed with non-mucinous ovarian carcinoma (4) and women with triple-negative breast cancer (16) are growing in strength (17–19). Using next generation sequencing for 21 tumor suppressor genes of 360 subjects, ~24% carried germline loss-of-function mutations: 18% in *BRCA1* or *BRCA2* and 6% in *BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C,* or *TP53* (20). The study also showed that 31% of women with an inherited mutation had no prior personal history of cancer or family history of breast or ovarian cancers (20). The National Comprehensive Cancer Network (NCCN) and Society of Gynecologic Oncology (SGO) guidelines suggest universal genetic counseling and testing of all women with ovarian cancer, including fallopian tube and peritoneal cancer (17, 19). Given the rate of *BRCA1/2* mutation in HGSOC, germline *BRCA1/2* testing is especially warranted in practice for this histology subtype. An immediate improvement to treatment opportunities would be to offer systematically genetic testing for *BRCA1/2* mutation to all HGSOC, although it has been reported that 20% of women with ovarian cancer in community hospital settings were referred for genetic testing (21). While this was shown to be improved in academic centers, referral for germline *BRCA1/2* testing was not systematic and did not reach the majority of patients (22). In clinical practice, there is a critical gap between the women eligible for *BRCA1/2* counseling and those receiving testing (23, 24). With the recent approval of olaparib, a PARP inhibitor, it is likely that referral for genetic testing of *BRCA1/2* status will improve.

KNOWLEDGE OF *BRCA1/2* MUTATION STATUS IMPACTS CLINICAL CARE OF WOMEN WITH OVARIAN CANCER

Knowledge of *BRCA1/2* status should be part of the standard of care at least for patients diagnosed with HGSOC. Indeed, there is a large body of evidence indicating benefits of targeting pathways involved in maintaining DNA integrity, including *BRCA1* and *BRCA2* signaling (25). Harboring a germline *BRCA1/2* mutation is described as predictive of platinum sensitivity (26). Moreover, based on the synthetic lethality concept – the simultaneous promotion of *DNA* double-strand breaks (DSBs) and hindrance of DSB repair by inhibition of PARP protein expression (27, 28) – PARP inhibitors have been developed. This effect was shown clinically in the pivotal international, multicenter, randomized, phase II study that evaluated olaparib (a PARP inhibitor) as maintenance treatment in women with HGSOC who had responded to platinum-based chemotherapy (29). The preplanned retrospective analysis of outcomes by *BRCA1/2* status in this study demonstrated that *BRCA*-mutated patients had better progression-free survival (PFS) with olaparib maintenance compared to those receiving placebo (11·2 versus 4·3 months; HR 0·18; $p < 0{\cdot}0001$) (30). The PFS benefit was still observed when somatic *BRCA*-mutated patients were included in the analysis. Additional evidence supporting the role of olaparib as maintenance therapy was reported from an international, multicenter, randomized, open-label study in women with platinum-sensitive relapsed HGSOC (NCT01081951) (31). In this phase II, olaparib was given with carboplatin/paclitaxel chemotherapy and continued as maintenance monotherapy. Overall, study findings show a significant PFS improvement when compared to chemotherapy alone (12.2 and 9.6 median PFS, respectively; HR 0.51; 95% CI 0.34–0.77; $p = 0.0012$). A greater benefit was detected in patients with a *BRCA1/2* mutation (PFS HR 0.21; 95% CI 0.08–0.55; $p = 0.015$) than in those without a *BRCA1/2* mutation. Further, study analysis revealed strong evidence that olaparib maintenance is most likely a key contributor to the improvement in PFS in this patient population (31). There are numerous ongoing PARP inhibitor studies investigating women with *BRCA1/2* mutations as well as mutations in other homologous recombination-deficient (HRD) genes, as data has shown HRD genes to exhibit *BRCA*-like behavior (32). To date, the use of olaparib maintenance has been approved in Europe after response to platinum-based chemotherapy in women with platinum-sensitive HGSOC who harbor a germline or somatic *BRCA1/2* mutation (30) and in US, as single agent therapy after three lines of chemotherapy in patients with germline *BRCA1/2* mutation HGSOC (33). Taken together, germline and somatic testing for *BRCA1/2* provides important information for patients with ovarian cancer and this knowledge can directly impact clinical care.

KNOWLEDGE OF GERMLINE *BRCA1/2* MUTATION STATUS IMPACTS OVARIAN CANCER PREVENTION

Germline *BRCA1/2* status is not only relevant to women with ovarian cancer but also to women without cancer, who may be at an increased risk of developing the disease and could therefore benefit from prevention strategies. Currently, few prevention options are available for women with germline *BRCA1/2* mutations. Women known to be at an increased genetic risk for developing OC, based on germline *BRCA1/2* mutation carrier status, are offered risk-reducing salpingo–oophorectomy (RRSO), which reduces the risk of ovarian cancer by 71–96% (34–39). Surgery is usually performed after the completion of childbearing and while the woman is still pre-menopausal. Guidelines from the NCCN and the Society of Gynecologic Oncologists suggest that RRSO be completed by the age of 40 (19, 40); however, the majority of women who undergo RRSO do not do so by this age (41). This may be due to the potential side effects, such as premature surgical menopause (42), osteoporosis (43), cardiovascular disease (44, 45), cognitive impairments (46), symptoms of depression and anxiety (47), and consequences on quality of sleep, depression, and sexual dysfunction (48) associated with early RRSO. In light of these side effects – and the compelling evidence that high-grade serous epithelial ovarian cancer can be derived from the fallopian tube and not the ovary (49–53) – a recent committee opinion published by the American College of Obstetricians and Gynecologists outlines the opportunity for surgeon-led

discussions with patients regarding the potential benefits of the removal of the fallopian tubes during hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy (54). Young *BRCA1/2* mutation carriers can be counseled for risk-reducing bilateral salpingectomy initially, with subsequent bilateral oophorectomy after childbearing, although additional randomized controlled trials are warranted to support the validity of this approach. Further studies of associated hysterectomy are warranted in the population to provide appropriate family counseling guidance (55, 56). These discussions are important as data from nine countries have shown that preventative practices in women with germline *BRCA1/2* mutations are varied despite guidelines (57). The study of 2677 women harboring germline *BRCA1/2* mutations, who were an average of 3.9 years following genetic testing, showed that only 57.2% had undergone prophylactic surgery. This reveals differing uptake of preventative options by their country of residence (57). It also highlights the lack of effective alternate strategies for individuals identified to be at high risk, often for years before clinical development of disease or risk reduction procedures like surgery can be offered.

GERMLINE *BRCA1/2* TESTING STRATEGY

The current germline *BRCA1/2* testing strategy is mainly based on patients diagnosed with cancer. As previously discussed, as a minimum, all patients with HGSOC should be approached for *BRCA1/2* testing as well as those patients diagnosed with non-mucinous ovarian cancer (**Figure 2**). Furthermore, knowledge of germline *BRCA1/2* status in women living with ovarian cancer directly impacts first-degree relatives (FDRs), who have a 50% probability of carrying the same mutation and are yet to be diagnosed, and therefore, could also benefit from risk-reducing prevention strategies (58).

While there has been much debate regarding the concept of population-based germline *BRCA1/2* screening (59), this targeted approach within the Ashkenazi Jewish community has been shown to be more effective than family history-based testing and cost-effective. A Canadian-led study comparing the detection of *BRCA1/2* mutation carriers through Jewish population-based genetic testing versus clinic-based genetic testing found that more unaffected women with a *BRCA1* or *2* mutation were identified as a result of a genetic testing program targeting all Jewish women (60). This evidence supports the provision of genetic testing to all Jewish women (60). Conducted between 2008 and 2012, around 6179 Jewish women were tested through the population-based program, which identified 93 mutation carriers (92 unaffected with cancer) in comparison to 38 female carriers identified through 487 referrals to the genetics center (29 unaffected with cancer). Study findings showed that population genetic testing does not contribute to increased genetic counseling time but in fact decreases the overall time required when utilizing a population-based approach. Of particular importance, the 38% of women identified as having a *BRCA1/2* mutation would have qualified for genetic testing but were either unaware of the recommendation or had not been referred by their health-care provider (60). Examining a similar approach, a randomized controlled trial of germline *BRCA1/2* gene mutation testing in Ashkenazi Jewish women that compared family based testing to population screening, successfully enrolled and randomized 1034 participants (691 women, 343 men), of which 1017 were eligible for analysis. Similarly, findings showed that overall 56% of carriers did not fulfill clinical criteria for genetic

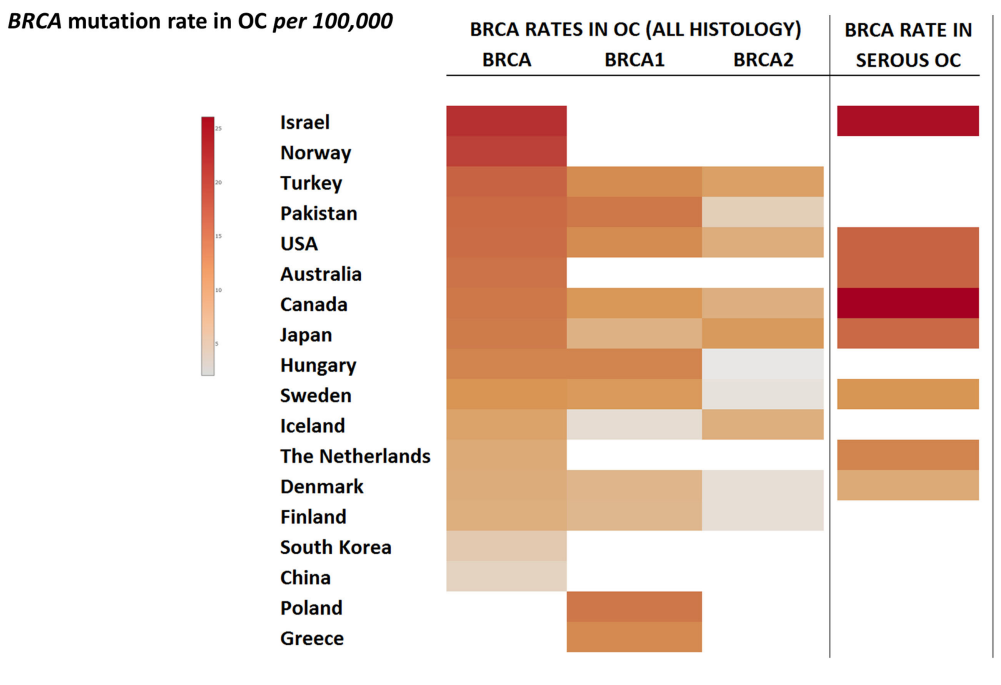

FIGURE 2 | Germline *BRCA1/2* mutational frequencies worldwide – examples.

testing, and germline *BRCA1/2* prevalence was 2.45%. The fact that more than half of participants did not fulfill testing criteria is in agreement with previous data (61, 62), in which carriers lacked a strong family history of cancer. Moreover, the study also provided evidence that population-based genetic testing of Ashkenazi Jewish women does not adversely affect short-term psychological or quality of life outcomes (63). Cost-effective analyses conducted in parallel to the above study show that even when incorporating *BRCA1/2* prevalence in family history negative individuals and genetic counseling costs, this specific population-based screening for germline *BRCA1/2* mutations is highly cost-effective compared to family history-based approaches in Ashkenazi Jewish women aged 30 years and older (15). Screening based on founder mutations is feasible if the type of mutation is well known and allows for population-based screening approaches, such as in the Ashkenazi Jewish population, where two founder mutations in *BRCA1* (185delAG and 5382insC) and one in *BRCA2* (6174delT) account for 98–99% of identified mutations (64–67). This population-based screening approach is cost-effective, as previously described, given that 2.5% of this population carry one of these three mutations (64), and these mutations account for 40% of ovarian cancer (68, 69).

Worldwide, variation in the distribution of *BRCA1* and *BRCA2* mutations is well recognized, and in certain countries and ethnic communities the germline *BRCA1/2* mutation spectrum is limited to a few founder mutations (70). However, both the number and frequency of germline *BRCA1* and *BRCA2* mutations vary among populations (**Figures 3** and **4**) (71–73). Findings from an international observational study of 19,581 *BRCA1* and 11,900 *BRCA2* carriers from 55 centers in 33 countries on 6 continents provide strong evidence that breast and ovarian cancer risks vary by type and location of *BRCA1/2* mutation (73). As such, much research is moving toward characterizing the functional significance of specific mutations or mutation locations (74, 75).

Located on the long arm of chromosome 17, *BRCA1* (MIM#113705) comprises 22 coding exons spanning 80 kb of genomic DNA and has a 7.8-kb transcript coding for an 1863-amino-acid protein (76). *BRCA2* (MIM#600185) is located on chromosome 13 and comprises 26 coding exons spanning 70 kb of genomic DNA and gives an 11.4-kb transcript that encodes a protein of 3418 amino acids (77). Multifunctional in nature, *BRCA* proteins play important control functions in homologous recombination, the DNA DSB repair pathway, and early cellular response to DNA damage. *BRCA1* also has a transcriptional activator or repressor function and possesses a central role in chromatin remodeling and centrosome regulation. *BRCA1* and *BRCA2* appear to behave as tumor suppressor genes, and mutations in either of these genes have been found throughout the entire coding region and at splice sites (78). In light of the structural and interactive complexity of *BRCA1/2,* international collaborations will not only continue to improve our understanding of *BRCA1/2* mutations and how mutation type and location influence breast and ovarian cancer risks (**Figures 3** and **4**) (71–73) but also help devise novel, targeted testing panels that

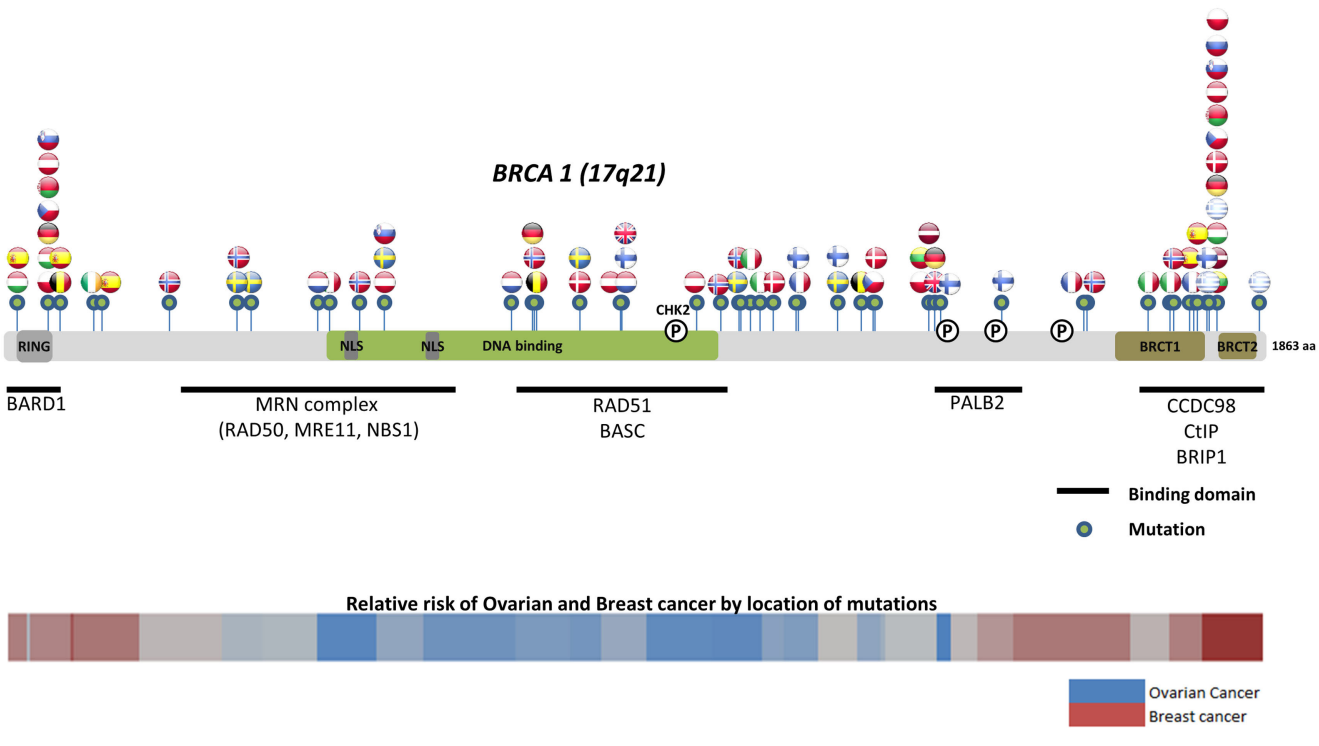

FIGURE 3 | Location of common and founder *BRCA1* mutations by country. Schematic of common and founder mutations by country modified from Janavičius (71) and Ramus and Gayther (72). Relative risk data taken from Rebbeck et al. (73).

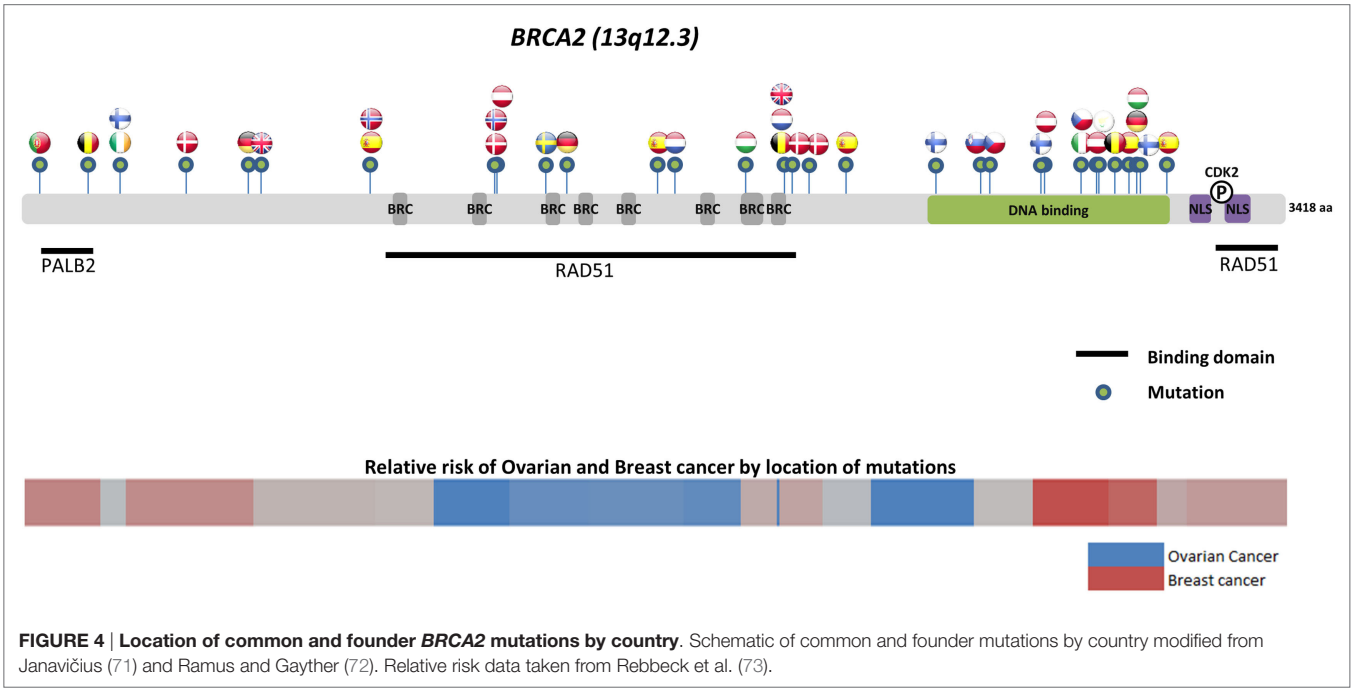

FIGURE 4 | Location of common and founder *BRCA2* mutations by country. Schematic of common and founder mutations by country modified from Janavičius (71) and Ramus and Gayther (72). Relative risk data taken from Rebbeck et al. (73).

can potentially support specific population-based genetic testing, similar to the Ashkenazi Jewish population.

TRANSLATING KNOWLEDGE INTO PRACTICE

To ensure successful uptake of germline *BRCA1/2* testing or preventative strategies, wide community engagement and education regarding ovarian cancer are imperative. Following Angelina Jolie's announcement that she carried a genetic mutation that increased her odds of developing breast and ovarian cancer, referrals for genetic counseling and *BRCA1/2* testing appeared to have increased the awareness of cancer, particularly for breast cancer (79–81). While celebrities can bring heightened awareness to health issues, there is a need for these messages to be accompanied by more purposeful communication efforts to assist the public in understanding and using the complex diagnostic and treatment information that these stories convey (82).

In a small US study, data show that despite a significant proportion of primary care patients requiring genetic counseling, there is compelling evidence that few are actually receiving these services (23). Data from the same study also indicate that while overall perceived cancer risk was higher among women with familial cancer risk, 27% of women with familial breast/ovarian cancer felt their risk was "low" and 32% felt their risk was lower than average – highlighting the need for educational interventions for patients as well as providers (23). This highlights the importance of considering the potential psychological impacts that may be associated with *BRCA1/2* testing over time. Employing qualitative interviews ($N = 49$) and reflective diaries, a study of 33 patients showed that the short-term impact of a positive *BRCA1/2* test result differs prior to, immediately following, and up to 24 months after having received test results (83). Conducted from December 2006 to March 2010, data show that while women with cancer initially undergo genetic testing for their children, on confirmation of a positive test, the focus temporarily shifts to decision-making around their personal health needs. In fact, the threat of further disease caused anxiety around nurturing children and personal survival, which remained unresolved until women underwent risk-reducing surgery and in many continued as cancer worry (83). Here, findings help to illustrate where additional support for women during the testing process may be most beneficial. The long-term effects of a positive *BRCA1/2* test result are also of relevance. A prospective single US centre study evaluating the long-term psychosocial effects of *BRCA1/2* testing in a cohort of 464 women who had undergone genetic testing found that at long-term follow up (median 5 years; range 3.4–9.1 years), when assessing cancer-specific and genetic testing distress, perceived stress, and perceived cancer risk, there is modest increased distress in *BRCA1/2* carriers compared to those women who received uninformative or negative test results (84). Despite the modest increase in distress, the group found no evidence of clinically significant dysfunction or impact of long-term psychological dysfunction due to testing (84). Data indicate that when patients receive counseling both before and after testing, they have more knowledge and experience less uncertainty and anxiety after learning the results of *BRCA1/2* test. Although, patient experiences may vary with test results (85). Therefore, when taken together, it is imperative that appropriate multidisciplinary, supportive structures are in place that women eligible for testing can rely upon, leading up to and following a positive test result, including at the time of risk-reducing surgery and during surveillance.

Testing positive for a germline *BRCA1/2* mutation goes beyond the patient herself potentially impacting her children

and other members of their family by allowing cascade testing to proceed, if warranted (86). Accurate communication of test results is therefore critical for subsequent members to be tested. Research suggests fractured information dissemination among families when a positive germline *BRCA1/2* test is communicated. In a systematic review of 29 publications from 26 studies, family communication regarding genetic risk is described as a deliberative process whereby the individual's personal risk is determined, within the context of family dynamics, family vulnerability and receptivity is assessed, which mediates what information will be conveyed, and ultimately, the appropriate time to disclose information (87). Numerous studies provide complementary data illustrating that issues impacting the communication of test results within families includes an individual's responsibility to inform, emotional and developmental readiness – such as when parents disclose *BRCA1/2* results to children (88) – and again, communicating in the context of the existing family culture (89, 90). A retrospective study highlighted many errors in the transmission of DNA-test results in families from early stages of probands recalling information directly from genetic counselors, to the interpretation of information by family members (91). Therefore, support provided by genetic counselors could improve the overall process, not only during communication to family members but also during the education of physicians regarding family centered genetic testing for the physicians who may have referred the patient for testing (92).

BRCA1/2 MUTATION IMPACTS MORE THAN OVARIAN CANCER TREATMENT AND PREVENTION

While the most described cancers driven by germline mutations in *BRCA1/2* have been breast and ovarian, there is also mounting evidence to support the role of germline *BRCA1/2* mutations contributing to other solid tumors, such as in prostate (93) and pancreatic (94, 95) cancers. In a United Kingdom study, Kote-Jarai et al. screened 1864 men with prostate cancer between 36 and 88 years of age and following analysis of the *BRCA2* gene, findings show that all carriers of truncating mutations developed prostate cancer at ≤65 years (93). In this study, the prevalence of *BRCA2* mutations was 1.27% (8/632) for cases diagnosed ≤55 years, 1.20% (19/1589) for cases diagnosed ≤65 years, and 0% (0/243) for cases diagnosed >65 years; $p = 0.14$ (81). It is estimated that germline mutations in the *BRCA2* gene confer an ~8.6× increased risk of prostate cancer by 65 years of age, corresponding to an absolute risk of ~15% by age 65. A higher risk is perhaps conferred due to mutations in the *BRCA2* ovarian cancer cluster region (OCCR) (96). Data suggest that routine testing of early onset prostate cancer cases for germline *BRCA2* mutations would further help refine the prevalence of risk associated with *BRCA2* mutations (93). A study examining other cancers in 268 *BRCA1* and 222 *BRCA2* families in the United Kingdom from 1975 to 2005 using person-years at risk analysis showed *BRCA2* mutation increased risks for pancreatic cancers (RR 4.1, 95% CI 1.9–7.8) and uveal melanoma (RR 99.4 95% CI 11.1–359.8). Study data also showed possible novel associations with upper gastrointestinal malignancies and *BRCA1* mutations, although this requires confirmation in future large prospective studies (96). Recently, a study provided evidence supporting current recommendations for hereditary breast and/or ovarian cancer screening of cancers other than breast and ovarian by the NCCN. In the study of 1072 patients who tested positive for a deleterious *BRCA1/2* mutation, 1177 cancers comprising 30 different cancer types were detected (97). Findings show that while individuals harboring *BRCA1* mutation did not have a significant increase in the development of cancers other than breast and ovarian, a trend in melanoma was observed. In addition, patients harboring a *BRCA2* mutation had a significantly higher number of observed cases compared to expected cases for pancreatic cancer (SIR 21.7, 95% CI = 13.1–34.0; $p < 0.001$) in both men and women and prostate cancer in men (SIR 4.9, 95% CI = 2.0–10.1; $p < 0.002$) (97). Taken together, germline *BRCA1/2* mutations bear significance in more than just breast and ovarian cancers. Future studies are warranted to provide evidence of access to *BRCA1/2* testing and counseling for these cancers as well.

CONCLUSION

Worldwide, give the high incidence of ovarian cancer, the opportunity to identify *BRCA1/2* carriers at the time of their cancer diagnosis – and those at risk for developing disease – can impact therapeutic interventions. Therefore, it also provides compelling evidence to improve and standardize *BRCA1/2* testing practices. This becomes further punctuated when the opportunity to prevent or diagnose disease early in FDRs is also considered. In appropriate settings, population-based testing may be effective in identifying individuals at risk, who, with current criteria, would otherwise be missed. Future research should strive to build novel, targeted testing panels that will facilitate treatment/prevention-based decision-making. Therefore, it will be important to invest in resources and approaches that will change how ovarian cancer and other solid tumors with *BRCA1/2* involvement are managed and prevented, to improve the current paradigm of care.

AUTHOR CONTRIBUTIONS

KK wrote the draft manuscript and reviewed the article. JB did the figures and reviewed the article. VB and AO reviewed the manuscript. SL worked on the concept, the manuscript writing, and the review of the article.

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The End of the Hysterectomy Epidemic and Endometrial Cancer Incidence: What Are the Unintended Consequences of Declining Hysterectomy Rates?

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Population-level cancer incidence rates are one measure to estimate the cancer burden. The goal is to provide information on trends to measure progress against cancer at the population level and identify emerging patterns signifying increased risk for additional research and intervention. Endometrial cancer is the most common of the gynecologic malignancies but capturing the incidence of disease among women at risk (i.e., women with a uterus) is challenging and not routinely published. Decreasing rates of hysterectomy increase the number of women at risk for disease, which should be reflected in the denominator of the incidence rate calculation. Furthermore, hysterectomy rates vary within the United States by multiple factors including geographic location, race, and ethnicity. Changing rates of hysterectomy are important to consider when looking at endometrial cancer trends. By correcting for hysterectomy when calculating incidence rates of cancers of the uterine corpus, many of the disparities that have been assumed for this disease are diminished.

Keywords: hysterectomy, corpus uterus, endometrial, cancer

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INTRODUCTION

Hysterectomy is one of the most frequently performed surgical procedures among women of reproductive age in the United States, second only to cesarean delivery. Approximately 600,000 hysterectomies are performed annually in the United States (1). An estimated 20 million US women have had a hysterectomy; more than one-third of all women have had a hysterectomy by age 60 (1–3). Multiple factors impact hysterectomy rates, including geography and race. Since the 1980s, alternative treatments for menorrhagia, fibroids, and endometriosis have been developed and increased in popularity, leading to decreasing rates of hysterectomy. An inadvertent consequence of these trends toward conservative surgical management of the female genital tract may be an apparent increase in the incidence of gynecologic malignancies specifically cancers of the uterine corpus. Women who have had a hysterectomy are no longer at risk of endometrial or cervical cancer. Failure to remove these women from the population at-risk leads to an underestimate of endometrial cancer incidence rates. Although a higher number of women at risk may lead to additional cases as hysterectomy rates decrease, the incidence rate should not be affected since it is

meant to measure the number of new cases per 100,000 women in the population at risk for disease. Gynecologic cancer trends over time also are impacted by changes in the proportion of women with their uterus retained, as they reach ages when these malignancies occur. This paper describes the potential impact of recent changes rates of hysterectomy over time by race and period cohorts.

HYSTERECTOMY TRENDS

The majority of hysterectomies are performed for benign indications, with fewer than 15% performed for a malignant preoperative diagnosis (2, 4, 5). The most common primary indications are abnormal uterine bleeding, uterine leiomyomata, and endometriosis (6). Alternatives to hysterectomy including hormonal management, operative hysteroscopy, endometrial ablation, uterine artery embolization, and use of the levo-norgestrel intrauterine device (IUD) as primary management of these conditions have become available and have been demonstrated to be safe (7, 8). The availability of these options has raised questions about potential overuse of hysterectomy. The decreased morbidity associated with uterus-sparing therapies has contributed to their popularity. In addition, the rising age of first pregnancy and improvements in assisted reproduction have made fertility concerns important to women later into life, and contributed to the popularity of uterine preservation. Lastly, although adnexal surgery (e.g., for ovarian cysts) historically triggered a hysterectomy in addition to oophorectomy, the automatic inclusion of hysterectomy in this setting has fallen out of favor. A more conservative approach to the management of ovarian cysts has become more standard, as growing evidence suggests that many ovarian cysts are low risk for malignancy and can safely be monitored by ultrasonography (9, 10). These factors combined have led to recently declining hysterectomy rates (2, 3, 5, 11–13). This decline has been most dramatic among postmenopausal women; the rate of decline has been mostly among white women compared to other racial and ethnic groups (2, 5).

Hysterectomy by the lesser invasive laparoscopic approaches has become more common than either vaginal or abdominal hysterectomy; minimally invasive hysterectomy has also been shown to be an increasingly safer procedure and can be done as an outpatient procedure (3, 4). Population level evidence suggests an increase in all-cause mortality with surgical menopause, resulting in many more women undergoing hysterectomy without oophorectomy (2, 5). Variations in totality of hysterectomy vary by race with black women less likely to have their cervix or ovaries removed with their uterus (14, 15). This trend may be leaving more women undergoing partial procedures in an effort to decrease morbidity and cost, despite the benefits associated with the performance of minimally invasive hysterectomy. Although these changes to patterns of surgical care may affect incidence rates of all gynecologic malignancies, we focus here on the consequences to rates of cancers of the uterine corpus.

FACTORS ASSOCIATED WITH HYSTERECTOMY

The prevalence of hysterectomy within a population varies by community and patient-level factors. Community-level factors include facility type. It has been observed that the procedure more frequently is performed in community hospitals than academic centers (3). Additional factors, such as physician gender, age, level of education, and local physician density, play a role in whether hysterectomy is recommended and performed (16, 17).

Furthermore, hysterectomy prevalence varies greatly by patient race and ethnicity. Several studies have estimated hysterectomy prevalence from population-based survey data and have shown that hysterectomy rates are markedly higher among black women compared to white and Hispanic women even in recent years (12, 18–20). Specifically, age-adjusted hysterectomy prevalence from 2004 to 2008 in women age 20 and older was 23% among black women compared to 20 and 17% among white and Hispanic women, respectively (18). Hysterectomy prevalence is lowest among Asian and Pacific Islanders (API) (6, 12) and Alaska Native/American Indian women have a prevalence intermediate between black and white women (14, 21). Moreover, hysterectomy prevalence has been declining in the Northeast region of the United States (2). Jamison et al. also showed a decline among white women from the early 1990s to 2008. However, hysterectomy was relatively stable among black women during this time period (**Figure 1**) (12).

There also are racial and ethnic differences in the prevalence of common benign gynecologic conditions and the use of surgical treatments. Specifically, black women reportedly have higher rates of fibroids, which are the most common benign indication for hysterectomy. Higher rates of hysterectomy are commonly attributed to the greater prevalence of uterine fibroids among black women, rather than a disparity in care. Black women had 3.3 times the odds of receiving a diagnosis of fibroid tumors by pelvic examination, ultrasound scans, or hysterectomy compared to white women in the Nurses' Health Study II (22). The higher frequency of hysterectomy in the South compared to other geographic regions of the United States is another potential reason that hysterectomy may be more common among black women (3, 18).

Several large studies have reported higher rates of hysterectomy among black women even when adjusted for common clinical and demographic factors that are associated with undergoing hysterectomy (15, 23, 24). An analysis of data from the CARDIA study found black women to have nearly four times the odds of undergoing hysterectomy, compared with white women, after controlling for BMI, polycystic ovarian syndrome, tubal ligation, depressive symptoms, age at menarche, education, access to medical care, geographic site, and a diagnosis of fibroid tumors (OR, 3.7; 95% CI, 2.4–5.6) (23). Similarly, the Study of Women across the Nation (SWAN) included self-reported hysterectomy for benign indications. Black women were 1.7 times more likely to undergo hysterectomy (OR, 1.7; 95% CI, 1.5–1.9) after controlling for education, geographic site, age, marital status, fibroid tumors, parity, smoking, and social support (24). Social determinants

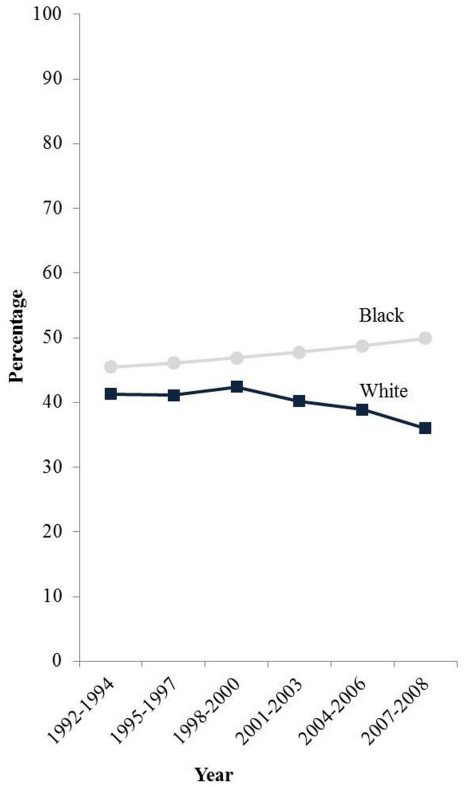

FIGURE 1 | E-adjusted hysterectomy rates by race among women age 50 and older in the SEER-13 states 1992–2008. Footnote: data from the Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention. States included are: California, Connecticut, Iowa, Georgia, Hawaii, Michigan, New Mexico, Utah, and Washington.

of health including differences in patient preferences, physician influence, quality of available care, and access to hysterectomy alternatives also likely influence hysterectomy rates between racial and ethnic groups (15).

IMPACT OF HYSTERECTOMY ON ENDOMETRIAL CANCER RATES AND TRENDS

Over 60,000 women in the US are expected to be diagnosed with cancers of the uterine corpus in 2001, making it the most common of the gynecologic malignancies (25). Incidence rates for endometrial cancer have continued to climb over the last decade and are projected to continue to increase (26–28). Incidence of uterine cancer has been shown to vary by race and ethnicity, with the highest rates among white women, and the lowest rates among Asian women (29). Incidence rates from the population-based Surveillance Epidemiology and End Results (SEER) program, from 2008 to 2012, were highest among white women (25.8 cases per 100,000 women) followed by black (24.0 cases per 100,000), Hispanic (20.7 cases per 100,000), and Asian Pacific Islander women (19.9 cases per 100,000) (30). Since women who have undergone a hysterectomy are no longer at risk for endometrial cancer, failure to remove them from the denominator of the population at risk results in differential underestimation of rates of disease among race and ethnic population (14, 18, 19, 31). Correcting incidence rates by removing these women from the population at risk has been shown to markedly change the rates in the population (18, 19, 21, 31–36). Uncorrected cancer incidence trends over time do not accurately represent the underlying risk of disease, as hysterectomy rates and indications have changed over time and vary by racial groups and geographic region.

The difference in uterine cancer rates between white and black women is diminished after correction for hysterectomy, while the differences between white and Hispanic women are accentuated (12, 18, 19, 31). Specifically, Siegel and colleagues recently reported that hysterectomy-corrected rates among white women in the US were 61% higher, 78% higher for black women, and 47% higher for Hispanic women. Correcting for hysterectomy changed the relative risk of endometrial cancer for black women in the US from 0.87 (95% CI 0.86–0.88) to 0.97 (95% CI 0.94–1.0) making the racial disparity in endometrial cancer incidence between black and white women no longer statistically significant. This underestimation varied greatly by state, which have different rates of hysterectomy. After adjusting for hysterectomy, black women still had a higher risk of uterine corpus cancers in Washington, DC, Florida, North and South Carolina, and a lower risk in Pennsylvania, New Jersey, and New York. The rest of the states with significant disparities lost their significance when corrected for hysterectomy (Alabama, California, Illinois, Indiana, Kentucky, Massachusetts, Michigan, Mississippi, Missouri, Ohio, Tennessee, and Virginia) (18).

Trends of uterine cancer over time also are distorted since hysterectomy rates are changing over time differentially with respect to race and geography (12). The hysterectomy-corrected incidence of uterine corpus cancers among black women is increasing significantly at 3.1% per year nearly double the 1.8% annual increase based on uncorrected incidence rates (**Figure 2**). Correction of the incidence trends also reveals a crossover where the incidence for black women is higher than for whites around the mid 2000s bringing the incidence rates of endometrial cancer for black women higher than that of whites (12). The incidence rates for white women have been decreasing since 1992, and the effect is attenuated without correction for hysterectomy. Specifically, incidence rates decrease 0.8% annually after hysterectomy correction compared to an annual decline of 0.5% uncorrected.

A recent analysis from the Epidemiology of Endometrial Cancer Consortium pooled data from seven cohort and four case-control studies and analyzed the effects of known risks for endometrial cancer in white and black women. Obesity, diabetes, smoking, and oral contraceptive use had similar effects on the risk of disease across groups, indicating that the prevalence differences of these risk factors may partially contribute to racial disparities in rates of uterine cancers (37). Adjusting cancer incidence rates corrected for hysterectomy prevalence, particularly when reporting for racial disparities in cancer rates is necessary, given the multiple factors affecting hysterectomy rates including geographic region, race, and ethnicity.

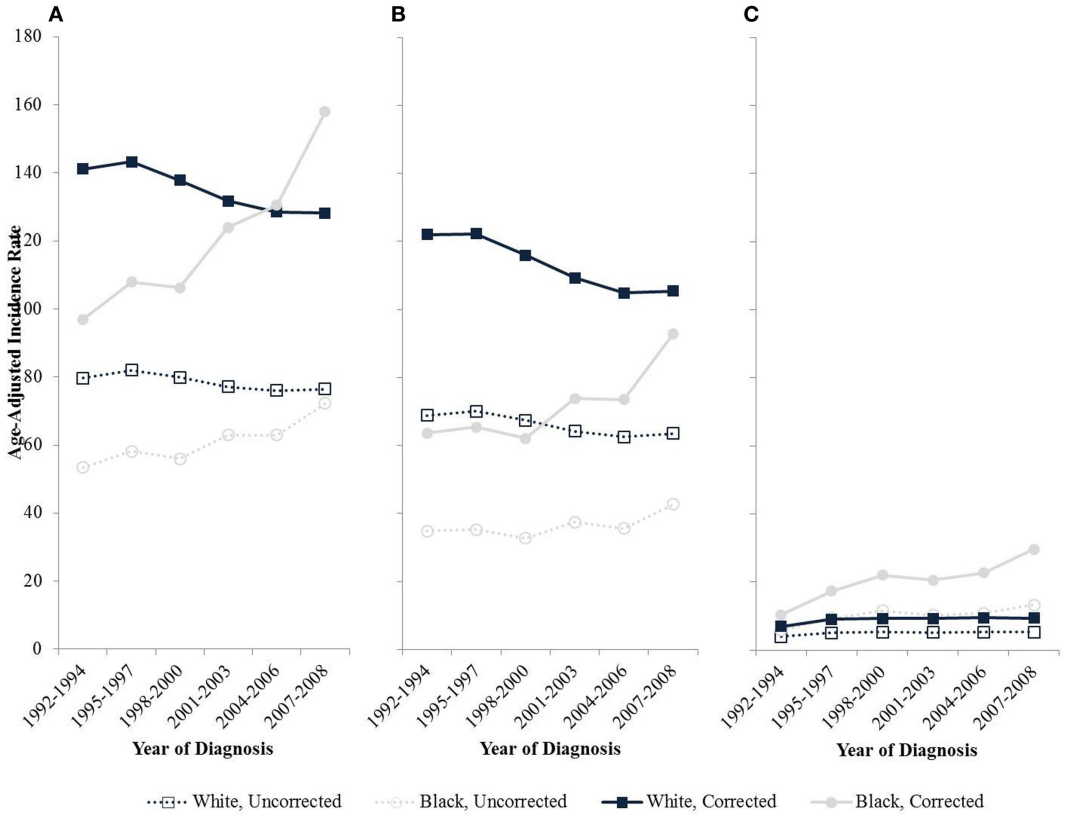

FIGURE 2 | Age-adjusted endometrial cancer incidence rates by race among women age 50 and older in SEER-13, 1992–2008. (A) All types; **(B)** Type I cancers; **(C)** Type II cancers.

RISK FACTORS AND TYPES OF UTERINE CANCER OVER TIME

The vast majority of cancers of the uterine corpus arise from the endometrium. Obesity and its associated high circulating estrogen concentrations, is the primary risk factor for the development of endometrial cancer. However, the aging population, the widespread decrease in the use of hormone replacement therapy, particularly progesterone-based agents, population level delays in childbearing, and the increasing prevalence of diabetes all likely factor in the changing incidence over time (26, 27, 38). Endometrial cancer tends to be diagnosed at an early stage with over 80% of the over 55,000 patients with uterine cancer diagnosed with local disease (39). Although the vast majority of women are cured following a diagnosis and intervention of early stage uterine cancer, in 2011, the incidence rate was 27.5 per 100,000 women and the 5-year relative survival rate was 83% for women diagnosed in 2005 to 2011 (39). This is compared to the mid 1970s when the incidence rate was higher at 35.5 per 100,000 women, and the 5-year relative survival was higher at 87% (40). Despite improvements in therapeutic options, 5-year survival appears to have declined (41).

This malignancy has been historically divided into a Type I and Type II based upon the typical biologic behavior of the disease. Type I disease is the more common, low grade form of this malignancy and tends to be diagnosed in younger women and is driven by excess estrogen states such as obesity. The Type I endometrial cancers are usually caught at an early stage where survival is likely. Type II endometrial cancer, including high-grade endometrioid, serous, and clear-cell carcinoma, and carcinosarcomas, however, is typically estrogen independent, occurs in older women and is more likely to be metastatic at diagnosis (42). Increasing proportions of Type II endometrial cancer are being seen in our population and may be due to the aging population where more women age with their uterus intact. This increases the proportion of higher risk and morbid uterine cancers.

Having undergone a hysterectomy for benign indications eliminates the risk for *de novo* development of endometrial cancer. But hysterectomy alternatives are likely altering endometrial cancer risk as well. Consideration can be given for the possibility that women who had a hysterectomy are more likely to have strong risk factors for Type I endometrial cancer (such as those with PCOS, endometriosis, or other hormonal imbalances leading to symptomatic benign gynecologic conditions). Hysterectomy may then selectively remove women at highest risk for low grade malignancies with low mortality rates. Additionally, as women are less likely to undergo hysterectomy and accept alternate therapy for menorrhagia, fibroids, or dysmenorrhea, they may be exposed

to hormonal agents such as the levo-norgestrol IUD and other long acting contraceptive agents. These hormonal interventions are protective against Type I endometrial cancer.

After correcting for hysterectomy prevalence, the difference in incidence rates for Type I cancer diminishes between white and black women over time, largely due to the increasing rates of Type I cancers among black women and the decrease in Type I cancers among white women. Much of this difference may be attributable to increased risk factors for endometrial cancer among black women compared to non-black women such as obesity, diabetes, and decreased use of oral contraception (19, 37).

Black women are diagnosed proportionally more frequently with aggressive Type II disease, compared with other racial/ethnic groups (41, 43–49). Uncorrected, incident invasive uterine cancer cases between 1999 and 2006 collected from the Centers for Disease Control and Prevention's National Program of Cancer Registries or the National Cancer Institute's SEER Program revealed that only 6.8% of all endometrial cancer patients are black but they represent 17.4% of type II endometrial cancers (48). Rates of Type II cancers appear to be increasing over time entirely due to an increase in incidence among black women (**Figure 2**) (12). While hormonal hysterectomy alternatives are known be protective against Type I cancers, their role in the development of Type II endometrial cancers is less clear.

The racial disparity in uterine cancer mortality is pronounced. Despite a 30% lower incidence of disease among black women, the mortality rate is 80% higher when compared to whites (49). Histologic differences have historically been used to explain differences in mortality rates between white and black women, and certainly, a larger proportion of Type II malignancies seen in black women contributes to this difference. As with other disparities however, the role of access to care cannot be overlooked. A recent, large analysis of women with Type II endometrial cancer using SEER-Medicare data suggested that controlling for treatment and socioeconomic differences, and medical comorbidities eliminated the difference in the disease-specific mortality between black and white women (50). Disparities related to access to care (specifically hysterectomy alternatives) may amplify the effects of interventions that change risks for the development of gynecologic malignancies. As our understanding of the molecular and genetic factors that correlate to prognosis expands through projects such as the TCGA, ensuring adequate minority participation to clinical trials must be a priority. More research is needed, but many of the disparities in endometrial cancer between black and white women may be explained by hysterectomy rates, access to hormonal hysterectomy alternatives, and differences in risk factors such as obesity.

CONCLUSION

An unintended consequence of non-surgical management of common gynecologic conditions appears to be rising incidence and mortality of cancer of the uterine corpus. Incidence and prevalence rates of cancer are useful indicators for assessing the health of a population. Accurate rates are needed in order to determine population level needs and to understand and health disparities among subgroups. As risk reducing surgical removal of other organs (e.g., breast, fallopian tubes, and ovaries) becomes increasingly common, this issue may extend to other cancer disease sites. In endometrial cancer incidence rates uncorrected for hysterectomy have been used to describe wide variations in geographic and racial and ethnic differences in risks of the development of disease. But hysterectomy-corrected rates may help to explain some of the variations as related to patterns of care, access to care, and other non-biologic factors and provide information for appropriately targeting populations to reduce other risk factors such as obesity.

AUTHOR CONTRIBUTIONS

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Decision-Making in the Surgical Treatment of Breast Cancer: Factors Influencing Women's Choices for Mastectomy and Breast Conserving Surgery

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One of the most difficult decisions a woman can be faced with when choosing breast cancer treatment is whether or not to undergo breast conserving surgery or mastectomy. The factors that influence these treatment decisions are complex and involve issues regarding access to health care, concerns for cancer recurrence, and the impact of surgery on body image and sexuality. Understanding these factors will help practitioners to improve patient education and to better guide patients through this decision-making process. Although significant scientific and societal advances have been made in improving women's choices for the breast cancer treatment, there are still deficits in the decision-making processes surrounding the surgical treatment of breast cancer. Further research is needed to define optimal patient education and shared decision-making practices in this area.

Keywords: mastectomy, breast cancer, breast conserving surgery, shared decision-making, contralateral prophylactic mastectomy

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INTRODUCTION

Medical decision-making has evolved over the last several decades from one based on paternalism, in which the physician decided on the best course of treatment according to his/her view of what was in the best interest of the patient, to one focused on patient autonomy, in which the informed patient makes decisions about accepting or declining treatment options based on his/her own values and priorities. In modern medical ethics, shared decision-making has been proposed as the ideal model for medical decision-making that both acknowledges patient autonomy and the role of the physician in providing expert medial opinion. Shared decision-making is a process that informs patients about what available treatments are most effective under particular circumstances, incorporates patients' needs and values into decisions, and improves the patient–clinician dialog about decisions (1, 2). Shared decision-making has been advocated as an ideal model to address treatment decisions in which no single treatment option is clearly indicated above others based on available medical evidence (2). Therefore, this model is particularly suited to treatment decisions in the management of the primary tumor in breast cancer, as a patient may face several surgical treatment options that result in equivalent oncologic outcomes.

One of the most difficult decisions a woman can be faced with when choosing breast cancer treatment is whether or not to undergo breast conserving surgery (BCS) or mastectomy. Notably, the

clinical research in breast cancer treatment, which supports the use of BCS, came about at the time when women were also becoming dissatisfied with the traditional paternalistic doctor–patient relationship model and were demanding to have more choice in their medical care. In his book, "The Breast Cancer Wars," Barron Lerner chronicles the convergence of the women's liberation movement and the rise of BCS as the standard of surgical care in the treatment of early stage disease (3). In 1971, the writer Babette Rosamond was diagnosed with breast cancer when one of the first proponents of BCS, Bernard Crile, was offering a partial mastectomy as opposed to the traditional one-step procedure in which a woman with a suspicious breast mass was consented for an excisional biopsy under anesthesia and if this mass was determined to be a cancer on frozen section, the surgeon would then proceed with a radical mastectomy, which included the removal of the breast, overlying skin, axillary lymph nodes, and pectoralis muscles. When Babette Rosamond was presented with the one-step procedure, she refused and only gave permission for the excisional biopsy. The excision demonstrated a small focus of breast cancer. She then refused the radical mastectomy and sought out the opinion of Dr. Crile at the Cleveland Clinic who cited data from retrospective studies of less aggressive surgery, resulting in acceptable outcomes. Ms. Rosamond wrote about her experience in an article, "The Right to Choose," in the popular woman's journal McCall's Magazine and ultimately published a book entitled, "The Invisible Worm." She joined a host of other women leaders of the time who were vocal proponents against the current medical establishment's support of aggressive breast cancer surgery who demanded choice in their cancer care and the option of less aggressive and more cosmetic procedures.

Concurrently, in the late 1960s, the surgeon Bernard Fisher developed and promoted a biological model of breast cancer in which he proposed that breast cancer was a systemic disease requiring both local and systemic treatment (4). Therefore, more radical surgery was not necessarily beneficial in the face of disseminated tumor cells. Although commending Crile and others for pursuing BCS, Fisher demanded more rigorous evidence to support less aggressive surgery by means of randomized clinical trials. Under his leadership, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 and B06 trials were conducted. The NSABP-B04 trial demonstrated that sparing the pectoralis muscles in mastectomy did not negatively affect oncologic outcomes (5). The NSABP-B06 trial established that BCS results in equivalent overall survival as mastectomy in patients with early stage breast cancer (6). The addition of adjuvant radiation treatment to BCS decreased the rate of local recurrence from 39 to 14% over 20 years. To date, there are multiple randomized clinical trials with long-term follow-up demonstrating no difference in overall survival between BCS with adjuvant radiation and mastectomy for the treatment of operable breast cancers (6–11). Refinement of radiation techniques and the addition of adjuvant systemic therapies have further decreased the rate of local recurrence in BCS to approach that of mastectomy (12, 13). Currently, one of the quality assurance standards for the National Accreditation Program for Breast Centers in the United States is that at least 50% of Stages 1–2 breast cancers amenable to BCS are treated with partial mastectomy.

MASTECTOMY AND BREAST CONSERVATION

Despite data supporting BCS in eligible patients, a significant percentage of women who would be candidates for BCS still decide to undergo mastectomy. The factors that influence these treatment decisions are complex and involve issues regarding access to health care, concerns for cancer recurrence, and the impact of surgery on body image and sexuality. Understanding these factors will help practitioners to improve patient education and to better guide patients through this decision-making process.

Access to health care is one of the major determinants of choice for breast cancer surgery, especially with regard to access to specialty providers and treatment facilities. Because adjuvant radiation therapy is usually recommended after BCS, multiple studies have focused on the availability of radiation oncology specialists. A recent publication using data from the surveillance, epidemiology, and end results (SEER) database and the Health Resources and Services Administration Area Resource File evaluated the association between the choice of breast surgery (mastectomy or BCS), the receipt of adjuvant radiation therapy after BCS, and the density of radiation oncologists in a particular area (ROD) (14). The study demonstrated that the likelihood of a woman undergoing BCS for early stage breast cancer increased as the ROD in an area increased. In addition, the likelihood that adjuvant radiation therapy was omitted after BCS decreased as the ROD in an area increased. The results from this study are consistent with those of a large study using the Medicare database that evaluated the use of BCS in older breast cancer patients and demonstrated that BCS was used more frequently in counties with a high density of radiation oncologists (15).

Numerous studies have also demonstrated that travel distance for radiation therapy may be associated with decisions regarding BCS and the actual delivery of adjuvant radiation therapy after BCS (16–21). The largest of these studies evaluated the use of BCS in women with early stage breast cancer using the SEER database (17). This study showed that the use of BCS was more common when women received treatment in a hospital with a radiation facility compared to women living a greater distance from a hospital with a radiation center. This was statistically significant for women who resided ≥15 miles from the nearest hospital with a radiation treatment center (OR 0.52, 95% CI 0.46–0.58). The study also demonstrated that for women who had BCS, a statistically significant decrease in the use of adjuvant radiation therapy was observed in patients who lived ≥40 miles from a hospital with a radiation facility, although this only accounted for 1.7% of the patients in the study. The use of accelerated radiation schedules, including shorter course whole breast irradiation given over 3 weeks and partial breast irradiation, may help to ameliorate some of these issues by providing patients with more manageable radiation schedules.

The use of multidisciplinary treatment teams is becoming more common in the management of breast cancer patients, especially at larger, academic institutions where breast cancer specialists are available in multiple disciplines. However, a significant percentage of patients still do not have the opportunity to meet with a medical oncologist or radiation oncologist before undergoing

surgery for breast cancer. One of the benefits of a multidisciplinary approach is that patients understand all the components of their breast cancer treatment prior to starting treatment, and this increased knowledge may have an impact on treatment decisions regarding surgery for breast cancer. In a study of elderly women aged ≥65 years with local or regional breast cancer treated from 1994 to 1995, those patients who had a consultation with a radiation oncologist preoperatively were 6.7 times more likely to have BCS compared to those who did not ($P \leq 0.001$). Furthermore, the odds of a patient receiving adjuvant radiation therapy after BCS were five times greater for patients who had a preoperative radiation oncology consultation ($P < 0.001$). Although this study was conducted at the time when multidisciplinary care was not as prevalent as it is today, it did demonstrate how multidisciplinary care may influence treatment choices (22). Several studies have demonstrated that surgeon characteristics including practice setting and gender have an impact on BCS rates (23–25). Surgeons who are affiliated with academic institutions, whether or not they have fellowship training in breast surgery or surgical oncology, use BCS more often than community surgeons (23). This may be due to the greater availability of other specialty providers at academic institutions and the use of multidisciplinary care in this setting. The number and availability of reconstructive surgeons at a particular institution have also been shown to impact rates of mastectomy and reconstruction and BCS (19). In an analysis of patients treated for breast cancer at National Comprehensive Cancer Network institutions, a greater number of reconstructive surgeons were associated with increased mastectomy and reconstruction rates, whereas long wait times for breast reconstructive surgery were associated with increased BCS rates.

Factors predicting the use of BCS, including clinicopathologic, socioeconomic, and patient characteristics, have been examined in numerous studies. Tumor characteristics, including tumor size, lymph node involvement, and stage, have all been shown to influence treatment decisions, with BCS used more frequently in patients with smaller tumors (23, 26) without lymph node involvement (15) and mastectomy used more often in patients with higher stage (27). Socioeconomic factors, including higher education, low poverty areas, and private insurance, are also associated with increased use of BCS (15, 21, 24). Significant geographic variation also exists in the use of BCS, both local and regional. Multiple studies have demonstrated that patients living in the Northeast and Pacific West are more likely to have BCS than those in the South (15, 23, 26, 28). In an analysis of older breast cancer patients, 70% of the patients in the Northeast had BCS compared to 48–50% of patients in the South ($P < 0.001$) (15). In this study, patients in metropolitan areas were also more likely to have BCS than patients in rural areas. This may simply reflect decreased access to health care and particularly breast cancer specialists. This geographic variation may also be influenced by other factors, including education and socioeconomic status.

Although some single institution studies have shown that younger patient age is associated with the use of BCS (15, 21, 23, 24), more recent analysis of large national databases suggest that this trend has reversed. Two reviews of the National Cancer Database have demonstrated in the setting of an overall increase of BCS, younger patients are being treated with mastectomy at higher rates than their older counterparts after adjusting for patient, facility, and tumor characteristics (28, 29). The subset of women aged ≤35 years was twice as likely to undergo mastectomy compared to women aged 61–64 years (29). These studies also reported similar trends with socioeconomic status, geography, and cancer stage outlined above, with a more recent narrowing of the BCS disparity in the South (28). In addition, access to radiation also appeared to influence BCS rates in these studies. It is unclear why younger women may be opting for more extensive surgery. This may be due to a concern for locoregional recurrence in younger patients (30), although more aggressive surgery does not appear to affect breast cancer-specific survival (31). Increased awareness of familial breast cancer syndromes may also be affecting mastectomy rates in younger women, who are at higher risk for having a deleterious genetic mutation and therefore may be choosing bilateral mastectomy for the treatment of a unilateral cancer.

When patients are diagnosed with breast cancer, they obtain support and advice from multiple sources when making decisions regarding breast surgery. The surgeon's recommendation or preference for care is frequently cited as an important factor in this decision-making process. In a survey study that examined breast cancer care in a group of 96 patients, women who chose BCS indicated that the most important factor in the decision was the surgeon (32). This was in contrast to patients who selected mastectomy with or without reconstruction, where fear of cancer and concern about radiation therapy were ranked as more significant factors.

One of the major goals for providers is to help patients make informed decisions about their care. The development and use of decision-making aids have been investigated by several groups as a way to help providers obtain a better understanding of patient preferences for treatment (33, 34). These aids may also enhance patient decision-making by improving delivery of information and facilitating communication between providers and patients. In one study, patients and surgeons were interviewed to identify key factors influencing breast cancer surgery decisions, which were then incorporated into a decision board that could be reviewed at the time of surgical consultation (34). For patients, information on options for reconstruction, quality of life, and body image was important factors, whereas for surgeons, details regarding treatment side effects were considered important. The decision board was administered to 175 patients and 98% reported that it was easy to understand and 81% indicated that it helped in the decision process. Surgeons also found the decision board to be helpful in presenting information to patients. A subsequent randomized trial comparing the decision board to usual care demonstrated that patients who had surgical consultations with the decision board had higher knowledge scores regarding treatment options (66.9 vs. 58.7, $P < 0.0001$), less decisional conflict (1.40 vs. 1.62, $P = 0.02$), and were more satisfied with the decision-making process (4.50 vs. 4.32, $P = 0.05$). In addition, patients in the decision board group were more likely to undergo BCS (94 vs. 76%, $P = 0.03$). A similar approach using an interactive CD-ROM decision aid showed that patients using the CD-ROM were more satisfied with the amount of information received, their treatment decisions, and the decision-making

process (33). However, the CD-ROM decision aid had no impact on treatment decisions. A recent meta-analysis of studies using decision aids in breast cancer patients, which included the above studies, demonstrated that in the three randomized trials of decision aids, women were 25% more likely to choose BCS over mastectomy if a decision aid was utilized (risk ratio 1.25, 95% CI 1.11–1.40) (35). In addition, decision aids increased patient knowledge by 24%, decreased decisional conflict, and improved the overall decision-making process.

BODY IMAGE AND BREAST RECONSTRUCTION

An important concern for women undergoing breast cancer surgery is the impact this will have on body image and sexuality. Some studies have demonstrated that women undergoing BCS have fewer concerns about body image compared to mastectomy patients (36–39), whereas others have found no difference between the BCS and mastectomy groups (40, 41). In a recent meta-analysis of 12 studies on body image after breast cancer surgery, Fang et al. demonstrated that BCS patients had a better overall body image than women undergoing mastectomy with reconstruction and scored higher on body stigma domain (42). However, reconstruction significantly improved body image in mastectomy patients compared to no reconstruction. In addition, cosmetic satisfaction in postmastectomy patients with reconstruction appears to be high (43, 44). Currently, in the United States, universal coverage for postmastectomy reconstruction is mandated based on the passing of the Women's Health and Cancer Rights Act in 1998. Despite the majority of patients do not undergo reconstruction (19). Factors associated with not receiving postmastectomy reconstruction include social and racial disparities, including black race, lower educational level and income, and public insurance (45–48). Although the racial disparity with breast reconstruction has been shown in multiple studies, a review of the Department of Defense cancer database shows that the receipt of reconstruction between White and Black women was equivalent, suggesting that the racial disparity with reconstruction may not be as evident when access is equal (49). Other factors associated with low reconstruction rates include older patient age, advanced disease, presence of comorbidities, and lack of access to reconstructive surgeons (19, 45–47). Although exogenous factors influencing reconstruction rates can be identified by institutional and database reviews, few studies have examined patients' perspective of decision-making about breast reconstruction. In a survey study of breast cancer patients sampled from the SEER database, the majority of mastectomy patients reported satisfaction with the decision-making process about reconstruction. Dissatisfaction was associated with race, with black and Latina women being less satisfied, but was not associated with income or educational level. The most common reasons cited by patients for not undergoing reconstructive surgery are to avoid additional surgery and that they did not feel reconstruction was important. The main systems barrier reported to obtain reconstruction was lack of insurance coverage, whereas knowledge of the reconstruction as an option and finding a reconstructive surgeon were not significant barriers (45).

CONTRALATERAL PROPHYLACTIC MASTECTOMY

Contralateral prophylactic mastectomy (CPM) is the removal of the healthy breast in the treatment of a unilateral cancer. Reviews of large national databases in the United States have demonstrated an increase in the rates of CPM in cases of operable breast cancer by over 150% (50, 51). This trend has also been reproduced in multiple single institution studies, with centers reporting CPM rates as high as 24% in the treatment of mastectomy patients (52, 53). These data are notable for the finding that patient factors are often more powerful predictors than tumor factors. Specifically, White race, higher socioeconomic status, and young age have been consistently identified as independent predictors for CPM (50, 52, 53). Despite the increasing frequency of CPM in the treatment of breast cancer, the oncologic benefit of this procedure is controversial in patients who do not have a genetic predisposition in developing breast cancer. Although CPM does reduce the risk of developing a contralateral breast cancer significantly, the incidence of contralateral cancers is low and has been declining over time due to advances in adjuvant chemotherapy and endocrine therapy (54). Currently, the incidence of contralateral breast cancer in patients can be estimated based on large retrospective cohort reviews and ranges from 0.3 to 1% per year depending on the age of diagnosis and characteristics of the primary tumor (54–56). The data on survival benefit of CPM are contradictory. Retrospective studies comparing unilateral mastectomy with CPM have demonstrated disease specific and overall survival benefit (57, 58). However, more recent data suggest that there is no difference in survival when breast conservation is compared with CPM (59). A recent meta-analysis conducted by Cochran Collaboration concluded that there was insufficient evidence to demonstrate a survival benefit with CPM (60).

Data on patients' motivations for choosing CPM indicate that the patient's choice for CPM appears to be dominated by a fear of developing another breast cancer, whereas the risk of a contralateral breast cancer and disease-specific death is routinely overestimated by patients (61–64). In a prospective survey of newly diagnosed breast cancer patients, Abbott et al. found that the mean estimated risk by patients for developing a contralateral cancer was 31% over 10 years, about ninefold the expected risk of most breast cancer patients. The perceived risk was not associated with stage, family history of breast cancer, or age of diagnosis (61). Similarly, in a qualitative study consisting of interviews with mastectomy and CPM patients, Covelli et al. noted that patients estimated a high, almost inevitable, risk of cancer recurrence and contralateral breast cancer development that they translated into a high risk of breast cancer-related death. Patients who chose CPM feared developing a contralateral cancer and the prospect of undergoing breast cancer treatment again at some point in the future (64). These results are similar to survey studies demonstrating that the most common reasons women report for choosing CPM are to avoid the development of a contralateral cancer and

to improve their survival (61, 63). Other common reasons women choose CPM in these surveys were to achieve a symmetric cosmetic result, to avoid future tests and breast cancer surveillance, and to allay concern that future screening would not identify a new cancer. Given the apparent discordance between patients' anticipated benefits of CPM and the expected oncologic benefit expected, many clinicians have called for improving communication practices and patient education in this area. Currently, the use of decision aids is being investigated as a tool to help clinicians and patients navigate decision-making in CPM (63, 65).

Although breast cancers secondary to a hereditary syndrome are uncommon, it is important to recognize that there is a population of women who do have a high risk of developing a contralateral cancer and therefore may benefit from CPM. Women with a deleterious BRCA mutation can have up to a 40% risk of developing a contralateral breast cancer over 10 years (66–68). CPM may also provide a survival benefit in deleterious BRCA mutation carriers (66, 69). Furthermore, patients with a strong family history without an identifiable genetic mutation appear to be at increased risk of developing a contralateral cancer, depending on age of diagnosis, whether the relative had a bilateral or unilateral cancer, and the degree of relative with breast cancer (first or second degree relative) (70). Genetic testing in breast cancer has also expanded to include next generation cancer panels in addition to testing for BRCA mutations. Panel testing may be appropriate for women with a strong family history without a BRCA mutation or those who have a family history indicative for more than one hereditary cancer syndrome. Unfortunately, the addition of expanded genetic testing is not without risk. Patients are more likely to test positive for a genetic variant of uncertain significance, which can make the decision-making process about prophylactic surgery even more confusing (71). Additionally, data on risk stratification for other mutations are often not as mature as the BRCA data on cancer risk, and thus even in the setting of a deleterious mutation, it is difficult to quote accurate risk to the patient. Therefore, it is important for women undergoing genetic testing to also be formally counseled on the significance of the results by a specialist trained in genetic counseling.

CONCLUSION

Choosing between mastectomy and BCS can be a difficult decision involving personal preferences about body image and sexuality. In addition, external factors can influence this choice, including socioeconomic status and access to adjuvant radiation therapy, surveillance imaging, and reconstructive surgeons. Although national rates of BCS for early stage breast cancers are on the rise, rates of mastectomy have increased in young patients for reasons that are unclear. Furthermore, bilateral mastectomy has also become a common procedure in the treatment of a unilateral cancer. Most breast cancer patients are at a very low risk for developing a contralateral cancer, and yet the choice for CPM appears to be motivated by fear of developing a new cancer in the healthy breast. Although significant scientific and societal advances have been made in improving women's choices for the breast cancer treatment, there are still deficits in the decision-making processes surrounding the surgical treatment of breast cancer. Further research is needed to define optimal patient education and shared decision-making practices in this area.

AUTHOR CONTRIBUTIONS

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REVIEW
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Challenges in Prevention and Care Delivery for Women with Cervical Cancer in Sub-Saharan Africa

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Virtually all cases of invasive cervical cancer are associated with infection by high-risk strains of human papilloma virus. Effective primary and secondary prevention programs, as well as effective treatment for early-stage invasive cancer have dramatically reduced the burden of cervical cancer in high-income countries; 85% of the mortality from cervical cancer now occurs in low- and middle-income countries. This article provides an overview of challenges to cervical cancer care in sub-Saharan Africa (SSA) and identifies areas for programmatic development to meet the global development goal to reduce cancer-related mortality. Advanced stage at presentation and gaps in prevention, screening, diagnostic, and treatment capacities contribute to reduced cervical cancer survival. Cost-effective cervical cancer screening strategies implemented in low resource settings can reduce cervical cancer mortality. Patient- and system-based barriers need to be addressed as part of any cervical cancer control program. Limited human capacity and infrastructure in SSA are major barriers to comprehensive cervical cancer care. Management of early-stage, locally advanced or metastatic cervical cancer involves multispecialty care, including gynecology oncology, medical oncology, radiology, pathology, radiation oncology, and palliative care. Investment in cervical cancer care programs in low- and middle-income countries will need to include effective recruitment programs to engage women in the community to access cancer screening and diagnosis services. Though cervical cancer is a preventable and treatable cancer, the challenges to cervical control in SSA are great and will require a broadly integrated and sustained effort by multiple stakeholders before meaningful progress can be achieved.

Keywords: cervical cancer, sub-Saharan Africa, human resources, surgery, radiation, palliative care

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CERVICAL CANCER AND THE WAY TO MEET GLOBAL DEVELOPMENT GOAL

Cervical cancer is a significant cause of cancer-related mortality for women living in sub-Saharan Africa (SSA). In 2013, 39 out of 48 countries, classified as part of SSA region, identified cervical cancer as the most common cause of cancer-related death for women, followed by breast cancer (1). Collectively, the 236,000 women who died from cervical cancer in 2013, 90% of them in developing nations, represent a failure of the health system to implement a functional cervical cancer control

strategy (2). The human and societal cost of cervical cancer in SSA is difficult to estimate. The average age at diagnosis is 48; in SSA, most women in this age are subsistence farmers, supporting four to seven or more children. Facilities to treat cervical cancer are scarce in SSA. When surgery and other medical care are available, families face a significant risk of debt and worsened poverty from both the costs of treatment and loss of work (3).

Many challenges stand in the path to develop a health system to address the rising incidence of cancer in SSA, including changing demographics, deficiencies of infrastructure and human capacity, and financial constraints. Multiple steps exist to optimize cervical cancer control: primary prevention with human papilloma virus (HPV) vaccine, secondary prevention with national screening program with HPV DNA test, cytology or visual inspection with acetic acid (VIA), and treatment for invasive cancer. More than 40% of the SSA population is younger than 15 years, and the aging of this population will contribute to a rapidly increasing burden from cervical cancer on these communities (4).

In the context of HPV vaccine where the target age for vaccination of girls and boys is 11 or 12, this young demographic profile in SSA nations can be harnessed to yield greater reward for an investment in primary cervical cancer prevention. The cost of current HPV vaccine is prohibitory for most SSA nations; the GAVI alliance, however, can make this investment more manageable for qualifying nations (5, 6). Models of HPV vaccination in SSA have shown that population-wide programs are highly cost-effective under various circumstances for both the quadrivalent and nonavalent vaccines (7). The current HPV vaccines are heat-labile and, therefore, require an effective "cold-chain" of refrigeration between production and patients. In SSA, where transportation is poor and supply chains can be unreliable, and where 80% of the population still lives in rural settings (World Bank), extensive and coordinated planning is needed to effectively vaccinate a high proportion of the population. The stunning success of the Rwandan vaccination effort is a demonstration of the value of meticulous planning and execution in large-scale implementations (8).

Invasive cervical cancer typically develops 10–30 years after primary HPV infection. Even the most effective vaccination program, therefore, would leave millions of women who are potentially already infected with HPV, at risk for cervical cancer. Screening and cervical cancer treatment are, therefore, critical components of cervical cancer control over the coming generation.

Screening for cervical cancer precursors can be achieved through the use of cytology, HPV DNA testing, or VIA. Cytology-based screening has been the basis of secondary screening in high-income countries for many decades. Cytology-based screening requires an extensive infrastructure, including reliable laboratories with reagents, specialized staff to read the specimens, information systems to notify patients, and caregivers of results and expectations for follow-up, and quality control processes for all of these components. The diagnostic performance of cytology-based testing, furthermore, is highly variable, with limited sensitivity and specificity in even optimal circumstances. The WHO recommends that only countries with established, high-quality programs with broad coverage of their target population utilize cytology-based screening (9).

Visual inspection with acetic acid has been advocated as a low-cost means of population-based screening. The advantages of VIA include limited infrastructure needs, limited initial cost, and an immediate diagnostic result, which in turn allows for "see and treat" programs in which women can be diagnosed and treated for pre-invasive cervical lesions in a single visit, limiting the burden on both patients and the health system by decreasing the need for patient tracking and follow-up (9). VIA has disadvantages as well. It is a subjective test: sensitivity and specificity vary with practitioner performance, making quality control a challenge as programs scale-up from closely monitored research settings to population-based screening. Because of the limited sensitivity of VIA, multiple rounds are needed in a woman's lifetime. A study led by Shastri and colleagues found that multiple rounds of VIA decreased death from cervical cancer, but did not decrease the incidence of cervical cancer, suggesting that any positive effect may have been more from a stage shift rather than prevention of invasive cancer *per se* (10). In SSA, where resources for the treatment of invasive cancer are limited, this might further decrease the benefit of VIA while increasing the burden on the health-care system and target population. The costs of the health-care work force and facility resources need to be accounted for during any new national cervical cancer screening program. As programs scale-up to population-based screening, robust information systems are needed to manage coverage of those at risk, schedule repeat screening, and avoid redundant testing.

Human papilloma virus testing offers advantages over cytology and VIA. It is an objective test, and, therefore, decreases the demands for human capacity and simplifies quality control. The high sensitivity and negative predictive value of HPV testing makes a single lifetime test a reasonable option for women who test negative.

As articulated by Farmer, global health programs, including in this case effective cervical cancer control, require "space, staff, stuff, and systems" (11). In other words, medical interventions will be sustainably effective and able to respond to crises when a robust health infrastructure is in place. Unfortunately, health infrastructure is a huge challenge in SSA as has been recently elaborated through the work of the Lancet Commission on Global Surgery and others (3, 12). As shown in **Table 1**, our experience and that of others suggest that the following are salient challenges to cervical cancer control in SSA: clinical diagnostic capacity, capacity for processing and diagnosis of pathology specimens, a lack of oncology specialists at all levels, a deficiency of operating theaters and other surgical services, a lack of radiotherapy equipment and staff (13), and locally contextual factors, including poverty and the financial barriers to treatment, religious and cultural beliefs and stigmas around illness and cancer, and other medical morbidities, particularly coexisting infections, such as HIV, poor nutrition, and obstetrical fistulae. Developing health systems are challenged in resource allocation across many non-communicable diseases. Ultimately, success of any cancer treatment program must take into account the burden of treatment for the patient and her family.

TABLE 1 | Essentials to a cervical cancer management program.

Elements to consider	
What is the clinical diagnostic capacity?	• Cervical cancer awareness among health professionals • Trained women's health-care providers (pelvic exam, cervical biopsy)
What is the pathologic diagnostic capacity?	• The who, how, and where of performing cervical disease pathology analysis
Human resources capacity in cervical cancer care	• Trained advanced gynecology surgeons or gynecologic oncologist, radiation oncologist, professional nurses, social workers
Access to cancer surgical services	• Operative room facilities, post-surgical recovery units, access to intensive care units • Surgical support team (nurses, doctors) • Essential surgical supplies and medicines
Radiation oncology facilities	• In-country or out-of-country radiation facility • Limitations due to cost and distance to facility
Contextual modifiers	• Financial barriers for patients and health system • Religious and cultural beliefs toward cancer care • Lack of care givers • Significant medical comorbidities (Urinary obstruction or fistula, HIV status, poor nutritional status)

To date, the majority of cervical cancer control programs in SSA are "vertical" efforts focused on primary or secondary prevention. We use the term "vertical" to describe interventions that are strictly focused on a single disease or condition. Given the paucity of medical infrastructure in SSA, this is most likely the most appropriate choice from the perspective of the single disease. Over time, however, very significant investments have been made in single disease-focused programs without lasting improvement of the overall health infrastructure (14). The U.S. invests $323 million each year for control of HIV in Uganda alone (15), but the sustained effect on medical infrastructure is unclear. Brown and colleagues found that, in Botswana, engagement in HIV treatment services was not associated with a decrease in the typically long interval between initial symptoms and diagnosis of cancer (16). We propose that more effort should be made to strengthen control of diseases within the rubric of overall health system strengthening.

TREATMENT FOR INVASIVE CERVICAL CANCER IN SUB-SAHARAN AFRICA

Primary and secondary prevention of cervical cancer are far more cost-effective than the treatment for invasive cancer and should rightfully be placed as the highest priority of any new cervical cancer control effort. Increasing cancer screening, especially in a context where screening has not been ongoing, will identify women with invasive cancers, incurring an ethical and functional need for management. If a screening program can offer no treatment or comfort for these women, it will both constitute a breach of implied trust and potentially turn the surrounding community against the program and future cancer control initiatives.

The treatment for invasive cervical cancer is determined by the stage of cancer at patient presentation and can range from minor surgery to radical surgery, chemotherapy, and radiotherapy. The development of cervical cancer treatment services requires advanced-level services within a broader integrated health system that includes robust information systems, a functioning consultation and referral network, diagnostic services including pathology and radiology, staffed and functioning operating rooms, perioperative care, radiotherapy services, and chemotherapy. In short, comprehensive management of invasive cervical cancer requires a breadth of services from primary to tertiary care. This raises a conundrum for nations planning a comprehensive cervical cancer control program: the greatest successes will only be seen when a broad and effective health system has been implemented. The exception to this is primary prevention: in our opinion, any effort to control cervical cancer should begin with the steps to implement a comprehensive HPV vaccination program, as this is known to be highly effective. A well-orchestrated campaign in a limited resource health system may succeed before the elements of an integrated and high-quality health system are in place. We do not, however, advocate HPV vaccination as a stand-alone program for cervical cancer control: given the 10–30 interval from HPV infection to the development of invasive cancer, millions of women already infected will be at risk for the next few decades.

The development of screening and treatment for cervical cancer faces significant challenges in SSA, including in information systems, human capacity, and health system infrastructure. Poverty also has a significant effect on cervical cancer control; accommodations should be made to render screening, prevention, and treatment feasible and affordable.

Health information systems in SSA are faced with high rates of illiteracy, limited health-specific knowledge, limited Internet capacity, and limited equipment for medical record-keeping. Most of the patients in SSA are the keepers of their medical record often traveling with medical cards across clinic. Increasingly, individual hospitals are successfully implementing electronic medical records and thereby facilitate improved coordination of care- and outcome-based research. The use of the OpenMRS platform at AMPATH in Eldoret, Kenya is an excellent example (17). Improved patient identification and health information systems will be needed for cervical cancer control. Recordkeeping is critical to facilitate recruitment and follow-up in screening and prevention and is central to the consultation and referral.

Mobile technology has been found to be effective in improving both recruitment and adherence in the treatment for HIV in SSA

(18), and active efforts are underway to refine the role of these technologies in recruitment and follow-up of cervical cancer screening patients. Many countries in SSA have both high rates of cell phone ownership and extensive areas of cellular coverage (19). While mobile technology can be developed to support vertical cervical cancer-specific prevention programs, thought should be given to developing information systems in the context of and in concern with developing electronic medical records in the overall health system.

Treatment for invasive cervical cancer varies with stage at diagnosis. For patients with cancer limited to the cervix, surgery is often the treatment of choice, while for women with more advanced cancer, chemotherapy and radiotherapy are usually needed. Cervical cancer survival is compromised when patients present at advanced stage in high-income countries, where complex multimodality treatments are available. In SSA, where treatment for advanced disease is typically not readily available, this trend is accentuated (12, 20). Delays in presentation and diagnosis can be defined as discrete components: patient delay, health-care providers' delay, referral delay, and diagnostic waiting time (**Table 2**) (21). Patient delay in SSA is understandable: due to better treatment for infectious diseases, decreased food insecurity, and an aging population, cancer is a relatively new problem, and many people, especially in remote settings, may have little knowledge of the disease. Even if patients have awareness of cancer, they may risk stigma or financial ruin with diagnosis and treatment. A woman diagnosed with cervical cancer may face abandonment or rejection from her spouse or community (22). Cervical cancer, furthermore, may present with pain bleeding or fistula formation: all issues that may be socially difficult to address in certain contexts. In areas with limited medical care, cancer may often be seen as a "death-sentence," making diagnosis even less worth the social risk. Even in areas where some level of medical insurance is available, it is common for families to face bankruptcy from medical care (23). Surgery and chemotherapy, when available, often require out-of-pocket expenditures, and time lost from work can be devastating for a patient and her family living on subsistence farming or otherwise in or close to poverty (24). Addressing patient delays, therefore, requires advocacy and public awareness, but more importantly requires structuring the health system and social support such that people are not risking insolvency if they seek care for symptoms or signs of cancer.

Qualified medical staff are scarce in SSA (25), and those who are available have been trained to manage infectious and other acute illnesses using limited resources; these practitioners often have received limited training in cancer diagnosis and management. There is the potential for patients to present to a medical facility with cancer and to go undiagnosed, leading to a health-care provider delay. In addition, high clinical demands, limited training about cancer and cancer treatment resources, limited information technology, and either an absence or inaccessibility of specialists may lead to referral delays. As discussed earlier, improvements in information technology may help; certainly, there are many examples of the use of connectivity to bring specialty expertise to remote locations (26). In SSA, there are few trained oncology providers; although relationships with outside specialists may help guide care in tertiary centers, it is less clear how to provide guidance for providers at the primary level.

In cases where cancer is suspected, there may be significant diagnostic waiting time. Diagnostic pathology facilities and staff are scarce, and diagnostic testing may be costly for the patient. Often backlogs of specimens develop (27), and this may be exacerbated by limited information systems, making follow-up for results cumbersome.

Late-stage of cervical cancer at presentation in SSA is, therefore, a highly complex multifactorial issue that both arises from and limits the growth of effective cancer control programs. Addressing the various gaps in care will require a comprehensive and integrated approach to each of these factors, from the effects of poverty on family and social structures to the training and availability of oncology specialists.

TABLE 2 | Delays in diagnosis and treatment for cancer in low resource settings.

Patient delays	• Limited awareness of cancer • Limited expectation of cure or palliation • Fear of financial ruin • Competing demands for time, money • Distance to treatment facility
Provider delays	• Limited training in cancer diagnosis • Competing/more acute clinical demands • Limited expectation of cure or palliation
Referral Delays	• Unclear referral networks • Absent or unavailable specialists • Limited information systems/medical record technology
Diagnostic delays	• Lack of sufficient pathology facilities and personnel • Backlog of specimens • Limited information systems for results reporting and follow-up with patients and providers

HUMAN RESOURCE CAPACITY FOR CERVICAL CANCER SERVICES

Cervical cancer treatment is multimodal. Early stages of cervical cancer can be treated with curative oncologic surgery, whereas advanced or recurrent cervical cancer is best managed with radiation therapy and chemotherapy (28). Current capacity to provide comprehensive women's cancer care in low- and middle-income countries is constrained by shortage in surgeons trained and experienced in oncologic surgery. The challenge to health-care human resources in LMICs encompasses all levels of the health-care work force, and innovative models to increase the capacity and capability of the health-care work force based on each region-specific conditions are fundamental to any national cancer control program. The current state of the surgical workforce in LMICs is in crisis, directly impacting oncologic surgical services.

The WHO estimates that 57 countries globally face a critical shortage of health professionals, and the number of surgeons and anesthesiologists are particularly scarce (29). Thirty-six of these countries are in SSA, where surgeon density maybe as low as 0.5 per 100,000 people (30, 31). Although the number

of health-care work force is only one of the factors impacting surgically treatable conditions, certainly, addressing this dire shortage in surgical work force will advance the neglected area of oncologic global health. An estimated 234.2 million major surgical procedures are performed worldwide each year, 3.5% of the procedures are performed among the poorest one-third of the world's population, pointing to a large unmet surgical need (32). Limited data exist on the number of oncology specialist in SSA, but reflecting on the state of the health work force in LMIC's, it can be assumed that health professionals trained in cancer care are soulfully lacking (33). In a report of radiation services in Nigeria, with a population of 160 million and estimated of 100,000 new cancer cases annually, there were 18 radiation oncologist, 8 medical physicists, and 18 radiation therapist to meet the nations radiation therapy (34, 35). Countries such as Rwanda are developing innovative models to meet the challenges, such as task shifting and partnerships, between high resource and low resource cancer centers (36). Beyond the LMIC's countries, challenges to meet the demands of an aging population on oncology services are anticipated in high-resource countries.

Challenges identified in meeting the demand for essential surgical services in LMIC's include "brain drain," the phenomena of losing trained staff from LMICs to high-income countries (37). World Health Organization (WHO) Global Initiative for Emergency and Essential Surgical Care (GIEESC) was launched in 2005 with the goal to scale access and delivery of surgical care in LMICs. The WHO Global Code of Practice on the International Recruitment of Health Personnel recognizes that a strong health system is critical to economic development of a nation and proposed a framework to address the shortage and migration of health-care work force in LMICs (38). A key component of supporting this WHO Global Code is for high-income countries to meet their own demand for health-care force by increasing training in their own country. In addition, a positive outcome of this code is the increased support of high-income countries by providing technical and monetary assistance for addressing health-care force shortage in LMICs.

ACCESS AND AVAILABILITY OF PALLIATIVE SERVICES AND MEDICINES IN LOW RESOURCE SETTINGS

Globally, lack of access to palliative care services and strong pain medications limit the quality of care patients with advanced or end stage cervical cancer can receive. A significant number of women in low resource settings present with advanced cervical cancer. At the time of presentation, cervical cancer symptoms of bleeding, pain, or urinary dysfunction can be debilitating to the patient (39). Approximately 40% of women diagnosed with cervical cancer in a tertiary center in India were staged III and IV (40). In addition, delay in diagnosis and time to initiation of treatment can be significant, resulting in progression of the disease and associated symptoms. Among cervical cancer patients in Ethiopia, 63% of patients were ultimately stage IIB/IV at the time of evaluation for radiation therapy (41). Patients allocated to palliative care group experienced the most significant delay in care (41). A similar pattern of disease presentation has been documented among underserved women in high resource setting (39). The loss of quality of life attributed to cervical cancer diagnosis is not limited to end stage disease. Patients with early-stage cervical cancer undergoing curative intent treatment experience significant anxiety, depression, sexual dysfunction, and treatment side effects, best managed by a multidisciplinary team approach (42).

Palliative care services can be implemented in every resource setting. Team approach to the palliative care is therapeutic to the patient, family, and health-care provider. A nurse, doctor, and social worker are integral to the team. As resources allow, skills provided by physical therapist, pain and palliative care physicians, and oncologist enhance the quality of palliative care services (43). Palliative cancer care provides improvement in quality of life with reduced health-care utilization when implemented early in the course of cancer management (44, 45). Cervical cancer patients may experience loss of appetite, fatigue, vaginal bleeding/hemorrhage, and pelvic pain that improve with initiation of cancer treatment. As cervical cancer progresses, pain, renal dysfunction, and fistulas can be hallmark of the disease. Pain management utilizing the WHO pain ladder remains the standard with incremental increase from non-narcotic to narcotic drugs (46). Establishing access to morphine is critical to alleviating patients suffering. Few global health priorities supersede the critical shortage in pain management in low resource setting (47). A margin 7% of medical use of opioids occurs in middle- and low-income countries, thus compounding barriers to palliative cervical cancer care (48).

CONCLUSION

In 2016, the means to prevent and treat cervical cancer are well known and widely available; a death from cervical cancer should be understood as a preventable and unnecessary death. The benefit from vaccination programs will not be realized for decades, leaving millions of women at risk. In areas with limited medical resources, programs of primary and secondary prevention can significantly decrease the burden of cervical cancer. Complete and comprehensive cervical cancer control, however, requires a broadly coordinated effort from multiple specialists and facilities. These specialists can only be trained, and such care can only be safely given, in the setting of a strong overall health system. We propose that outreach efforts in cervical cancer control should broaden their targets beyond process-based and disease-based metrics and work to more broadly strengthen the overall health system.

AUTHOR CONTRIBUTIONS

TR and RH wrote this review together in an equal and collaborative fashion.

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ORIGINAL RESEARCH
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A Delay from Diagnosis to Treatment Is Associated with a Decreased Overall Survival for Patients with Endometrial Cancer

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Objectives: While Caucasian women are more likely to be diagnosed with endometrial cancer compared to African-American women, the rate of mortality is higher for African Americans. The cause of this disparity is unknown. We analyzed the time interval from diagnosis of endometrial cancer to treatment as it pertains to race and socioeconomic factors and its possible impact on survival.

Methods: This was a retrospective, single institution chart review using a cancer registry database. We identified 889 patients who were diagnosed with endometrial cancer between January 2005 and June 2012. Clinicopathologic characteristics, demographics, insurance status, distance from medical center, body mass index (BMI), dates of diagnosis, and treatment were obtained from the medical records. Survival and association was determined by a one-way ANOVA test.

Results: At the time of the study, 699 patients were alive and 190 dead. The average age was noted to be 62 years (24–91 years). Stages I–IV disease accounted for 69, 6, 15, and 10%, respectively. White race accounted for 64%, African Americans 24%, and Hispanics 7% of our study population. Majority of patients were privately insured (n = 441) followed by Medicare (n = 375). The mean interval time from diagnosis to treatment was 47.5 days (0–363). A statistically significant difference was noted for this time interval with regard to both race and insurance status: white and African Americans (42.6 vs. 57.3 days, p = 0.048), privately insured and Medicare (38.4 vs. 54.1 days, $p < 0.001$). There was a significant association with increased risk of death with a longer delay (43.3 vs. 64.8 days, $p < 0.001$). No statistically significance was noted for distance from medical center or BMI.

Conclusion: A significant increase in interval of time from diagnosis to treatment of endometrial cancer was seen in both race and insurance status. A longer interval from diagnosis to treatment was associated mortality. The causes of these delays are likely multifactorial but deem further investigation given these data.

Keywords: endometrial cancer, disparities of care, delay in treatment, overall survival, insurance, health, race

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INTRODUCTION

According to National Cancer Institute Surveillance Epidemiology and End Results (SEER), it is estimated that 49,560 women were diagnosed and 8,190 women died from cancer of the uterus in 2013 (1). Endometrial cancer, which accounts for 95% of cancer of the uterine corpus, is the most common gynecologic malignancy (2). Racial differences in the incidence and mortality of endometrial cancer have been noted with higher incidence in Caucasian women compared to African-American women; however, the mortality rate is 85% higher for African-American women (1). The cause of this disparity in mortality rates among Caucasian women and African-American women is thought to be multifactorial. Some studies have shown that African-American women present with poor prognostic features, such as higher grade tumors (Grades II and III), advanced stage (Stages III or IV), and non-endometrioid (Type II) endometrial cancers (3). In one study by Setiawan et al., African Americans and Latinas had higher proportions of high-grade tumors (32.7 and 29.5%, respectively) compared to whites (19.2%) as well as more aggressive histology among African Americans (30.9%) and Latinas (26.2%) compared to whites (8.7%) (4). Other authors have suggested that the type of initial treatment offered to African-American women may have increased the mortality rate with Caucasian women being more likely than African Americans to receive surgery and radiation therapy (5). Another possible explanation is that the molecular phenotypes of endometrial cancers that arise in African-American women tend to have a higher rate of TP53 inactivation and decreased expression of PTEN (6). p53 tumor suppressor gene inactivation has been associated with more adverse histologies and advanced-stage disease, while PTEN mutation, the most frequent molecular alteration observed in endometrial cancer, is associated with a more favorable outcome (6).

Few studies have explored interval between diagnosis of endometrial cancer and the time of treatment. Minority races have been associated with lower socioeconomic status that may limit access to care. The objective of this study is to examine the interval from diagnosis to treatment in relation to race, socioeconomic status, and payor status at a single tertiary care institution.

MATERIALS AND METHODS

Using the Cancer Registry at Rush University Medical Center, we performed a retrospective chart review of patients diagnosed with and/or treated for endometrial cancer from January 1, 2005 to June 1, 2012. The Rush University Medical Center Internal Review Board approved this study. Patients were selected if they were diagnosed with primary cancer involving the uterus and were initially diagnosed and/or treated within the Rush University Medical Center network. Of note, all patients were treated by an attending gynecologic oncologist; there is no house staff clinic present at this institution. Patients whose primary tumor was outside the uterine corpus, who were diagnosed with primary cervical cancer or with uterine sarcomas, were excluded. The following information was extracted from patient charts: age at initial diagnosis, race/ethnicity, body mass index (BMI), insurance status, zip code, date of initial diagnosis, date of initial treatment, type of initial treatment (either surgical, radiation therapy, or chemotherapy), stage, histological type, and vital status (dead or alive) at the time of data collection. Time of diagnosis was determined from the date a pathological specimen was collected (day 0) either by endometrial sampling or from the initial surgery for a non-malignant cause (18.3%). For 20 cases, no treatment date was available and these patients were excluded from further analysis in this study. Date of treatment was determined using the date of patient's surgical staging procedure or for patients who did not undergo surgery the initial date of radiation/chemotherapy treatment; for patients who underwent a hysterectomy for another cause (prior to diagnosis of endometrial cancer), the date of their hysterectomy was used. The interval treatment time was determined by the number of days between the dates of diagnosis and treatment. Distance from Rush University Medical Center was determined using patients' listed home zip code and calculating the distance from that zip code against that of the medical center, this calculation was performed in the standard fashion. Analysis of the data was performed using the analytical software SPSS statistics 21.0; chi square test was used to analysis stage and vital status. For analysis of race and insurance status on treatment delay, we performed ANOVA. To see the relationship of BMI and distance from treatment center and its impact on delay in treatment time, we performed a regression analysis. A multivariate analysis was also performed.

RESULTS

A total of 964 charts were reviewed for this study. Seventy-five charts did not meet inclusion criteria leaving a total of 889 charts for analysis. Demographic information is outlined in **Table 1**. Average age of all patients was 62 years old (range 24–91 years). Of the cases reviewed, 64.3% were white, 24.3% were African-American, 7.0% were Hispanic, 0.7% Asian, and 3.6% were of other or unknown race. In terms of stage of disease at time of diagnoses, Stage I disease accounted for 68.8% (612/889), Stage II 6.4% (57/889), Stage III 14.5% (129/889), and Stage IV 10.1% (90/889); one patient stage was unknown. The majority of the histologic types were grades 1 and 2 endometrioid adenocarcinoma, 31.6% (281/889) and 30.3% (271/889), respectively. Poorly differentiated cancers made up 26.1% (232/889) including a combination of grade 3 endometrioid adenocarcinoma, serous, carcinosarcoma, and leiomyosarcoma. The remaining histologic group was defined in the registry as "cell type not determined" (11.8%). Majority of patients, 49.6% (441/889), had private insurance, followed closely by Medicare 42.1% (374/889) and Medicaid 4.4% (39/889). Average distance from health center was noted to be 23.5 miles (range 0–1,022 miles); for one patient, no information on zip code was available and thus unable to calculate distance. Average BMI of patients in study was 35 kg/m^2; however, information was missing for 145 (16%) patients. At the time of data collection, 699 (78.6%) patients were alive and 190 (21.4%) were dead. As it would be expected, vital status varied between stages with majority of Stage I patient being alive at the time of analysis of this study. For stage I disease, 89.9% (550) patients were alive vs. 73.7% for stage II, 59.7% for stage

TABLE 1 | Demographic of patients.

Demographics	Number of patients
Race	
White	572 (64.3%)
African-American	216 (24.3%)
Hispanic	62 (7%)
Asian	7 (0.7%)
Other/unknown	32 (3.6%)
Stage of disease	
Stage I	612 (68.8%)
Stage II	57 (6.4%)
Stage III	129 (14.5%)
Stage IV	90 (10.1%)
Stage unknown	1 (0.1%)
Insurance	
Private	441 (49/6%)
Medicaid	39 (4.4%)
Medicare	374 (42.1%)
Self-pay	16 (1.8%)
Other/unknown	18 (2%)
Body mass index	
Mean	34.6 mg/m^2
Distance from hospital	
Mean	23.5 miles

TABLE 2 | Mean treatment time (days) in relationship to race, insurance status, and vital status.

Demographics	Mean treatment time (days)	*p* value
Race		
White	42.6	$p = 0.048$
African-American	57.3	
Hispanic	58.2	
Asian	28.6	
Other	54	
Total	47.6	
Insurance		
Private	38.4	$p < 0.001$
Medicaid	78.1	
Medicare	54.1	
Self-pay	53.5	
Other/unknown	63.6	
Total	47.9	
Vital status		
Alive	43.3	$p < 0.001$
Dead	64.8	
Total	47.9	

TABLE 3 | Mean treatment time in relation to insurance per stage.

Insurance	Stage I	Stage II	Stage III	Stage IV
	Mean treatment interval (days)			
Private	39.0	50.8	34.4	37.3
Medicaid	53.1	275.0	40.4	179.0
Medicare	53.6	65.4	48.3	38.9
Other/unknown	109.0	46.0	40.0	3.5
Total	46.4	66.3	42.8	47.0
	$p = 0.01$	$p = 0.06$	$p = 0.489$	$p = 0.03$

III, and only 33.3% for stage IV. It is important to note that the cause of death was unknown and deaths include all causes for mortality. The mean interval from diagnosis to initial treatment was 47.9 days and ranged from 0 to 363 days. This interval when compared to survival and was noted to be statistically significant with patients who were still alive having a mean treatment interval of 43.35 days compared to those who were dead having a mean interval of 64.84 days ($p < 0.001$).

In terms of insurance status, the longest treatment interval was noted in the Medicaid group with a mean treatment delay of 78 days followed by Medicare with 54 days (**Table 2**). The shortest interval was noted within the private insurance group with 38.4 days and was found to be clinically significant ($p < 0.001$). Even when stratified by stage of disease, Medicaid and Medicare participants continued to have longer treatment intervals (**Table 3**).

Analysis of stage and insurance status as it pertains to survival demonstrated similar results (**Table 4**). For Stage I disease, 97.1% of patients with private insurance were alive compared to 95.8% in Medicaid and 77.1% for Medicare; 2.9% of private insurance patients were dead compared to 4.2 and 22.3%, respectively, for Medicaid and Medicare groups. Similar results were seen in Stage III disease with alive status for 72.7, 62.5, and 53.4% in private, Medicaid, and Medicare groups, respectively. In Stages II and IV, the private and Medicare patients had similar results in terms of survival. Of note, data are only available for all cause mortality.

Racial differences were noted in time to treatment intervals. Caucasian women had a shorter mean treatment interval (42.6 days) as compared to African-American women (57.3 days) and Hispanics (58.2 days). The shortest treatment interval time was noted in Asian patients with 28.6 days. These differences were found to be statistically significant between groups ($p = 0.048$) (**Table 2**).

Of note, a multivariate analysis was performed but was felt not to show any further informative statistics. The analysis shows that three effects remain in the multiple regression analysis – a dummy code for private insurance, a dummy code for Medicare, and a dummy code for African-American race. The two insurance codes are associated with shorter intervals, being African-American is associated with longer intervals. The interval variable was transformed to better meet assumptions of normal residuals (a square root transformation). These results are in rough agreement with the univariate results, and much of the difference may be accountable to collinearity between these measures (e.g., African-American and/or Hispanic race/ethnicity with use of Medicaid).

Distance from the health center and BMI were not found to be statistically significant for a time to treatment interval.

DISCUSSION

In our study, patients with endometrial cancer without private insurance experienced significantly longer interval time to treatment compared to patients with private insurance. In addition, we

TABLE 4 | Stage and insurance status as it pertains to survival.

Insurance	Stage I		Stage II		Stage III		Stage IV	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Medicaid	23 (95.8%)	1 (4.2%)	2 (100%)	0 (0%)	5 (62.5%)	5 (37.5%)	0 (0%)	5 (100%)
Medicare	171 (77.7%)	49 (22.3%)	21 (70%)	9 (30%)	39 (53.4%)	34 (46.6%)	17 (34%)	33 (66%)
No insurance	14 (93.3%)	1 (6.7%)					1 (100%)	0 (0%)
Private	331 (97.1%)	10 (2.9%)	18 (75%)	6 (25%)	32 (72.7%)	12 (27.3%)	11 (34.4%)	21 (65.6%)
Other/unknown	11 (91.7%)	1 (8.3%)	1 (100%)	0 (0%)	0 (0%)	3 (100%)	1 (50%)	1 (50%)
Total	550 (89.9%)	62 (10.1%)	42 (73.7%)	15 (26.3)	77 (59.7%)	52 (40.3%)	30 (33.3%)	60 (66.7%)

also found increased time to treatment interval to be associated with a decreased survival. Race, BMI, and distance to treatment center were all not significantly correlated with interval treatment time. This confirms our hypothesis that socioeconomic status appears to negatively impact survival. This study supports the findings of Fedewa et al., who also found a significantly improved survival in patients with private insurance (7). The authors speculated that patients with public insurance are less likely to be managed by a gynecologic oncologist. In contrast, a gynecologic oncologist treated all the patients in our sample. Our finding of increased time to treatment interval adds another possible explanation for both Fedewa's findings and ours. Our results mirror the greater body of literature regarding insurance disparities in cancer mortality between the underinsured and the privately insured, especially with regards to breast cancer, which has partially been attributed to decreased cancer surveillance in this population (8, 9). Interestingly, in the breast cancer literature, this disparity in surveillance persisted even in high income adults without insurance (10). Our findings did correlate with the overall body of literature on insurance status and cancer disparities and wait time (7, 11–14).

Medicaid covers a disproportionately high percentage of minorities, specifically black patients, although whites make up a higher percentage of total Medicaid beneficiaries (12). Furthermore, many studies have found race to be a significant predictor of poor outcomes despite equal insurance status and providers (15). These studies did not assess wait time, and thus, perhaps race had an effect there. Increased interval wait time is of particular concern because patients with Medicaid and without insurance are more likely to present at diagnosis with more advanced disease, and thus, this population requires timely treatment (12). A perceived inability to afford medical care could be a major contributor to advanced presentation in the uninsured (8). It is unclear, however, in our study if insurance inequality within races accounted for significance of delay in treatment and decrease survival with racial groups or if race itself was a confounder in the delay in treatment within insurance groups.

Elit et al. reported that a delay in treatment was related to a decrease in overall survival for patients with uterine cancer in a Canadian population (11). In this study, they demonstrated that a wait time of more than 12 weeks had a significantly worse survival than patients with a wait time of 2.1–6 weeks [HR 0.79 (95% CI 0.7–0.91)] and wait time 6–12 weeks [HR 0.8 (95% CI 0.71–0.91)]. They postulated that the delay in treatment may be due to centralization of uterine cancer surgical care to gynecologic oncologist at teaching hospitals and less availability of operating room times. They also state that this increase in wait times to surgery may counteract any benefit seen as a result of additional expertise from gynecologic oncology regarding surgical staging. Our study demonstrates a similar correlation between survival and time to treatment. However, all mean delay in treatment time in our study was <12 weeks (84 days), with the longest mean delay in treatment time seen being 78.1 days (11 weeks) in the Medicaid group. Our study differs from the Elit study in that it was done in a single teaching institution with patients who receive surgical care from only gynecologic oncologists; therefore, our delay in treatment cannot be justified by less availability to operating room times or delay in referral time alone. Our study was also done in a different health care system where different insurance statuses exist and not the national health care system in Canada.

There were some limitations to our study. Our population was geographically limited to one tertiary care institution in Chicago. Our sample was also not nationally representative due to its inclusion of patients seeking care at a tertiary care institution. Additionally, we could not account for patient factors, including adherence to treatment recommendations, provider preference, or comorbidities, which could have limited a definitive surgical option. We also did not account for cancer histology, which is a known prognostic indicator. Information on cause of death was not available; hence, cancer-specific deaths could not be identified.

Future studies focusing on time to treatment interval, specifically at what time to treatment interval is survival affected, are needed. Further study of the relationship of race, socioeconomic status, and time to treatment will aid providers in optimizing care in an era of increasing restriction of resources.

In conclusion, we found a significant decrease in survival with longer delay between diagnosis and treatment. In addition, this delay was directly associated with insurance status and race in our population of endometrial cancer patients treated at a large, tertiary care institution.

AUTHOR CONTRIBUTIONS

SD and DD wrote the manuscript, conducted the chart abstraction, and managed the project; AM and DD abstracted charts and helped write the manuscript; LF performed statistical analysis and consulting and edited the manuscript; BR, EY, JR, and AG edited the manuscript.

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REVIEW
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The Application and Outcome of Standard of Care Treatment in Elderly Women with Ovarian Cancer: A Literature Review over the Last 10 Years

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The rising number and increasing longevity of the elderly population calls for improvements and potentially a more personalized approach to the treatment of cancer in this group. Elderly patients frequently present with a number of comorbidities, complicating surgery and chemotherapy tolerability. In the case of ovarian cancer, elderly women present with more advanced disease, making the issue of providing adequate treatment without significant morbidity critical. Most studies support the application of standard of care treatment to elderly women with ovarian cancer, yet it seems to be offered less frequently in the elderly. The objective of this review is to examine the application and outcome of standard of care treatment in elderly women with ovarian cancer. The aim is to ultimately improve the approach to treatment in this group.

Keywords: ovarian cancer, elderly, age, treatment, care, chemotherapy, outcomes

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INTRODUCTION

The elderly population, defined as 65 years and older, is expected to reach 80 million in the United States over the next two decades (1). Ovarian cancer is common among older women, with estimates suggesting that half of the women living with ovarian cancer are over 65 years old (2, 3). Over two-thirds of new cases are in women over 55 years old, with the median age at diagnosis being 63 (4). While some cancers, such as breast, generally become more indolent with increasing age, the reverse is seen in ovarian cancer (5), resulting in increasing complexity of treatment. Many studies continue to investigate why survival in the elderly differs so much from that of younger cancer patients. Freyer and colleagues in a 2013 review proposed various theories to explain these higher death rates. They proposed that this could be due to more aggressive cancer with advanced age, inherent resistance to chemotherapy, multiple concurrent medical problems, and physician and healthcare biases toward the elderly that lead to inadequate surgery, less than optimal chemotherapy, and poor enrollment in clinical trials (6).

Both treatment administered and outcomes observed in the elderly ovarian cancer population have differed from their younger counterparts. For example, a Surveillance, Epidemiology and End Results (SEER) data analysis of almost 10,000 elderly women (>65 years) between 1991

and 2007 found that over the past couple of decades, primary surgery had significantly decreased from 63.2 to 49.5%, while primary chemotherapy doubled from 19.7 to 31.8% (7), as later described in **Figure 3**. In addition, a German study found that ovarian cancer patients aged 15–54 had a strong continuous trend of improving survival, as did patients aged 55–74, yet elderly patients >75 years saw no improvement in survival during the 1979–2003 study period. As the age gradient substantially widened over time, reaching a relative survival difference of 50% between the two groups, it was the strongest age gradient observed among 15 examined cancers after a 20-year analysis **Figure 1** (8). Both of these examples illustrate how treatment and outcomes continue to differ from women in younger age groups. Acknowledging these differences as well as the deficits in the literature is the objective of this review. Once these deficits are better defined, research can be initiated.

METHODS

A PubMed literature review was conducted using various combinations of the following search terms: "ovarian cancer," "elderly," "gynecologic(al) cancer(s)," "treatment," and "care." The articles were screened for original articles and reviews published between 2005 and 2015. Only English articles were reviewed. Seventy-six articles met these inclusion criteria.

Baseline Variables Predictive of Outcome

Several studies have examined the diagnosis of ovarian cancer in elderly patients. Ovarian cancer is a disease of the elderly as the average age of diagnosis is 63. For example, in a large study by Poynter et al., older age at baseline was the only significantly associated risk factor for developing ovarian cancer in elderly women (9). Although ovarian cancer is typically diagnosed at an advanced stage, an even larger proportion (80%) of elderly women present with Stages III–IV disease (6). Analysis of SEER data from 1988 to 2001 found that in over 28,000 women, younger women were two to three times more likely to be diagnosed with early-stage (I–II) disease than their elderly counterparts (10). Other studies have shown similar results (11). A separate SEER analysis of 4,000 advanced ovarian cancer patients diagnosed between 1992 and 1999 illustrates the consequence of elderly women being diagnosed with higher stages of disease, as survival is significantly associated with stage (12). These SEER data are also described in **Figure 3**. When comparing the elderly (65–74 years) with the very elderly (≥75 years), increased age was also associated with advanced stage and higher grade (13). While other studies may not support this trend (10, 11, 14–18), the majority suggest the importance of age as a baseline that affects treatment outcomes.

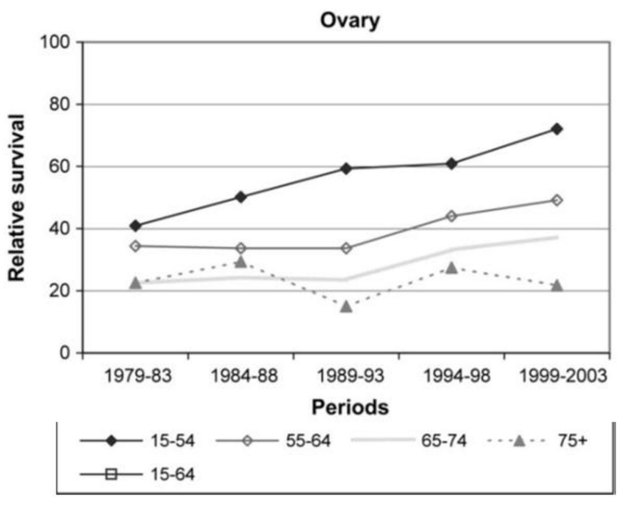

FIGURE 1 | Relative survival rates by age in ovarian cancer patients over 20-year study period (8).

Comorbidities are common in all elderly women, regardless of cancer status, but women with ovarian cancer in general had a much higher incidence of comorbidities than cancer-free women. Because of this, understanding the role of comorbid conditions in elderly ovarian cancer treatment and outcomes will be crucial for optimal personalized treatment in this group (19). The complexity of ovarian cancer treatment, including surgery and chemotherapy, may limit the ability of elderly women with comorbidities to tolerate radical surgery and toxic therapeutic regimens.

Because of this, having a prognostic tool to predict the impact of covariates on overall survival (OS) would be of value in this complex patient population. The GINECO study used three separate phase II trials to develop a new prognostic tool, called the geriatric vulnerability score (GVS), which can be utilized to predict survival in elderly (≥70 years) patients with advanced ovarian cancer. The best-fitting model delivered a survival score equal to exp(0.327 × GVS), where the GVS is the sum of the following of a scale of 0–5 (each with a value of one): albumin <35 g/l; activities of daily living (ADL) score <6; instrumental activities of daily living (IADL) score <25; lymphopenia <1 G/l; and Hospital Anxiety and Depression Scale (HADS) >14. The GVS was significantly differentiated between two groups: those with a score <3 having an 82.1% chemotherapy completion rate, while those over 3 only observed 65.5% completion rates. Women with a GVS ≥3 were over twice as likely to have grade ≥3 non-hematological toxicities, twice as likely to have serious adverse event, and experienced more unplanned hospital admissions (20).

Primary Surgical Treatment

Initial therapy for ovarian cancer following diagnosis includes a combination of surgery and chemotherapy. Patients with the best prognosis include those who undergo surgical cytoreduction to no gross disease and receive platinum and taxane-based chemotherapy, with some receiving treatment through an intraperitoneal infusion.

Many recent studies have examined how primary treatment in the elderly compares to younger women with ovarian cancer (**Figure 2**). For example, in an analysis of over 10,000 patients with ovarian cancer, the elderly were less likely to receive comprehensive surgical care, as defined by International Classification of Disease, 9th Revision (ICD-9) diagnosis and procedure

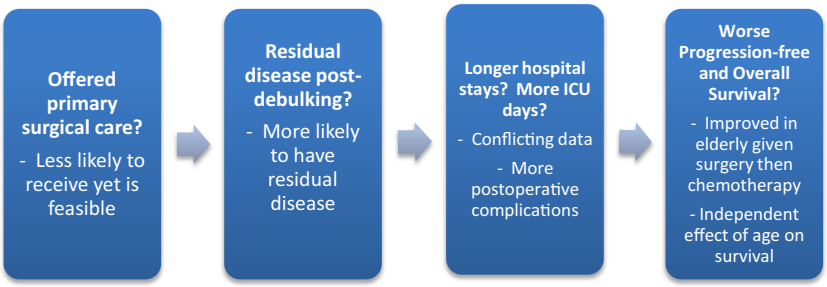

FIGURE 2 | **Primary surgical treatment for elderly women with ovarian cancer**.

Authors	Years	SEER Sample	Key Findings
Wright, et al	1991-2007	9,565 women >65 years with stage II-IV EOC	• Use of primary surgery decreased • Use of primary chemotherapy increased • Primary treatment had minimal effect on overall survival
Chan, et al	1988-2001	28,166 women (all ages) with EOC	• Younger women more likely to be diagnosed with early-stage (stage I-II) EOC and had survival advantage compared to elderly
Janda, et al	1992-1999	3,994 women ≥65 years with advanced (stage III-IV) OC	• More advanced stage and higher age were associated with worse survival • Receiving both surgery and chemotherapy improved survival compared to either alone
Nurgalieva, et al	1991-2002	9,361 women ≥65 years with OC	• Non-platinum chemotherapy regimens increased hospitalization rates and toxicities • Age and comorbidities predicted hospitalization stay • Peripheral neuropathy increased with taxane and platinum-taxane chemotherapy when compared to no chemo, with no. of cycles increasing risk

FIGURE 3 | **Summary of Selected Surveillance, Epidemiology and End Results (SEER) data (7, 10, 12, 54, 55)**.

codes (21). Similarly, an analysis of over 23,000 advanced ovarian cancer patients in the Netherlands found that about one-third of elderly patients received no therapy (22). Other studies support the trend in elderly women receiving suboptimal treatment (11, 13, 15, 18, 22–27). A 961-patient study even found elderly age to be independently predictive of not receiving cytoreductive surgery and standard combination chemotherapy (24). A SEER analysis of 28,165 women with ovarian cancer found that younger women were significantly more likely to undergo primary surgical procedures than the elderly (10) (**Figure 3**). This was supported by other studies as well (23). Although some studies did not confirm this difference in treatment based on age (16, 17, 28, 29), the bulk of the data demonstrates a disproportionate number of elderly women receiving suboptimal treatment.

Interestingly, most studies do indicate that optimal treatment in the elderly is feasible and acceptable, with similar outcomes observed between age groups (15, 16, 23, 24, 27, 30–32). After adjusting for age and stage of ovarian cancer, optimal treatment had a significant impact on survival, suggesting that focus should be placed on optimal treatment for patients of all ages with ovarian cancer (32). When comparing the elderly and very elderly, multiple studies found no significant difference in perioperative complications, with progression-free survival (PFS) and OS being similar (16, 29, 33).

While surgery may be feasible, the residual disease volume post-debulking surgery has been found to be higher for elderly patients, which significantly impacts PFS and OS (11, 16, 27, 29, 34–36). A Mayo Clinic study of women with advanced ovarian cancer found that residual disease had a larger and more significant impact in the very elderly, with a fourfold decrease in median survival when compared to younger patients (37). With perhaps a higher rate of residual disease left at the time of surgery and a greater impact on outcomes, such as survival, some question the use of this aggressive treatment in this population.(23, 38), However, elderly women who do undergo primary debulking surgery have better disease-free survival and OS than those who had interval debulking (33). Yet, the elderly have also been found to have a statistically higher rate of large bowel resection than their younger counterparts (15). Hospitalization data are conflicting, with some studies showing days of hospitalization or ICU stay to be longer in the elderly (28, 33), while others contradict this (23). Discrepancies are likely influenced by selection bias. Further investigation with larger sample sizes is warranted.

In a Maryland state-wide study, it was observed that university-type hospitals were significantly less likely to have admitted the elderly patients when compared to younger patients, with the majority of elderly admissions being for surgeries under emergency conditions. Interestingly, older women with ovarian cancer were also significantly more likely to have a different operating surgeon than the attending physician of record. The elderly also had a higher adjusted cost of hospital-related care with more billable procedures, and a 30-day mortality rate 2.3 times higher than that of younger patients. When analyzing surgeon-type, elderly patients of high-volume surgeons (≥10 cases/year) billed twice as manyprocedures, had nearly a tripled cost of hospital care, and twice as many comorbidities as younger patients. Interestingly, 62% of elderly women saw high-volume surgeons even though these surgeons only represented 3.4% of the surgeons in the study. Similarly, while only 18.4% of hospitals in the study were considered high-volume (≥20 cases/year), the majority (60%) of elderly women were treated at these hospitals and had more procedures billed and more comorbidities (28).

Earle et al. examined the impact of surgeon specialty on outcome for 3,067 elderly ovarian cancer patients and found that those treated by gynecologic oncologists had superior outcomes to those treated by general gynecologists or general surgeons. Advanced-stage disease patients were more likely to undergo debulking if the surgery was performed by a gynecologic oncologist as opposed to a general gynecologist or general surgeon. Survival among patients operated on by gynecologic oncologists or general gynecologists was far better than that among patients operated on by general surgeons (39). This is supported by another study, which found surgeries performed by non-gynecologic oncologists observed the risk for mortality to double (31).

A study of 2,087 women with ovarian cancer from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database found there to be a high risk of perioperative mortality and morbidity within 30 days in elderly patients with ovarian cancer (40), as supported by other data outcomes on high risk women (12, 38). The elderly were also more likely to develop pulmonary and septic complications, and were nine times more likely to die and 70% more likely to develop complications within 30 days of surgery (40). Similarly, Moore et al. demonstrated elderly patients may not tolerate surgery and combination chemotherapy, paying a high price in post-operative complications and death (41).

Different types of procedures have been examined in the elderly as well. One study examined the effects of interval debulking after neoadjuvant chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) in the elderly with advanced ovarian cancer as an alternative to initial complex surgery. This study found that the elderly group did not receive benefit from the interval cytoreduction with HIPEC treatment and instead experienced postoperative morbidity, with the most common being grade 4 hemoperitoneum and grade 3 intra-abdominal fluid collection in 22.2% of women (17). Another study that evaluated the feasibility and safety of extensive upper abdominal surgery (EUAS) in elderly patients with advanced ovarian cancer found no significant difference to that of younger patients, and concluded that EUAS procedures are feasible in this elderly population (35).

The impact of nutritional status on survival outcomes was examined by Alphs et al., who found that poor nutrition was associated with poor survival outcomes. Albumin levels ≥3.7 g/dl were associated with a 40% reduction in risk of mortality in the elderly population and, overall, elderly women had a 2.6-fold greater risk of mortality when compared with younger women (31).

Most conflicting, however, was univariate and multivariate analysis on the impact of age on treatment outcomes. Multiple studies showed increased age was independently associated with a significant, negative impact on survival (10, 12, 18, 22, 25, 31, 34, 40, 42, 43), while others show no significant, age-related impact on survival (15, 16, 23, 24, 26, 27, 30–32). Some of these studies include disease-free survival outcomes, which may help explain the conflicting data. The Centers for Disease Control and Prevention (CDC)-funded cancer registries examined the impact of age on survival in 2,367 women with ovarian cancer. Survival rates were lower in the oldest groups, especially in those with advanced disease. For example, 3-year survival in patients with stage IV was only 13% in the elderly compared to 50% in women under 35 years old. The adjusted risk of death doubled from 40% in younger women to 80% in the elderly. The CDC confirmed the independent adverse effect of age on survival in this patient population (25).

Significant survival advantages were seen in the younger patients with early-stage disease, as young age was an independent prognostic factor for increased survival. Advanced-stage disease had poorer survival in the elderly (10). As defined above, optimal treatment includes cytoreductive surgery with combination chemotherapy, and a 1992–1999 SEER analysis of almost 4,000 advanced ovarian cancer patients supports this treatment with the observation that elderly patients who received both surgery and chemotherapy showed significantly improved survival compared to either treatment alone (12) (**Figure 3**). However, it is worth noting that these findings may be influenced by selection bias. A retrospective analysis also evaluated each treatment individually

and found that primary surgery was more beneficial than primary chemotherapy on survival outcomes (30, 44).

While NACT in elderly women only demonstrated a trend to improved PFS and no improvement in OS, NACT benefits were clearly demonstrated in a 62-patient study. Nearly a threefold increase in the rate of cytoreduction to no macroscopic disease was seen in women who received NACT when compared to those without. The NACT patients also had significantly less blood loss during surgery and required fewer small bowel resections (45).

In a study of almost 600 women with ovarian cancer, elderly women had a much poorer prognosis, possibly related to the significantly higher incidence of suboptimal treatment in this group. While no significant difference in PFS was observed between the two groups, median OS was over twice as long in the younger population (18). With no difference in PFS observed, the difference in OS may instead be attributed to comorbidities preventing second- or third-line chemotherapy treatment as opposed to strictly the result of suboptimal treatment.

An analysis of the OVCAD consortium, including 275 patients with ovarian cancer, found that the postoperative 60-day mortality rate was 5.25-fold higher in the elderly than in younger patients. The elderly also had a significantly worse median PFS and OS. Interestingly, age itself was not a prognostic factor for PFS in multivariate analysis, reiterating the significant role of optimal treatment on survival outcomes in the elderly (26). These results also demonstrate the confounding impact of age, grade, and stage on PFS outcomes.

Adjuvant Chemotherapy

The indications for using of standard adjuvant chemotherapy in the elderly are inconsistent. As noted above, whether age is an independent prognostic factor for survival is unclear. Some studies show increasing age to be significantly associated with poorer survival outcomes (37, 43, 46–48), while others demonstrate no significant differences in survival outcome among the elderly (11, 16, 49–51). Not receiving adjuvant chemotherapy was found to negatively impact OS (34), and having more than three chemotherapy cycles was found to be an independent prognostic factor for OS in the elderly (18). When comparing the elderly (70–75 years old) to the very elderly (>75 years old), there was no difference in toxicity, dose reduction, and treatment delay or discontinuation (16). Even given these data, suboptimal chemotherapy administration in the elderly continues to be observed in most studies (13, 24, 27, 50–53). However, the impact of selection bias on these data cannot be underestimated.

While it is apparent the elderly do not receive equivalent standard of care chemotherapy treatment as their younger peers, some studies suggest that the elderly do not tolerate this regimen (41, 43). In one study of 109 patients, elderly women were less likely to complete all planned cycles of intraperitoneal chemotherapy when compared to a younger cohort. In addition, more intravenous chemotherapy was completed by elderly women who were optimally debulked as compared to those with residual disease (49). Another study found that the very elderly were prescribed combination chemotherapy much less frequently than younger patients, had significant differences in delayed initiation of chemotherapy, and six-cycle completion rate was only half that of the younger group (47, 52). The very elderly also had a 30-day mortality rate fourfold that of their elderly counterparts (46).

Common chemotherapy toxicities in the elderly across multiple studies included: grade 3–4 hematologic and gastrointestinal toxicities (16) and grade 3–4 neutropenia (51), with the use of paclitaxel as an independent prognostic factor for worse survival and increasing toxicities (48). While these trends in toxicity among the elderly are worth noting, the small study sizes may be misleading, as many studies show no significant difference in toxicities between age groups (11, 14, 50, 52).

A SEER analysis from 1991 to 2002 found that non-platinum chemotherapeutic regimens (administered in 18% of women) had higher rates of hospitalizations for gastrointestinal and hematologic conditions or infections compared to platinum-based or platinum–taxane combination regimens in 9,361 elderly women with ovarian cancer. While age was a significant predictor for hospitalization due to infection and cardiovascular diseases, older age did not predict gastrointestinal and hematologic toxicities (54). A separate, larger SEER analysis among over 9,000 women with ovarian cancer during the same 1991–2002 period found taxane therapy to double, and platinum–taxane therapy to triple, the risk of peripheral neuropathy when compared to elderly not receiving chemotherapy treatment. Risk was greater with an increasing number of cycles. Monitoring of peripheral neuropathy in this patient population receiving these chemotherapy regimens is warranted (55). The results of both SEER analyses are summarized in **Figure 3**.

A National Cancer Institute Common Toxicity Criteria (NCI CTC) analysis found that younger women received standard-dose chemotherapy nearly three times as often as the elderly (52). One study examined dose-delay in chemotherapy among elderly ovarian cancer patients and found that it was associated with a decrease in OS, even after controlling for age, stage, residual disease, and number of chemotherapy cycles received. This is of significance, as elderly patients frequently require chemotherapy dose reductions and delays in administration, and multivariate analysis suggested that dose-delays are an independent factor associated with decreased OS (56). However, a retrospective, multi-center analysis demonstrated no difference in survival outcomes between the reduced-dose and standard-dose elderly patients, and with the elderly more commonly on reduced-dose regimens, the authors suggested that carboplatin/paclitaxel may be better tolerated and equally as effective in this elderly population (51).

The 779-patient AGO OVAR-3 phase III study evaluated first-line platinum/paclitaxel in ovarian cancer patients, and found that ECOG performance status 2, measurable disease, and early discontinuation of therapy were much more common in the elderly (14). Another analysis of the same study found that young patients achieved no residual tumor after surgery more often and had significantly better survival when compared to the elderly, even when comparing those that were completely debulked across ages (43).

In a study of over 450 women with ovarian cancer, elderly women were more likely to receive carboplatin monotherapy, while younger patients were more likely to receive

paclitaxel-containing chemotherapy. Only about half of the elderly patients received 100% paclitaxel relative dose intensity (RDI), while over two-thirds of the younger patients did. While the median OS of younger patients was significantly longer than that of older patients, PFS did not differ significantly between the two age groups (11). A similar study examined platinum–taxane chemotherapy outcomes in the elderly, and with only half of elderly women getting platinum-based chemotherapy, an examination of treatment outcomes is warranted. The study found that age was not independently associated with outcomes in this 292-patient study of women with advanced ovarian cancer (50).

Finally, when examining treatment by physician type, elderly women seen by gynecologic oncologists were significantly more likely to receive adjuvant chemotherapy than those seen by general gynecologists and general surgeons (39).

Recurrent Ovarian Cancer

In patients with advanced disease, nearly 85% will relapse even after adequate initial treatment (57). In these cases, treatment usually involves follow-up chemotherapy, avoiding surgery and surgery-related morbidities. To address this problem, a small study examined cytoreductive surgery and HIPEC in elderly women (57). No patients died immediately after surgery or from HIPEC-related complications. Median hospital stay was 13 days, with 20% of patients presenting G3–G4 complications. Median OS was 35 months, with median disease-free survival of 15.6 months. When the extent of carcinomatosis was assessed using the peritoneal cancer index (PCI), there were significant differences observed. For example, all patients with PCI >13 relapsed during the 2-year follow-up, and the authors concluded that in patients with PCI < 13, maximal cytoreductive surgery associated with HIPEC may improve the disease-free survival of elderly, recurrent ovarian cancer (57). Further studies with HIPEC are necessary, as it is a controversial treatment option with conflicting data.

The CALYPSO sub-study compared carboplatin–pegylated liposomal doxorubicin (C–PLD) with carboplatin–paclitaxel (C–P) in patients with late-relapsing recurrent ovarian cancer in elderly versus younger patients. While the elderly women had significantly fewer ≥Grade 2 allergic reactions, they had more ≥Grade 2 sensory neuropathy. Myelosuppression and completion rates of treatment did not differ between groups. Within the elderly patients, C–P was associated with more ≥Grade 2 alopecia, sensory neuropathy, arthralgia/myalgia, and severe leukopenia plus febrile neutropenia, while C–PLD was associated with more ≥Grade 2 hand–foot syndrome, providing a better therapeutic index with less toxicity in this elderly population (58).

The SOCRATES study assessed the pattern of care in patients with recurrent platinum-sensitive ovarian cancer at 37 Italian sites. Among the 493 patients analyzed, the recurrence-free interval (RFI), PS, and number of disease sites were similar between the elderly and younger women, but fewer elderly patients underwent secondary cytoreduction. The mean number of chemotherapy lines received for recurrence was similar, with the elderly patients more frequently receiving single-agent platinum at second line. The response rate to second-line chemotherapy was higher in younger patients, demonstrating a significant increase in median OS from recurrence. At multivariate analysis, age at recurrence was independently associated with survival, and the authors conclude that age is an unfavorable factor independently associated with a worse prognosis (59).

Quality of Life

Quality of life (QoL) data available for review are extremely limited. The phase III AGO OVAR-3 trial evaluated QoL in elderly ovarian cancer patients using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire, and found no significant differences between the elderly and younger subgroups (14).

Also relating to QoL, in an analysis of over 8,000 elderly women with ovarian cancer, nearly 20% of women developed bowel obstruction after cancer diagnosis, of which all non-adhesion-related obstructions were considered pre-terminal events regardless of treatment type. Because of this, the authors suggest that patient comfort, not survival, should be the primary focus in this patient group (60).

CONCLUSION

The data available for analysis regarding treatment outcomes in elderly ovarian cancer patients are conflicting; however, some general trends can be noted. As elderly women present more often with advanced stage (III–IV) disease, having prognostic tools to optimize treatment will be crucial in future care in this population. Most studies focused on the primary treatment for elderly women with ovarian cancer, with many suggesting that the aim should be focused on delivering optimal treatment, regardless of age. When providing suboptimal treatment to the elderly because of their age, numerous studies demonstrate suboptimal results with significantly lower survival outcomes. It would be important to develop tools to determine which elderly patients can actually tolerate aggressive therapy. While there is no consensus on whether age alone is an independent prognostic factor in this patient population, there seems to be consistency that optimal treatment (cytoreductive surgery with no residual disease remaining and combination chemotherapy) warrants further investigation in this population. To improve consistency among data, future studies should aim to determine an appropriate age defining "elderly."

With a growing elderly population expected to double over the next couple of decades, further investigation into how to best treat this population is essential in optimizing future healthcare delivery to elderly women with ovarian cancer.

AUTHOR CONTRIBUTIONS

GF, ST, and DC all provided writing assistance and general support to SG in the preparation of the tables, figures, and drafting of the manuscript. All authors read and approved the final manuscript.

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REVIEW
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Fertility Preservation: A Key Survivorship Issue for Young Women with Cancer

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Fertility preservation in the young cancer survivor is recognized as a key survivorship issue by the American Society of Clinical Oncology and the American Society of Reproductive Medicine. Thus, health-care providers should inform women about the effects of cancer therapy on fertility and should discuss the different fertility preservation options available. It is also recommended to refer women expeditiously to a fertility specialist in order to improve counseling. Women's age, diagnosis, presence of male partner, time available, and preferences regarding use of donor sperm influence the selection of the appropriate fertility preservation option. Embryo and oocyte cryopreservation are the standard techniques used while ovarian tissue cryopreservation is new, yet promising. Despite the importance of fertility preservation for cancer survivors' quality of life, there are still communication and financial barriers faced by women who wish to pursue fertility preservation.

Keywords: fertility preservation, cancer survivorship, cryopreservation, fertility sparing surgery, counseling

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INTRODUCTION

Cancer in females of reproductive age accounts for nearly 10% of new cancer diagnoses, impacting 87 per 100,000 women annually (1). The most common cancers presenting in this cohort include breast, thyroid, cervical, uterine, melanoma, lymphoma, and colon cancer (**Figure 1**) (1). Over the past four decades, advances in surgery and adjuvant therapy have led to improved 5-year survival rates for breast (85.5%), endometrial (91%), cervical (83.2%), and ovarian cancers (79.5%) (2). These improved outcomes have resulted in an increased number of cancer survivors in the United States, rising from 3 million to nearly 14 million in the past 40 years (1). While improved treatments have increased survivorship rates in women with cancer, many therapies are harmful to the ovaries and put women at risk of premature ovarian failure and infertility. This is significant as nearly 25% of today's cancer survivors are reproductive-aged woman who may wish to have children. With approximately half of women in the United States delaying childbearing into their thirties, the need for fertility preservation treatment has never been greater (3).

Fertility is a major concern for women with newly diagnosed cancer (4). A recent survey of young women undergoing treatment reported that 51.7% felt that having children was "most important" in their life (5). Potential fertility loss is related to emotional distress, fear, anxiety, and even moderate or severe depression. These symptoms, especially depression, are more commonly

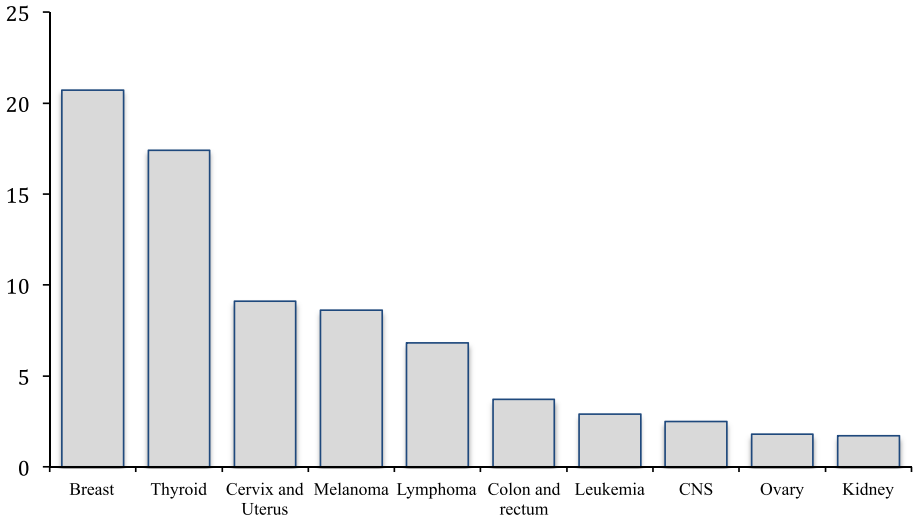

FIGURE 1 | **Most common cancer in women 15–39 years old**. *Incidence rates per 100,000 (1).

observed in young, non-white, and nulliparous women (6, 7). A number of studies suggest the risk of infertility with cancer therapy may adversely impact treatment decisions (8, 9). One survey evaluating women with early-stage breast cancer demonstrated that 0.6% of women elected not to receive chemotherapy due to fertility risks, whereas 1.9% chose one chemotherapy regimen over another to reduce impact on fertility. Similarly, 15.5% of women reported rejecting or shortening endocrine therapy for fertility reasons (9).

In recent years, an increasing number of female patients with cancer have presented to fertility specialists to discuss ways to preserve fertility prior to treatment to allow them to become biological mothers as cancer survivors (10). The most commonly utilized fertility preservation treatments include embryo, oocyte, and ovarian tissue cryopreservation (11). Other options include adoption or utilization of an egg donor, but studies show that the majority of women prefer to have biologically related children (10, 12, 13). The American Society of Clinical Oncology (ASCO) and the American Society of Reproductive Medicine (ASRM) both recognize fertility preservation as a key survivorship issue and recognize fertility preservation treatment as a key measure of quality of care (11, 14). Therefore, early referral to a fertility specialist and counseling women about their infertility risks prior to initiating cancer therapy are essential elements of comprehensive cancer care (15, 16). Although fertility preservation is a well-recognized survivorship issue, many barriers exist for women who may choose to pursue fertility preservation treatment (4, 17).

The objective of this review is to discuss the impact of cancer treatments on fertility in young, female cancer survivors and to appraise the fertility preservation treatment options available for reproductive-aged women. Additionally, we highlight research advancements in the field of fertility preservation and review current challenges faced by cancer survivors who may pursue fertility preservation treatment.

EFFECT OF CHEMOTHERAPY ON FUTURE FERTILITY

Females are born with approximately one million oocytes, stored as primordial follicles in the ovarian cortex. The number of follicles decreases with increasing age, eventually leading to cessation of menses and onset of menopause when their supply is depleted (18). However, in women who undergo cancer treatment, this process is often accelerated due to the cytotoxic effect of chemotherapeutic drugs. These agents primarily affect dividing cells and negatively impact follicular maturation. They are directly toxic to primordial follicles which may lead to premature ovarian failure (19). The risk of premature ovarian failure varies by age, chemotherapy agent or combination used, cumulative dose, and duration of treatment (18). Girls and young women have a rich ovarian reserve. When they undergo chemotherapy, they have a lower risk of ovarian failure than older women undergoing the same chemotherapy treatment (20). Larsen et al. demonstrated that in teenage females undergoing chemotherapy, the risk of premature ovarian failure increased by a factor of 4, while for women 21–25 years old the risk increased by a factor of 27 (21). Regarding the specific chemotherapy agent used (**Table 1**), alkylating agents deliver the highest risk of ovarian failure compared to other cytotoxic agents. Alkylators alter DNA base pairs, leading to cross-links and introducing single-strand DNA breaks (22).

EFFECT OF RADIOTHERAPY ON FUTURE FERTILITY

The oocyte is extremely sensitive to ionizing radiation, and radiation therapy causes a dose- and age-related reduction in the ovarian follicular pool (23). The extent of damage depends on volume treated, total radiation dose, fractionation technique, field arrangement, and patient age (24). Multiple fields are used

TABLE 1 | Risk of ovarian failure according to the chemotherapeutic agent used.

High risk
Alkylating agents
Cyclophosphamide
Ifosfamide
Nitrosoureas
Chlorambucil
Melphalan
Busulfan
Procarbazine
Medium risk
Alkylating agents
Cisplatin
Carboplatin
Doxorubicin
Low or no risk
Alkylating agents
Bleomycin (antibiotic)
Dactinomycin (antibiotic)
Antimetabolite agents
Methotrexate
Mercaptopurine
Fluorouracil
Antimicrotubule agents
Vincristine
Vinblastine

to minimize radiation-induced toxicity by dividing the exposure of normal tissue into multiple different regions. Reproductive organs are affected directly, if they are included in the radiation field, or indirectly by scattered radiation (24). Current techniques such as intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT) have been used to maximize the dose to tumor and minimize toxicity to surrounding tissue (25).

As with chemotherapy, older females with fewer oocytes prior to treatment are most susceptible to ovarian failure (26). Additionally, radiation exposure to the uterus may produce tissue fibrosis, scarring, and decreased blood supply. This can result in infertility as well as poor obstetrical outcomes such as miscarriage and preterm birth (27–29). Moreover, brain irradiation can damage the hypothalamic–pituitary–gonadal axis, resulting in infertility due to anovulation secondary to hypothalamic amenorrhea (24).

EFFECT OF SURGERY ON FUTURE FERTILITY

The diagnosis and initial treatment of gynecological malignancies implies performing surgical procedures to remove the affected reproductive organs. Both ovarian and endometrial cancers are surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO), whereas cervical cancer is staged clinically (30, 31). The cornerstone of therapy for women with ovarian, fallopian tube, and peritoneal cancer is surgical cytoreduction to the presence of no gross residual disease, which is associated with increased survival (32). Ovarian cancer cytoreduction entails total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, peritoneal biopsies, and collection of pelvic washings (32). Similarly, the standard staging procedure for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy (30). Omentectomy is only performed when there is serous or clear cell histology. Moreover, pelvic- and para-aortic lymphadenopathy is performed selectively depending upon the presence of high-grade histology, extend of myometrial invasion, and tumor size >2 cm (33). Furthermore, one of the standard treatment options for women with early-stage cervical cancer (stage IA or IB1) is a hysterectomy (either simple or radical, depending on the clinical stage) with pelvic lymphadenectomy (34). All of the aforementioned surgical procedures have a direct impact on fertility rendering women with cancer infertile or menopausal after bilateral removal of the ovaries. Therefore, it is necessary to extensively counsel reproductive-aged women regarding the risks and benefits of surgical treatment and the implications of treatment on fertility. It is also vital to discuss more conservative surgical alternatives, if safe, which potentially are fertility-preserving.

FERTILITY PRESERVATION OPTIONS FOR WOMEN PRIOR TO CANCER TREATMENT

The ideal fertility preservation treatment should be individualized. It is dependent on the following patient factors: age, diagnosis, partner status, preference regarding use of donor sperm, time available before treatment, and her desire for future childbearing. The primary fertility preservation options today include embryo, oocyte, and ovarian tissue cryopreservation. Additional modalities include ovarian transposition and fertility-sparing surgery. **Table 2** summarizes the fertility preservation treatment modalities detailed below.

Embryo Cryopreservation

Embryo cryopreservation is a widely established method for preserving reproductive capacity in women. Due to its high pregnancy rates, it is considered the "gold standard" fertility preservation option offering the best chances of a live birth in the future (18). Among women with cancer, one retrospective study reported a life birth rate of 44.4% (35).

Embryo cryopreservation requires a woman to undergo an *in vitro* fertilization (IVF) cycle that involves 10–14 days of controlled ovarian hyperstimulation utilizing gonadotropin injections. When follicles reach the appropriate size, oocyte retrieval is performed *via* transvaginal ultrasound-guided needle aspiration of follicular fluid while the patient is sedated. Oocytes are then fertilized *in vitro* and cryopreserved, typically at the blastocyst stage, for future use (18). Most women with a male partner choose embryo cryopreservation, whereas some women without a male partner may choose this method by using donor sperm (24). Studies have shown conflicting results regarding the number of eggs harvested from female cancer patients compared to those without cancer. In most studies, cancer survivors possess a lower, but still adequate, number of oocytes when compared to age-matched controls without

TABLE 2 | Fertility preservation options for young cancer survivors.

Fertility option	Ideal patient	Success rates	Benefits	Drawbacks
Embryo cryopreservation	• Has male partner or willing to use donor sperm • Has time for ovarian stimulation prior to treatment	• Cumulative pregnancy rate of 66% among women with cancer	• Standard technique • Predictable likelihood of success	• Financially costly • Requires time to stimulate ovaries to retrieve eggs
Oocyte cryopreservation	• Postpubertal women without a male partner or who do not wish to use donor sperm	• Pregnancy rate per cycle of 50.2% or per embryo-transfer 55.4%	• Standard technique • For women with ethical or religious objections to embryo • For women in countries where embryo cryopreservation is prohibited freezing • Greater reproductive flexibility	• Financially costly • Requires time to stimulate ovaries to retrieve eggs
Ovarian tissue cryopreservation	• Prepubertal girls or young women who do not have time for ovarian stimulation to retrieve eggs	• Pregnancy rate of 25% among women with cancer	• Experimental • No delay in the initiation of cancer therapy • Male partner and ovarian stimulation are not required	• Requires surgical procedure to harvest tissue • Ovarian tissue could potentially be seeded with malignant cells
Ovarian transposition	• Females with planned pelvic radiation therapy	• Success rate (preservation of short-term menstrual function) varies from 16 to 90%	• Ideal for patient requiring local pelvic radiation	• Requires surgical procedure
Fertility sparing surgery	• Women with certain early-stage gynecological malignancies	• Cumulative conception rate after trachelectomy 53% • Pregnancy rate after progestin therapy for endometrial cancer 34.8%	• Ovaries and/or uterus are preserved	

cancer (36–39). Of note, however, Oktay et al. demonstrated that women with the *BRCA1* mutation appear to have a significantly lower ovarian response and produce fewer eggs per ovarian stimulation cycle (7.4 vs. 12.4) than women without the mutation (40).

The primary drawbacks to IVF include the time required, cost, and risk of ovarian hyperstimulation syndrome (OHSS) (6, 24). Medical expenses for an IVF cycle for fertility preservation are often not covered by private- or government-based insurance (41). The standard controlled ovarian hyperstimulation protocol starts at the onset of menses, which could result in a delay of 2–4 weeks (42, 43). While the conventional ovarian stimulation protocol is initiated at the beginning of the follicular phase, "random start" protocols may be initiated at the late follicular, periovulatory, or luteal phase (18). The latter protocols have similar numbers of oocytes retrieved, oocyte maturity, and fertilization rates than conventional-start protocols (44). Thus, random start protocols have proven to decrease total time to starting the IVF cycle, and cancer treatment, without compromising oocyte or embryo yield (44–47). An important risk to women undergoing IVF cycles is OHSS. Severe OHSS is a rare but serious complication of controlled ovarian stimulation. Women with OHSS may present with lower abdominal discomfort, nausea, vomiting, abdominal distension, ovarian enlargement, and ascites due to increased vascular permeability and third-spacing of fluid. Serious complications can include venous thromboembolism and stroke. Fortunately, there are techniques available to help prevent this iatrogenic condition, which may contribute to a delay in initiating cancer therapy (48).

Oocyte Cryopreservation

Oocyte cryopreservation is a fertility preservation treatment most suitable for single or adolescent women. It is often chosen by women without partners or by those with a partner who desire maximum reproductive flexibility. Oocyte cryopreservation is also an option for women with religious or ethical objections to embryo freezing (14, 18). This fertility preservation modality was considered experimental until 2013. At that time, the Practice Committees of ASRM and the Society for Assisted Reproductive Technology (SART) concluded that mature oocyte cryopreservation should no longer be considered experimental. Therefore, they recommended this strategy for patients facing infertility due to chemotherapy or other gonadotoxic therapies when embryo cryopreservation is not possible (49).

Major drawbacks of oocyte cryopreservation include the time needed for ovarian stimulation as well as its decreased efficiency compared to embryo cryopreservation. Oocyte cryopreservation is technically more difficult than embryo cryopreservation due to the oocyte's increased water content, making it more prone to cryoinjury. An egg's meiotic spindle, cytoskeleton, and cortical granules are sensitive to damage by ice crystals during freezing and thawing (50). Also, hardening of the zona pellucida after cryopreservation hinders fertilization (51). However, in recent years, there have been remarkable advances in oocyte cryopreservation techniques, which have allowed 70–90% of cryopreserved oocytes to survive the freeze-thaw process (52, 53). Intracytoplasmic sperm injection (ICSI), in which a sperm is directly injected into a mature egg, allows fertilization despite zona pellucida hardening (54).

Slow-freezing and vitrification are the two primary cryopreservation techniques. Vitrification leads to an ultra-rapid freezing of cells or tissues by direct contact with liquid nitrogen without ice crystal formation. Vitrification has quickly evolved to become the most widely used method of egg cryopreservation due to the improved oocyte survival (85 vs. 65%) and fertilization rates (79 vs. 74%), compared to the slow-freeze method (55, 56). Conversely, the slow-freeze method involves use of a cryoprotectant that permeates and dehydrates the cell as it is slowly cooled, minimizing the intracellular ice crystal formation. After cryopreservation, when the woman is ready to pursue childbearing, the oocytes are thawed and fertilized *in vitro*. The patient can then undergo transcervical embryo transfer into the uterus, with excess embryos cryopreserved for future use.

In vitro fertilization outcomes with cryopreserved oocytes are comparable to fresh IVF and ICSI rates (57). One retrospective study showed that oocyte cryopreservation/thaw cycles had no significant difference in live-birth rate per mature oocyte retrieved when compared to fresh IVF cycles (2.7 vs. 4.2%, respectively) (58). Furthermore, randomized trials performed in infertile couples with supernumerary oocytes and donor oocyte populations also reported no significant differences in fertilization rate (88.3 vs. 84.9%) and clinical pregnancy rate per cycle (50.2 vs. 49.8%) between fresh and vitrified oocytes (59, 60).

Special Considerations for Embryo or Oocyte Cryopreservation in Female Cancer Survivors

For women with estrogen-sensitive tumors (i.e., endometrial or estrogen receptor positive breast cancer), alternative ovarian stimulation protocols have been developed to circumvent the theoretical risk of supraphysiologic estradiol levels on cancer growth. Selective estrogen receptor modulators (tamoxifen) or aromatase inhibitors (letrozole) have been utilized for this purpose (42, 43). In such protocols, letrozole is used in addition to the standard gonadotropin dosing. Letrozole, most commonly used today, minimizes a women's serum estradiol level during controlled ovarian hyperstimulation. Published reports demonstrate a similar number of total oocytes retrieved, length of ovarian stimulation, and fertilization rate when compared with protocols without letrozole (43, 44, 61). A prospective study of 79 women with breast cancer who underwent ovarian stimulation using letrozole plus gonadotropins or gonadotropins alone for oocyte/embryo cryopreservation demonstrated a recurrence rate and survival that was similar at 2- to 3-year follow-up to those who underwent no fertility-preserving procedure (62).

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation involves harvesting and freezing ovarian tissue, allowing preservation of oocytes within primordial follicles located in the ovarian cortex. In the future, the tissue can be autotransplanted into the cancer survivor or immature oocytes could be harvested and matured *in vitro* (18). Major benefits of ovarian tissue cryopreservation include that it can be performed in prepubertal females, it eliminates the need for sperm donation, and it can be performed immediately without a cancer treatment delay. Of note, it is the only fertility preservation option available for prepubertal girls. Moreover, tissue can be obtained quickly, and there is potential to have more oocytes available for future fertility treatment than can be retrieved from a single IVF stimulation (18, 63, 64). This procedure entails ovarian tissue harvesting prior to cryopreservation. Ovarian tissue is either harvested laparoscopically or at the time of a laparotomy under general anesthesia, regardless of menstrual cycle phase. Since many young girls undergo chemotherapy port placement under general anesthesia, laparoscopic ovarian tissue harvesting can be piggy-backed to this procedure. Due to the location of the oocyte-containing follicles in the outer millimeter of the ovary, cryopreservation can be limited to only a cortical strip of tissue. After cancer treatment, the ovarian cortex tissue is thawed and transplanted either orthotopically to remaining ovarian tissue or pelvic peritoneum, or it can be transplanted heterotopically to the forearm, abdominal wall, or chest wall (18, 65).

Ovarian cryopreservation should ideally be performed before the initiation of gonadotoxic therapy since certain chemotherapies can significantly decrease ovarian reserve with each cycle. A prospective study of women that underwent ovarian tissue cryopreservation compared the ovarian reserve of those who had received chemotherapy (ranged from one to seven cycles) with those who had not, with the aim of quantifying the effects of alkylating and non-alkylating agents on ovarian infrastructure. The authors demonstrated a significantly lower primordial follicle counts in women who received chemotherapy compared to controls. This effect was accentuated when women were treated with alkylating agents compared to those patients who did not receive these agents or did not receive chemotherapy (66).

Cryopreservation of ovarian tissue is a new, yet promising, fertility preservation treatment. The first live birth after autotransplantation of human ovarian tissue was reported in 2004 (67). To date, there have been at least 60 live births after ovarian tissue reimplantation (68). The slow-freezing cryopreservation technique was used in the majority of these cases while only two used vitrification. In a series of 80 cases from 4 fertility centers, the pregnancy rate was of 25.0%. Of note, two women each delivered three babies, reflecting potential long-term efficacy of ovarian cryopreservation (68, 69). Ideal candidates for this fertility preservation modality are girls/women under age 35 with at least a 50% risk of ovarian failure after cancer therapy (70).

Ovarian Transposition

Ovarian transposition, or oophoropexy, is a strategy that can be offered to women with planned pelvic radiation. It is commonly considered for young women with locally advanced cervical cancer. This surgical procedure involves moving one (most commonly) or both ovaries out of the pelvis and away from the radiation field by laparoscopy or laparotomy (71). The ovary can be transposed to the lateral abdominal wall along the ipsilateral paracolic gutter, or with ligation to the uterosacral ligament for midpelvic or abdominal radiation, respectively (18). In all ovarian transposition cases, marking the boundaries of the ovary with

surgical clips will help to identify the ovaries during radiotherapy mapping (18). This technique is commonly done unilaterally but a combined approach with cryopreservation of one ovary and transposition of the other can be also implemented (72). In the case of post-treatment failure of the non-transposed ovary, oocyte retrieval from the transposed ovary can be performed transabdominally if the ovary is not repositioned (18). The overall success rate as judged by preservation of short-term menstrual function is approximately 50%, although there is a wide variation in the reported success rates ranging from 16 to 90% (14, 73). Failure of this method is due to scatter radiation, compromise of the transposed ovary blood supply, patient age, radiation dose, whether the ovaries are shielded during the radiation procedure and whether concomitant chemotherapy is used (73). Complications related to ovarian transposition include infarction of the fallopian tubes and chronic pelvic pain (73, 74).

Fertility-Sparing Surgery

Conservative surgical and medical techniques have been increasingly used for the management of early-stage gynecologic malignancies, given the impact of fertility preservation on quality of life (75). Fertility-sparing surgery entails the preservation of at least a portion of one ovary and the uterus, and it is more commonly offered to women with borderline ovarian tumors, non-epithelial ovarian cancers, early-stage cervical cancers, and select women with grade 1 endometrioid adenocarcinoma of the endometrium (75). Women with an apparent unilateral stage I borderline ovarian tumor or low grade ovarian malignancies who desire future fertility can be managed in some cases with a unilateral salpingo-oophorectomy, omental and peritoneal biopsies, and collection of pelvic washings rather than full staging for ovarian cancer (76). However, the National Comprehensive Cancer Network (NCCN) suggests consideration of completion surgery upon meeting childbearing goals for women with a remaining ovary (77).

There is limited data about the use of fertility-sparing surgery in women with early-stage epithelial ovarian cancer. In a large retrospective study of 240 women with epithelial ovarian cancer confined to the ovaries who underwent fertility-sparing surgery, 11.3% of the women relapsed and 4.6% died of progressive disease after a median follow-up of 9 years. The authors proposed a conservative approach (cystectomy or unilateral oophorectomy, omentectomy, pelvic washings, at least eight peritoneal biopsies, endometrial biopsy, and evaluation of pelvic and para-aortic lymph nodes) for appropriately selected young women with cancer. However, they recommended careful monitoring of women with grade 3 disease given the higher risk of distant recurrence (78).

Fertility-sparing surgery is particularly relevant for women with cervical cancer, given that this disease presents in women of reproductive age. Thus, women with tumors ≤2 cm and without evidence of obvious lymph node metastases can undergo cervical conization or radical trachelectomy, depending on disease stage, rather than radical hysterectomy (77). Conization is recommended for women with stage IA1 disease and without lymphovascular space invasion (79). A study of women 40 years or younger with stage IA1 disease using the Surveillance, Epidemiology, and End Results (SEER) database found no significant difference in 5-year survival between cervical conization and hysterectomy (80). Conversely, radical trachelectomy is recommended for women with stage IA1 disease with lymphovascular space invasion or stage IB1 disease (81). After the latter procedure, a 52.8% 5-year cumulative conception rate has been reported while reported preterm birth rate is in the range of 48–60% (81, 82). Several ongoing prospective trials, including a phase 2 trial at MD Anderson Cancer Center (NCT01048853), are underway to examine the safety of performing pelvic lymphadenectomy with cervical conization or simple hysterectomy for cervical cancer treatment. This study has an estimated enrollment of 100 participants and includes women with squamous cell carcinoma, FIGO stage IA2 or IB1, tumor diameter ≤2 cm, no lymphovascular space invasion on biopsy or cone and <10 mm of cervical stromal invasion (83).

In the case of uterine cancer, women with grade 1 or 2 endometrioid cancer confined to the endometrium may be candidates for progestin therapy such as megestrol acetate and deferral of surgical staging until after completion of childbearing. These women should have a dilation and curettage and imaging studies performed before medical therapy with the aim of excluding high-grade disease or advanced stages (84). A systematic review by Gunderson et al. of women treated with progestin therapy for grade 1 endometrioid carcinoma demonstrated a complete response rate of 48.2%. The time to complete response, which included women with hyperplasia, varied from 1 to 18 months (median 6 months). Moreover, the pregnancy rate for women with a history of carcinoma was 34.8% (84).

COUNSELING AND REFERRAL OF WOMEN INTERESTED IN FERTILITY PRESERVATION

It is well established that health-care providers should convey information about fertility risks and fertility preservation treatment to their patients as part of a comprehensive treatment plan. Open-ended dialog should include discussion of key points such as scientific data, advantages and disadvantages, anticipating delay of childbearing, patient preferences, and reproductive potential (11). Moreover, in order to improve information sharing, it is also beneficial to provide women with written material before and after counseling (16).

According to the ASCO Clinical Practice Guidelines, health-care providers should discuss with women interested in fertility preservation several key issues (11). The first key point is to discuss the feasibility of pursuing fertility preservation options depending on each patient's recurrence risk and prognosis. Then providers should inform women of their individual risks of infertility or early menopause from oncologic therapy, taking into account individual factors. Patients should be told whether their treatment would place them in high, medium, low or non-existent risk. Next, fertility preservation treatment options, including those considered experimental, should be reviewed with their respective success rates. Health-care providers should

communicate to women regarding the limited data available on oocyte cryopreservation and its decreased efficacy compared to embryo cryopreservation. It should be explained that these procedures may be subject to time constraints and treatment may be delayed. Patients should be informed that insurance coverage is improving for fertility preservation, and they should be encouraged to consult with their insurance companies. Providers should explain that even though there is a paucity of data, there appears to be no increased risk of cancer recurrence from fertility preservation interventions or pregnancy. Finally, an expeditious referral should be made to a fertility specialist for more information. Meeting with a social worker may also be beneficial for assessment of distress and to suggest advocacy organizations, which may provide financial resources.

BARRIERS TO PURSUING FERTILITY PRESERVATION

Fertility preservation is of paramount importance for the quality of life of cancer survivors. Yet, this topic is not consistently addressed in clinical practice despite the aforementioned ASCO recommendations (14, 85). Moreover, there are still many factors that impact patients' access to fertility preservation options. For example, both health staff and patients have their own concerns when it comes to discussing the effects that cancer therapy has on fertility. Although qualitative, a study reported that health-care providers voluntarily avoid this subject due to their beliefs that fertility in cancers such as Hodgkin's lymphoma would not be affected by first-line chemotherapy and that fertility preservation treatments are not effective. Additionally, fertility preservation discussion may be avoided due to the sense of urgency in providing cancer care without delay (4).

Conversely, there are a number of reasons why young women may refrain from discussing the topic with health-care providers, such as being overwhelmed with their cancer diagnosis or unaware of the consequences that cancer treatment may have on their fertility. They often fear that delaying cancer treatment to pursue fertility preservation may negatively impact their survival (11, 86). These concerns reflect communication and information barriers, which can be addressed with education to both health-care providers and patients. Thus, it is important to inform patients that there is no significant delay in cancer treatment when pursuing fertility preservation options and that a prompt referral to a fertility specialist optimizes the lag time between diagnosis and start of cancer treatment (87, 88). A retrospective study demonstrated no difference in time from initial diagnosis to chemotherapy in women that underwent oocyte retrieval vs. women who did not (71 vs. 67 days, respectively, $p < 0.27$) (87). Likewise, another observational study of breast cancer patients showed that women referred to a subspecialist before surgery had a shorter time interval from initial diagnosis to initiation of ovarian stimulation (42.6 vs. 71.9 ± 30.7 days; $p < 0.001$, respectively) and to initiation of chemotherapy (83.9 vs. 107.8 days; $p = 0.045$) than women referred after surgery. Early referral can also allow repeated stimulation cycles, resulting in a larger number of oocytes or embryos for cryopreservation prior to cancer treatment (88).

Several studies have reported that up to 50% of young female cancer survivors did not receive sufficient education regarding fertility preservation options (89, 90). Furthermore, a population-based study demonstrated that only 56.3% of adolescent and young adults with cancer recalled discussing fertility preservation options and only 6.8% reported making arrangements to pursue any of those options. The authors also described that those discussions were less likely to occur if women were raising children or if they lacked private insurance. Additionally, 38% of the women reported not making arrangements for fertility preservation because they were unaware of the options, whereas 19% reported having cost issues. Strikingly, the study showed that men with cancer were more than twice as likely as women to report discussion of fertility preservation options and to make arrangements for fertility preservation (85). The sex differences found in these and other studies may be related to the costs and complexity of female fertility preservation options and to the fact that oocyte cryopreservation was experimental when women in the study were initially diagnosed (4, 85).

In addition to unmet communication needs, financial expenses are one of the most relevant barriers that cancer survivors face when making a decision about their reproductive future. The current costs of ovarian stimulation drugs ($2000–$5000), egg harvesting ($5000–$8000), annual storage ($500–$1000/year), and each attempt at embryo transfer ($4000–$5000) make it challenging to cover these expenses out-of-pocket (41). Unfortunately, insurance does not cover fertility preservation treatment for most female patients. The laws and regulations that address insurance coverage for fertility treatment define infertility as an inability to conceive after 1 year of regular and unprotected intercourse and do not mention the infertility caused by cancer therapy. Thus, there are no codified insurance mandates that would cover the expenses for fertility treatment specifically of cancer survivors (41). Moreover, as the laws pertaining to insurance coverage for infertility and IVF procedures vary among and within states, the obstacles that the survivors encounter when attempting to assess these services also vary widely (41). Conversely, due to the experimental nature of ovarian tissue cryopreservation, health insurers are not required to cover this service. This therefore limits the options for fertility preservation for prepubertal girls and young women (41).

Rationale behind the lack of insurance coverage for assisted reproductive technology in cancer patients are related to the view of these procedures as elective and not medically necessary (91). Fortunately, in recent years, there has been a slight increase in insurers covering fertility preservation treatment on a case-by-case basis. This highlights the importance of advising patients to contact their insurance companies regarding insurance coverage. Patients should also be encouraged to reach out to non-profit organizations that provide women with financial assistance for preservation treatment (92).

CONCLUSION

Fertility preservation has become a significant aspect of comprehensive cancer care (24). The idea of not having a

child of her own is a key source of distress in women with cancer undergoing gonadotoxic therapy. Health-care providers should discuss with women about their fertility wishes and counsel them regarding fertility preservation treatment options. Moreover, determining the need and best technique for fertility preservation requires an individualized assessment that is best performed by a fertility specialist. Barriers to fertility preservation counseling and receiving treatment continue to exist.

AUTHOR CONTRIBUTIONS

AA contributed to conception and design, manuscript writing, and final approval of the manuscript. CJ contributed to conception and design, manuscript writing, and final approval of the manuscript. AF contributed to conception and design, manuscript writing, and final approval of the manuscript. MC contributed to conception and design, manuscript writing, and final approval of the manuscript.

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OPINION
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Early Integration of Palliative Care in the Care of Women with Advanced Epithelial Ovarian Cancer: The Time Is Now

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Keywords: ovarian cancer, palliative care, hospice, end of life, integration

Despite tremendous advances in surgery, primary chemotherapy, and novel treatments for recurrent disease, the diagnosis of advanced epithelial ovarian cancer in 2016 remains ultimately fatal in the majority of cases. Additionally, both the disease and the associated adjuvant treatment are not without substantial effect on overall quality of life. The cancer causes symptoms, but the treatment can cause even more significant problems, including neuropathy, nausea, fatigue, anorexia, and pain, among others. As oncology providers, we have a natural tendency to focus on the cancer and response to treatment rather than on the suffering of our patients related to treatment. Our patients in turn are reluctant to report their symptoms for fear that we will stop or change their treatment. As a result, though the cancer may be temporarily beaten into submission by aggressive surgery and adjuvant therapy, the patient may be simultaneously suffering from treatment-related symptoms that in some cases are permanent.

The early integration of palliative care in the treatment of women with advanced epithelial ovarian cancer allows us to address this quandary and not only improve quality of life but in some cases also prolong life. In the most well known of the randomized studies in cancer patients, 151 patients with newly diagnosed metastatic non-small cell lung cancer were randomized to integration of outpatient palliative care from the time of cancer diagnosis versus usual oncologic care (1). The early palliative care integration group not only had significant improvements in quality of life and mood but also (unexpectedly) had a statistically significantly improved overall survival (11.6 versus 8.9 months, $p = 0.02$), despite less aggressive intervention at the end of life. The results of this study have been confirmed by other studies in oncology patients (2–8). Our own Society of Gynecologic Oncology has advocated for inclusion of palliative care in the care of women with gynecologic cancer in their Choosing Wisely campaign.

What exactly is palliative care and how is this care best provided? The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual".[1] Said another way, the palliative care approach to the patient is a holistic one that encompasses all aspects of the person and her caregivers/family, including those that many oncologists are ill equipped to address. Palliative care services are divided into primary palliative care and specialty primary care services. Most oncologists are trained to provide and feel comfortable providing primary palliative care for the patients; in the case of gynecologic oncologists, these services include basic symptom management and aligning treatment choices with patient goals. By contrast, specialty palliative care is provided by a team of providers, including a palliative care trained physician, nurse or advanced practice provider,

[1] http://www.who.int/cancer/palliative/definition/en/ Accessed Jan 2016

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social worker, chaplain, pharmacists, nutritionists, rehabilitation therapists, and direct care workers, among others. The specialty palliative care team aims to address all of the domains of palliative care, including not only the physical but also the emotional, spiritual, and social domains of care. A complete assessment of palliative care needs includes all of these domains and so requires a multidisciplinary approach to the patient and her family. Thus, the early integration of palliative care allows us as oncology providers to continue to care for our patients with ovarian cancer while also addressing their suffering and improving overall quality of life.

Why then have we not embraced the early integration of palliative care into the care of women with advanced ovarian cancer? The most important barrier to early integration is a lack of understanding about exactly what the term "palliative care" means (9). Both patients and providers mistakenly consider palliative care to be synonymous with end-of-life care and, thus, incompatible with anticancer therapy. Patients are concerned that the introduction of palliative care means that the oncologist is "giving up," and data from providers have shown that many mistakenly consider palliative care to be synonymous with end-of-life care and, thus, incompatible with anticancer therapy (9, 10). The Institute of Medicine report "Dying in America" concluded that "one of the greatest remaining challenges is the need for better understanding of the role of palliative care among both the public and professionals across the continuum of care so that hospice and palliative care can achieve their full potential for patients and their families".[2] Said Misconceptions about the role of hospice and the hospice benefit are also prevalent, resulting in few patients with ovarian cancer taking advantage of the hospice benefit at the end of life and very late hospice referral (11).

There are other important barriers to the integration of palliative care early in the course of a malignancy, such as advanced ovarian cancer. These include the lack of availability of outpatient specialty palliative care services, poor reimbursement for palliative services, and a perceived lack of training and exposure by oncologists in provision of basic palliative care services. While most NCI-designated cancer centers have access to outpatient specialty palliative care services, these services are much less common in the community setting (12). Reimbursement for palliative care services remains poor, contributing to the lack of availability. Until recently, providers were not reimbursed for discussing advance care planning with their patients, a discussion that when done well can take a lot of time from a busy oncology clinic. Finally, surveys of both medical and gynecologic oncology fellows suggest that the trainees feel ill prepared to provide primary palliative care, to have difficult conversations, and to discuss end-of-life planning with their patients (13, 14). There is clearly room for improving the palliative curriculum and exposure in gynecologic oncology fellowships.

How then can we accomplish the early integration of palliative care into the care of our patients with advanced epithelial ovarian cancer? The first step should be improved and continuing education of both the public and health care providers regarding what services palliative care provides and regarding the value of these services. It may be as simple as re-naming palliative care to supportive care in some cases while we further the education effort to avoid the confusion of palliative care with end-of-life care (15, 16). Early referral should be prioritized in the setting of a disease like advanced ovarian cancer, as patients will gain the most benefit from this approach (17). We also need to focus on better education of our trainees regarding palliative care and end-of-life care, and we need to lobby for appropriate reimbursement for these time-intensive services. Finally, palliative care services will help our patients but will also help us as oncology providers by their ability to "share the load" (9).

Our patients with advanced ovarian cancer deserve the best overall care we can provide to them and to their families and caregivers. This best care includes the most aggressive surgery required to achieve complete cyto-reduction, the most effective chemotherapy (with clinical trial options), and the most appropriate and modern management of the inevitable disease recurrence; critical skills that all gynecologic oncologists learn and then master during their careers. But we must also be mindful of the important contribution of the early integration of palliative care services to our patients' overall well-being. While the oncologist holds the "keys to the chemo," resulting in a patient less likely to vocalize debilitating symptoms or non-medical concerns, the palliative care team is able to focus on other aspects of the patient and her family's care. Our ultimate goal should not be only to improve overall survival, but also to improve overall survival in the context of improved quality of life in all domains.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

[2]https://iom.nationalacademies.org/~/media/Files/Report%20Files/2014/EOL/Report%20Brief.pdf Accessed Jan 2016

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MINI REVIEW
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The Relevance of Gynecologic Oncologists to Provide High-Quality of Care to Women with Gynecological Cancer

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Gynecologic oncologists have an essential role to treat women with gynecological cancer. It has been demonstrated that specialized physicians who work in multidisciplinary teams to treat women with gynecological cancers are able to obtain the best clinical and oncological outcomes. However, the access to gynecologic oncologists for women with suspected gynecological cancer is scarce. Therefore, this review analyzes the importance of specialized care of women with ovarian, cervical, and endometrial cancer. In addition, the role of gynecologic oncologists who offer fertility-sparing treatment as well as their role in assisting general gynecologists and obstetricians is also reviewed.

Keywords: gynecologic oncologists, ovarian cancer, vulvar cancer, endometrial cancer, cervical cancer, centralization of care, fellowship-training program

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INTRODUCTION

It is estimated that over a million new cases and half million deaths are due to gynecological cancers that occur annually worldwide (1). Even though general gynecologists commonly treat these diseases across the world, the sub-specialization in gynecologic oncology has been progressively increasing in developed countries since 1972 (2, 3).

According to the definition of the American Board of Obstetrics and Gynecologist, gynecologic oncologist is "a specialists in obstetrics and gynecology who is prepared to provide consultation on comprehensive management of patients with gynecologic cancer and who works in an institutional setting wherein all the effective forms of cancer therapy are available" (4).

Gynecologic oncologists have an essential role when treating women with gynecological cancer. They are in a unique position to enrich the global health community with opportunities for education, training, and policymaking as it pertains to women's cancers. In addition, they are in a privileged position to make decisions regarding the integration and sequencing of all modalities of treatment.

Specialized physicians who work in multidisciplinary teams to treat women with gynecological cancers obtain the best clinical and oncological outcomes (5–7). We think that by this approach, gynecologic oncologists not only play an important role in performing an optimal surgery but they can also provide a better overall quality of care by having a holistic conception of women. However, in countries with a high number of gynecologic oncologists, only a minority of women with gynecological cancer receives care by specialized physicians at referral institutions (8). For example, it has been demonstrated that approximately one-third of women with ovarian cancer are treated by gynecologic oncologists in the U.S. Therefore, this article will review the role of gynecologic oncologists who treat women with different gynecological malignancies.

OVARIAN CANCER

Ovarian cancer probably represents the best example of how a well-prepared specialist can positively modify the clinical and oncologic outcomes of women. Ovarian cancer is the most aggressive gynecological cancer with a 5-year overall survival of 40% (9). There are well-documented independent prognostic factors at advanced-stage disease, including tumor histology and grade of differentiation, patient's age, stage of disease, performance status, and surgical debulking (10). However, the latter is the only modifiable factor, which means that it is amenable for direct influence, and therefore, seems to be of the utmost importance when considering efforts aiming toward improving outcomes of this disease.

The relevance of an adequate surgery was highlighted in multiple studies, which associated a significant improvement in oncological outcomes after a complete tumor resection at the time of primary surgical cytoreduction in comparison with cases in which there was some amount of residual disease at the end of the surgical procedure (9–11). Thus, according to the last Gynecological Cancer InterGroup (GCIG) consensus conference, "the mainstay of treatment of advanced ovarian cancer is primary surgery aiming at complete tumor resection followed by platinum and paclitaxel chemotherapy" (12).

However, the final decision as to whether or not to perform a tumor debulking depends on the surgeon's training and confidence (13). Many studies suggest that patients operated on by gynecologic oncologists with previous training in cytoreductive techniques are more likely to undergo an adequate surgical staging in the early stage of the disease, and a better rate of complete cytoreduction in advanced stages in comparison with those patients treated by general gynecologists or general surgeons (5–7). More specifically, when gynecologic oncologists perform the surgery, there are twice as many probabilities of obtaining a complete cytoreduction (5). As a consequence, according to the results of meta-analyses, patients operated on by gynecologic oncologists have significantly better oncological outcomes, which resulted in an increased overall survival of 10 months, in comparison with those patients treated by general gynecologist or general surgeons (5–7).

A recent document launched by the European Society of Gynecological Oncology (ESGO) regarding the quality indicators in ovarian cancer surgery states that "Surgery is performed by a certified gynecologic oncologist or, in countries where certification is not organized, by a trained surgeon dedicated to the management of gynecologic cancer (accounting for over 50% of his practice) or having completed an ESGO accredited fellowship. Skills to successfully complete abdominal and pelvic surgery procedures necessary to achieve complete cytoreduction must be available" (14).

However, ovarian cancer surgery is not an easy task, and it requires an adequate institutional support, as well as establishing evidence-based clinical guidelines. Even though gynecologic oncologists should lead these surgeries, it is recommended to work in a multidisciplinary surgical team involving other specialists, such as general surgeons, anesthesiologists, and infectologist. This strategy is aimed to offer the best quality of care for the patient (**Figure 1**).

ENDOMETRIAL CANCER

The majority of endometrial cancers are low-risk disease with excellent oncological outcomes (15). Thus, the potential positive impact of subspecialty care in endometrial cancer might be more difficult to demonstrate (16). However, gynecologic oncologists can have an important role in the implementation of minimally invasive surgery with their well-known advantages over open surgery (17). In this regard, a recent U.S. epidemiological study demonstrated that 86% of robotic surgeries for endometrial cancer were performed in 19% of the analyzed hospitals. Each additional 25 patients (above the mean surgical volume) were associated with over a 2.5-fold increase in odds of robotic surgery (OR = 2.65, 95% CI: 1.82–3.86; $p < 0.0001$) (17).

In addition, another epidemiology study performed in the U.S. evaluated 18,338 women with endometrial cancer, 4,489 of whom at stages II–IV (24.3%) (18). Patients who underwent surgery by a gynecologic oncologist were more likely to receive a more extensive lymph node resection (16 lymph nodes; 22 vs. 17%; $p < 0.001$), have more aggressive histologic cell types, such as serous and clear-cell (11.6 vs. 6.1%; $p < 0.001$), presented with advanced-stage disease (stages III and IV; 21.9 vs. 14.6%; $p < 0.001$), were more likely to received chemotherapy (22.6 vs. 12.4%; $p < 0.001$), as well as to received radiotherapy (38.9 vs. 30.7%; $p < 0.001$). In addition, surgery performed by gynecologic oncologist was an independent prognostic factor and was associated with a 30% increase in overall survival in comparison with other type of surgeons (HR, 0.71; 95% CI, 0.62–0.82; $p < 0.001$) (18). Other studies did not find significant differences in the survival rate, probably because they only included early-stage disease (19), or due to the fact that they only analyzed a small number of patients (16, 19).

CERVICAL CANCER

Worldwide, cervical cancer accounts for over 500,000 cases and 275,000 deaths each year (20). However, there is a great disparity

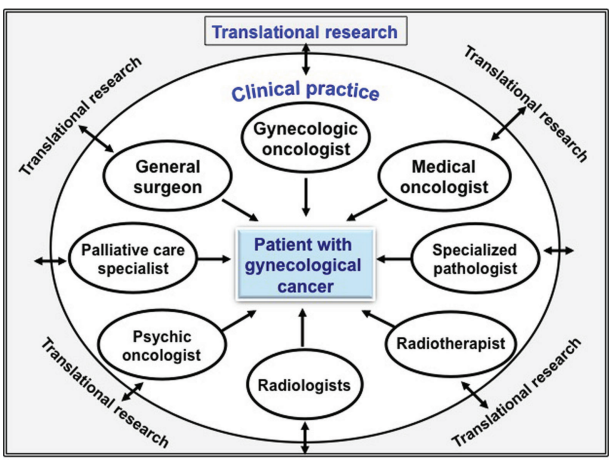

FIGURE 1 | Multidisciplinary team to treat women with gynecological cancer.

among high- and low-income countries due to successful implementation of cervical cancer screening programs in developed countries (21). In addition, the reduction in the incidence of cervical cancer should continue with the increased use of human papilloma virus (HPV) vaccination (22). Therefore, the majority of women with cervical cancer in developed countries are diagnosed at early stages with a 5-year overall survival rate of over 90% (23).

No studies have specifically addressed the impact on survival of women with early-stage cervical cancer treated by gynecologic oncologists. One U.S. epidemiological study, however, studied 27,660 women with cervical cancer FIGO stage IIB–IVB who were treated at hospitals with different case volumes. The study showed that the median rate of survival of patients treated at the lowest and highest volume centers were 42.3 months (95% CI 39.8–44.8) and 53.8 months (50.1–57.5), respectively ($p < 0.001$). On multivariable analysis, higher facility volume independently predicted improved survival ($p = 0.022$), increased likelihood of receiving brachytherapy ($p < 0.0005$) and chemotherapy ($p = 0.013$), as well as shorter time to radiotherapy completion ($p < 0.0005$) (24).

VULVAR CANCER

Squamous cell cancer of the vulva is a rare disease with an annual incidence of 2–3/100,000 women (25). There is evidence that demonstrates step-by-step nodal metastases in human cancer (26). Therefore, the first regional lymph node, called sentinel node, receiving lymphatic fluid from the tumor is initially removed. All regional lymph nodes are only dissected in case of disease in the sentinel node. Thus, this technique significantly reduces the incidence of postoperative complications, such as wound breakdown or cellulitis, and long-term morbidity including lymphedema (27). However, failure in the sentinel node detection is mainly seen when specialists with low case-volume (<10 cases/year) perform the procedure (27). Failure of this procedure can mean leaving the sentinel node in place, probably with tumor cells and with fatal consequences for patients. Therefore, some authors recommend that sentinel node detection in patients with vulvar cancer should be offered to well-selected patients by well-trained and informed gynecologic oncologists who work in centers with at least 10 cases/year (27, 28). In addition, it is also recommended that this technique be performed by multidisciplinary team involving gynecologic oncologists, specialists in nuclear medicine, and specialized pathologists (27).

ROLE OF GYNECOLOGIC ONCOLOGISTS IN SPECIAL CIRCUMSTANCES

Fertility Preserving Treatment in Women with Gynecological Cancers

It is estimated that over 21% of women with gynecological cancer are diagnosed in their reproductive age (29). In addition, it has been demonstrated a continuum increase of women age at first pregnancy (30, 31). Both factors explain why fertility preservation in women with gynecological cancer is currently a very important issue. The recommended treatment for the great majority of gynecological cancer includes radical removal of the uterus and ovaries, annulling any possibility for future pregnancies. However, fertility-sparing treatment in young patients with women's cancer is possible in very select women without compromising long-term survival (32). A recent survey of the ESGO revealed that only a minority of young women candidates to fertility-sparing treatment is aware of the opportunity to preserve their fertility (33). The main reasons include the surgeon's being unaware, skeptic, or untrained to perform fertility-sparing surgical procedures (33). Despite the fact that fertility-sparing surgery is technically not difficult (except for radical trachelectomy for cervical cancer), a more complicated task can be to select the appropriate candidate for such specific treatment. Therefore, according to an ESGO statement, these patients should be managed in a multidisciplinary team coordinated by gynecologic oncologists in conjunction with medical reproductive endocrinologists, perinatologists, pathologist, psychologists, and assisted reproductive specialists (33).

Surgical Assistance to General Gynecologists and Obstetricians

Even though gynecologic oncologists are intensively trained in all aspects of women's cancer care, their main area of expertise is focused on performing complex surgical procedures. Therefore, their role in clinical practice often extends beyond women's cancer. For instance, they can be of assistance to general gynecologists/obstetricians at certain moments during difficult surgical procedures, such as being a surgical resource to obstetricians during challenging peripartum hemorrhage, (34–36) as well as in cases of complex pelvic anatomy or pathological placentation (37). A recent study performed at Massachusetts General Hospital revealed that gynecologic oncologists can assist general gynecologists at the time of intraoperative consultation in 98 out of 794 benign gynecological surgical procedures (12.3%). The main reasons for unplanned consultation included adhesive disease, bowel injury, ureter visualization, cancer, and bleeding control (34).

CENTRALIZATION OF CARE – MULTIDISCIPLINARY MANAGEMENT

Gynecological cancer is a challenging, complex, and multidisciplinary disease. It is not only important how well trained the physicians are but also how many physicians of different specialties are involved (38). The concept of the holistic conception of patient care under a multidisciplinary team approach is crucial from the diagnosis to the demise of the disease, and this model should not be restricted to the operating room setting.

A correct collaboration with dedicated pathologists, medical oncologists, radiotherapists, biologists, palliative care specialists might help avoid unnecessary mismanagements, and therefore, reinforce the holistic conception of patients with gynecological cancer with an improvement on their perceived quality of care. Moreover, the recent molecular biology, genetic, and immunology discoveries are opening new optimistic frontiers for the future treatment and cure of this disease. Many authors agree that close exchanges between the clinical practice and basic research are

crucial for consolidating these progresses (39, 40) (**Figure 2**). A recent meta-analysis demonstrated that women with gynecological malignancies who receive care from a multidisciplinary team by specialized physicians live for a significantly longer period of time (7).

Centralization of care in women with gynecological cancer is another crucial issue. In some regions, gynecologic oncology cases have been centralized (41) in centers with higher patient volumes and interdisciplinary collaboration (42). These centers receive referrals from less-specialized hospitals within a network, region, or defined catchment area. Under this model of care, women are referred to specialized units, which are a team built by multiple specialized physicians focused on the comprehensive care of women affected by gynecological cancer. Every case is discussed inside in a multidisciplinary tumor board where the best strategy of treatment is based on multiple points of views, taking into consideration all aspects regarding each individual patient expectancy beyond the disease itself (**Figure 2**).

Results of different studies consistently show that patients with ovarian cancer treated at high-volume hospitals receive better quality of care, which is accomplished by better surgical staging and better optimal cytoreduction rate (5–7), as well as better chemotherapy administration rate and schemes (43, 44).

One study, performed in England, showed that the survival of patients with gynecologic cancer improved significantly after centralization in comparison with the pre-centralization period (hazard ratio: 0.71; 95% confidence interval: 0.64–0.79) (45). Similar findings were also reported for cervical, endometrial, and ovarian cancer after the implementation of the U.K. National Health Service cancer plan in 2000 (46).

Despite the consensus recommendations (12) and the advantages previously explained, population-based studies indicate that access to specialist care in gynecologic oncology for women with suspected gynecological cancer is uncommon (47–49). Reports from countries such as U.S. (8, 50) and U.K. (49, 51) have showed that over 60–80% of patients with advanced stage ovarian cancer are treated in low-volume hospitals by low-volume surgeons (8, 52, 53).

Common barriers to the quality of cancer care have been identified by multiple investigators and include the extremes of age, minority race, low socioeconomic status, rural residence, patient's and physician's unawareness of gynecologic oncologist resources, ineffective recognition of the disease, and third-party payers (8, 47).

FELLOWSHIP-TRAINING PROGRAM

Gynecologic oncologists have also an important role in teaching and educating fellow colleagues. Physicians who want to be gynecologic oncologists need to undergo a long and specific period of training and education process. After finishing medicine school, physicians must complete a 4- to 5-year residency-training program in obstetrics and gynecology. Then, they need to be accepted in accredited referral institutions to complete their specific fellowship-training program for 2–4 more years. The training, skills, and knowledge base required of a gynecologic oncologist are rapidly expanding. In addition to the original areas of radical pelvic surgery, chemotherapy, radiation therapy, and pathology, new areas of training include radical upper abdominal surgery, minimally invasive and robotic surgery, translational medicine and research, and palliative medicine (54).

In 1972, the first gynecologic oncologic fellowship-training programs were introduced in the U.S. with two accredited fellowships. Since then, 46 fellowship programs exist with 126 approved positions (55). Currently, there is a uniform system of training developed by the American Board of Obstetrics and

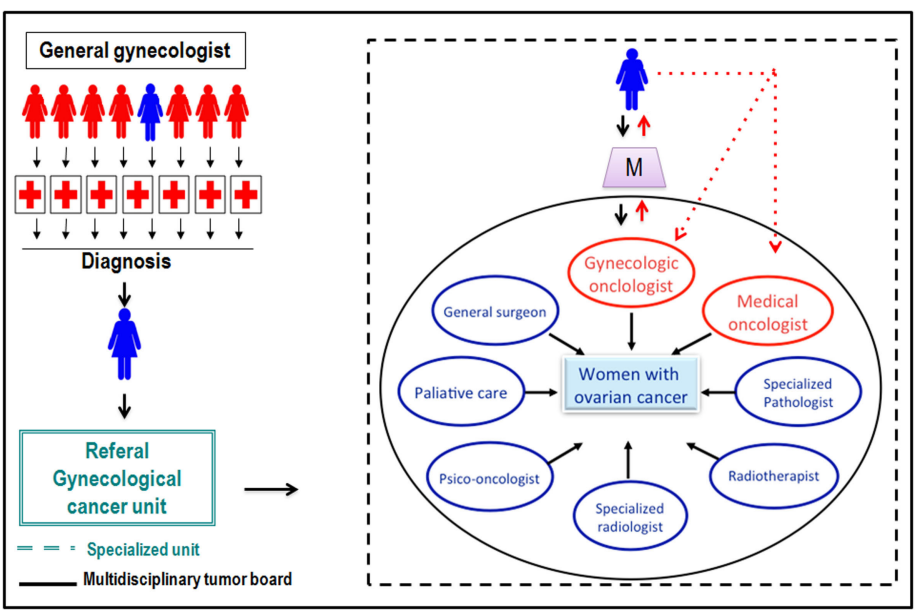

FIGURE 2 | Multidisciplinary care in a gynecological cancer unit.

Gynecologist who provide the training resource documents for the development of a curriculum in gynecologic oncology (4). Australia, Canada, U.K., and recently, the European Union are other examples of renowned gynecologic oncologic fellowship-training programs around the world (2). However, the number of gynecologic oncologists per patient is still scarce worldwide, and it is expected that the number of fellowship positions will continue to increase through the following years (56).

CONCLUSION

When women with gynecological cancers are treated by gynecologic oncologists in referral cancer centers, they are able to live longer and with a better quality of life. Therefore, patients should be ideally referred to high-volume physicians/hospitals to increase their life expectancy as well as its quality. Expanding fellowship-training programs worldwide as well as highlighting the existence and relevance of gynecologic oncologists in the general population and medical community is crucial to increase the patient's accessibility to a specialist's care.

AUTHOR CONTRIBUTIONS

All of the three authors of the present paper declare that there are no conflicts of interest and have actively participated in the study providing input including (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting of the article, or provision of critical revision for important intellectual content; and (3) final approval of the version to be published.

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The Value of Ultrasound Monitoring of Adnexal Masses for Early Detection of Ovarian Cancer

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Although ultrasound has so far been found to be ineffective as a screening tool for ovarian cancer, it is commonly used as a means of evaluating or following ovarian or adnexal masses once they are detected. We review the use of serial ultrasound for the management of adnexal masses and propose an approach to monitoring based on an understanding of the overall risk of cancer among the population in question and an assessment of how the potential benefit of monitoring compares with potential risk. In our approach, masses that are symptomatic, large (>10 cm), associated with an elevated CA 125 level or overt signs of malignancy, or that are determined to have a worrisome appearance by stringent ultrasound criteria should be evaluated surgically. Women with masses that have none of these characteristics should be offered monitoring. Short-term initial ultrasound monitoring carries significant potential benefit in terms of aiding detection of early malignancy and avoidance of unnecessary surgery. However, if a mass remains stable but persistent, the potential benefit of ongoing monitoring wanes with time, whereas the potential harms, in terms of patient anxiety, cost, and the risk of incidental findings and unnecessary surgery increase. Therefore, monitoring of stable lesions should be limited in duration in order to limit potential harms from overtreatment and overdiagnosis.

Keywords: ultrasound detection, adnexal diseases, ovarian neoplasms, early detection of cancer, overtreatment

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INTRODUCTION

Although the majority of women with epithelial ovarian cancer present with late stage disease, approximately 15% have early stage disease at diagnosis (1). Many early stage cases present with a large mass or worrisome clinical signs, but for a small subset, the initial presentation is a small, asymptomatic adnexal mass with no other factors that would raise suspicion of cancer. Biopsy of adnexal masses is generally not recommended since ovarian cancer is known to spread by direct peritoneal extension, and therefore, if a mass is malignant, biopsy could theoretically worsen prognosis. As a result, concern that a mass in an older woman may represent an early cancer leads many women with small masses to undergo unnecessary surgery with accompanying morbidity, despite the fact that the overwhelming majority of these masses are found to be benign.

The alternative to immediate surgery for masses of uncertain nature is ultrasound monitoring. Here, we discuss when monitoring of masses in postmenopausal women should be considered, the distinction between initial short-term ultrasound monitoring and prolonged monitoring in terms of potential value, as well as potential harms. Based on these considerations, we propose an approach

to ultrasound monitoring for adnexal masses based on published clinical data that aims to maximize benefit and minimize harm.

WHEN SHOULD MONITORING BE CONSIDERED?

Surgery is appropriate for symptomatic masses and masses that are associated with other signs of malignancy, such as elevated CA125 (in postmenopause), ascites, or evidence of metastatic disease, or in women at high genetic risk for ovarian cancer. Surgery is also appropriate for large masses (>10 cm), which are less likely to regress, have a higher risk of symptoms, and are often more difficult to characterize on ultrasound. Therefore, the women for whom ultrasound monitoring is an option are women whose presentation does not include any of these characteristics: average risk women with smaller, asymptomatic masses.

WHAT IS THE RISK OF CANCER?

Appropriate management of women with smaller asymptomatic masses should be based on the risk of cancer – the lower the risk of cancer is for a group, the lower the rate of surgery should be. Unfortunately, there is little "real world" data on what the risk of cancer is among women who are potential candidates for monitoring. The traditional teaching within gynecology has been that complex adnexal masses in older women are cancer until proven otherwise. However, this view was not based on the subset of women with characteristics that would make them candidates for observation, and it was often drawn from referral populations where the prevalence of cancer is elevated (2–5). Furthermore, this impression of risk was established during an era when most masses came to the attention of patients and providers due to symptoms or being palpable on exam. It is clear that with rising rates of utilization of imaging of all types, including office ultrasound, adnexal masses are increasingly found incidentally in studies obtained for an entirely separate concern (6–8). Trial data demonstrate that among older women who have an adnexal mass identified through ultrasound screening, the overall risk of invasive cancer is approximately 1–2% (9–11). In the UKCTOCS trial, an ongoing randomized controlled screening trial of over 20,000 postmenopausal women in the United Kingdom, of 48,230 women who had an initial ultrasound screen, 9.1% had an abnormal scan, and among these women, the absolute risk of epithelial ovarian cancer over the following 3 years was 1.08% (9). Although the risk of cancer for women identified by screening is expected to be lower than the risk for women found to have a mass in clinical practice, the degree to which they differ will depend on the proportion of women in clinical practice who are diagnosed with a mass as the result of signs or symptoms related to ovarian malignancy. One in every three physicians reportedly engage in ovarian cancer screening of low-risk women despite evidence to date that ovarian cancer screening using transvaginal ultrasound and CA125 tumor marker testing is ineffective at reducing ovarian cancer mortality (12). In addition to inappropriate screening, the widespread use of ultrasound effectively results in inadvertent screening. Unlike mammography, which is rarely used for any indication other than screening, pelvic ultrasound is used for a range of clinical indications, such as checking IUD placement or evaluating fibroids. If the UKCTOCS experience holds, each ultrasound exam on a postmenopausal woman has a 9% chance of incidentally finding an adnexal mass. Although large masses or masses associated with ascites are usually diagnosed as a result of symptoms, the women who are candidates for ultrasound monitoring are women with small isolated asymptomatic masses. For these reasons, the difference in the risk of malignancy observed for women identified by screening compared to women who undergo monitoring may not be as great as expected. We evaluated the risk among women who were found to have small masses in the course of routine care by identifying a population-based cohort of 1363 women over age 50 with complex masses <6 cm in size not associated with other evidence of cancer (13). A total of 7 cancers and 11 borderline tumors were found with 24 months of follow-up. The majority (994/1363, 73%) underwent ultrasound monitoring, with 5 of the cancers and 7 of the borderline tumors found in the monitored group during follow-up for an overall risk of 1.3%, and 0.5% for invasive cancer specifically.

TRIAGE TO SURGERY VERSUS OBSERVATION

Several strategies have been proposed to better identify masses that are likely to be malignant. Although elevated CA125 levels raise the likelihood of cancer, a normal value is seen in approximately 50% of early stage cases (14), and therefore, does not exclude possible cancer. Whether longitudinal measurement of CA125 over time, evaluated by the risk of ovarian cancer algorithm (ROCA), will be effective as a screening method for low-risk women is a question currently being studied within the multimodality screening arm of UKCTOCS (15). A number of algorithms that combine clinical and ultrasound criteria have been proposed. The risk of malignancy index (RMI) is a score generated by assessment of ultrasound features, menopausal status, and the serum CA125 level (international unit per milliliter). The ultrasound features in RMI are multilocularity, solid areas, and bilaterality (16). The International Ovarian Tumor Analysis (IOTA) group developed two logistic regression models (LR1 and LR2), which rely more heavily on ultrasound features and also include age, personal history of ovarian cancer, and tenderness of the mass on physical exam (LR1) to predict malignancy (17). The ultrasound findings that lead to a higher score are ascites, blood flow in papillary projections, solid nature of the tumor, maximum diameter of the largest solid component, irregular internal cyst wall, lack of acoustic shadows, and higher degrees of vascular flow. The group also developed and evaluated a set of "simple rules (SR)" that produce a score based solely on the presence or absence of benign or malignant ultrasound features, in which malignant features are defined as irregular solid tumor, ascites, at least four papillary projections, irregular multilocular solid tumor at least 10 cm, and very strong intratumoral blood flow (18). Recently, they reported an analysis of their studies in which they found that all IOTA strategies (LR1, LR2, SR, and combinations of the above) were superior to RMI for predicting malignancy among masses with

sensitivities in the range of 90–96% and specificity of 74–79% (19). Interestingly, they found LR1 was only slightly more sensitive but significantly less specific than "subjective assessment" alone which relied entirely on expert radiology impression (93.7, 77.6 versus 92.5, 87.7, respectively). However, the generalizability of these findings is debatable due to a higher prevalence of cancer in the populations studied as well as a level of radiology expertise that may not be reproducible in other settings (20). Finally, investigators from the Kentucky ovarian screening study developed a "morphology index" (MI) based on mass volume and proportion of solid component, and found that in their study, 85% of cancers and borderline tumors had a score of at least 5 at the time that the decision was made for surgery (21). Although debate continues regarding the superiority as well as generalizability of one strategy compared to another, from a practical standpoint, clinical criteria, such as personal history of ovarian cancer, elevated CA125, and evidence of ascites or metastases, as well as large mass size >10 cm, are already generally considered sufficient reason to direct a woman with a mass to immediate surgical evaluation. Therefore, further triage of women without these characteristics to either ultrasound observation versus surgery relies mainly on ultrasound characteristics. Among the ultrasound features that are associated with malignancy, the presence of large solid areas is the most consistent characteristic included in ultrasound-based prediction strategies. The significance of solid areas has also been demonstrated in screening trials. In UKCTOCS, masses without solid elements had an absolute risk of 0.4%, whereas masses with solid elements had an absolute risk of 4.45% (9). Analysis of the ultrasound abnormalities seen in PLCO also found that both the size of the mass and the presence of solid components correlated with risk of malignancy, with all masses <5 cm and larger masses without solid areas being low risk (22). Requiring solid components to demonstrate vascular flow by Doppler has been shown to increase the specificity of morphology for malignancy (23–26). Given the overall low risk of malignancy among women who are candidates for monitoring, the ultrasound criteria used to exclude women from initial short-term monitoring should be highly specific, in order to avoid exposing women to excessive unnecessary surgery. In our practice, we support excluding only masses that demonstrate significant solid vascular components from consideration of initial monitoring.

SCHEDULE OF MONITORING

When considering ultrasound monitoring, a distinction must be made between initial, short-term repeat exam, limited monitoring for up to 1–2 years and indefinite, potentially lifelong monitoring of stable masses. Initially, monitoring serves to identify masses with aggressive growth patterns, and it helps to avoid surgery on masses that are benign or transient in nature such as hemorrhagic cysts. The Society of Radiologists in Ultrasound published guidelines in 2010, based on committee consensus opinion, which recommended a follow-up interval of "6–12 weeks" for indeterminate masses among premenopausal or perimenopausal women, but immediate surgical consideration for postmenopausal women (27). However, there is growing consensus that a repeat exam in 6–8 weeks is safe and does not negatively impact stage at diagnosis (28–30). In the Kentucky ovarian cancer screening study which used serial transvaginal ultrasound as well as CA125, it was found that over 75% of cystic and solid lesions resolved on monitoring over 12 months (28). The investigators credit the use of serial ultrasound in decreasing the rate of false positive results and did not find that initial monitoring resulted in more advanced stage at diagnosis. A similar strategy is used in the ultrasound only arm of the UKCTOCS trial in which women with initial ultrasound abnormalities are directed to undergo a repeat ultrasound 6–8 weeks later that is performed by a more experienced ultrasonographer (30). Only if the mass is persistent at that time is a clinical assessment made regarding the suspicion for cancer. Indeterminate masses that are stable on the initial 6- to 8-week exam can be further monitored. The American College of Obstetrics and Gynecology (ACOG) Practice Bulletin on Management of Adnexal Masses states "Repeat imaging is recommended if there is uncertainty regarding a diagnosis …. The frequency of repeat imaging has not been determined" (31). Although the optimal interval between follow-up studies for stable masses has not been rigorously studied, reimaging stable masses at 3-month intervals has been adopted by many as a reasonable schedule (26, 28, 29, 32). In our study of postmenopausal women with small complex masses, all five cancers diagnosed during follow-up demonstrated growth on the first repeat ultrasound, done 2–7 months later (13). All patients who had reimaging done within 6 months were found to have stage I disease at surgery. These results support the view that 3-month intervals between exams provide an opportunity to detect worrisome growth while still supporting early detection. If progression of the mass is seen on repeat imaging, surgical removal is appropriate. In our experience, women also elect eventual surgery due to cumulative anxiety or because a follow-up ultrasound raises concerns for progression even though the mass is unchanged, due to variability in ultrasound technique and reporting styles. Therefore, if monitoring is to be effective, follow-up studies should state explicitly whether any changes observed are potentially due to variation in image acquisition, in order to differentiate masses that are equivocably changed from those that are definitely changed.

DURATION OF MONITORING FOR STABLE MASSES

The question of how long monitoring should be continued for stable but persistent masses is best viewed from the standpoint of potential benefit versus potential risk. Since the only potential benefit of monitoring asymptomatic masses is to identify masses that are malignant by observing growth over time, the longer a mass is observed to be stable, the less likely it is to represent a malignancy, and therefore the lower the potential benefit of further monitoring. Within the population-based cohort we studied, all five epithelial cancers as well as nine borderline tumors demonstrated clear growth on their first follow-up ultrasound (13). Similarly, in the Kentucky study, all malignant tumors were identified as worrisome within a relatively short time frame from

initial detection, with malignant tumors receiving only 2.1 scans over a mean 2.3 months prior to removal (21). The recognition that ovarian cancers are heterogeneous in behavior with some tumors having more indolent growth patterns than others has led to a new paradigm that categorizes ovarian cancers as Type 1 or Type 2 based on their purported pathogenesis (33, 34). Type 2 cancers, which include high grade serous histology and represent the majority of ovarian epithelial malignancies, are thought to arise primarily from fallopian tube rather than ovarian precursors, which helps explain the failure of screening trials to detect these cancers at early stage. Type 1 cancers, which include low grade endometrioid, clear cell, and mucinous histologies, are thought to arise from endometriosis or ovarian precursors and generally demonstrate a more indolent growth pattern. Therefore, the paradigm raises the question of whether screening, or indefinitely prolonged monitoring of stable masses, which eventually becomes tantamount to screening, confers significant benefit for early detection of Type 1 cancers. This is an open question. However, any prediction of benefit from detection of Type 1 cancers must take into consideration the fact that benefit is realized only if the stage at diagnosis is earlier than would otherwise occur. Since this subset of cancers come to clinical attention much more often at early stage (35), such benefit is less likely. In our study, three of the seven cancers were Type 1 and all demonstrated growth on follow-up ultrasound within 7 months with no additional cancer diagnoses within 24 months of follow-up (13). Similarly, in UKCTOCS, all of the Type 1 cancers found among women who demonstrated an abnormality on initial ultrasound evaluation were diagnosed within the first year of follow-up (9). No measurable benefit from monitoring of stable masses beyond 2 years has ever been demonstrated.

POTENTIAL HARMS OF MONITORING

Although the potential benefit of monitoring wanes over time, the potential harms are cumulative. The most significant harm occurs from unnecessary surgery for a benign asymptomatic mass. Benign adnexal masses are known to be extremely common. Depending on the size threshold of what constitutes a "mass," autopsy studies have shown that between 17 and 56% of postmenopausal women who died from non-gynecologic causes harbor ovarian cystic or solid masses at the time of death (36, 37). Although surgical removal is appropriate for symptomatic masses, there is no clear benefit of removal of a benign asymptomatic adnexal mass. Thus, surgery that is done for an asymptomatic mass that does not reveal cancer is appropriately considered as a harm in cancer screening trials. Although minimally invasive techniques have lowered overall morbidity of surgery, such procedures were still found to be associated with an average 6% serious complication rate across screening trials (11). If bilateral salpingo-oophorectomy is done, depending on patient age, there is also potential harm from loss of hormone function, as negative impacts on cardiovascular health, bone health, and possibly cognitive function have been reported in women whose ovaries were removed prior to 50 years of age (38). Costs to the health-care system from surgery and complications as well as both direct and indirect costs to patients are substantial. Although initial monitoring helps to avoid immediate surgery, prolonged monitoring of stable masses increases the likelihood of unnecessary surgery for incidental findings. It is not uncommon for a woman who is being followed for a stable adnexal abnormality to be found on repeat imaging to have a new adnexal abnormality, given the high prevalence of adnexal lesions, which then triggers another round of evaluation with either surgery or observation.

CONCLUSION

In summary, ultrasound monitoring of adnexal masses is valuable in identifying early cancers among women who have small masses are asymptomatic and do not demonstrate other signs of cancer such as elevated CA125 or ascites. However, the overall risk of cancer for these women is very low. A short-term repeat ultrasound at 6–8 weeks to evaluate for either regression or growth helps to avoids surgery on transient masses and does not appear to worsen prognosis in the event that the mass represents an early cancer. In this population, the ultrasound criteria used to label adnexal masses as "highly worrisome," and therefore excluded from consideration of any monitoring, should be clearly defined and relatively stringent, given the overall low risk of malignancy. The presence of significant solid components that demonstrate vascular flow appears to be the ultrasound characteristic for which there is the greatest consensus as to its specificity for malignancy. Masses demonstrating clear progression during monitoring should be removed. For stable masses, repeat ultrasound at 3-month intervals, to observe for worrisome growth or changes in complexity is appropriate. However, since the potential benefit in terms of cancer identification wanes with time, the duration of monitoring of stable masses should be limited to 1–2 years in order to limit potential harms from overtreatment and overdiagnosis.

AUTHOR CONTRIBUTIONS

ES-B: literature review and manuscript writing. WK: literature review and manuscript editing.

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Reducing Overtreatment in Gynecologic Oncology: The Case for Less in Endometrial and Ovarian Cancer

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A growing awareness of the harms of overtreatment in cancer care has reached physicians, patients, health policy makers, and medical researchers. Overtreatment exposes patients to the risk of adverse events from procedures or medications that were not necessary. This review examines common practices in gynecologic malignancies that are unlikely to produce direct benefit to patients with these malignancies, but are likely to produce harms. Specifically, we will explore the utility of lymphadenectomy and adjuvant radiation for women with early-stage endometrial cancer; and screening for recurrence and continuous chemotherapy for advanced-stage ovarian cancer patients.

Keywords: gynecologic cancer, ovarian cancer, endometrial cancer, overtreatment, cancer care delivery

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INTRODUCTION

The development of practical quality care measures has become a priority within the US health-care system. The Institute of Medicine (IOM) has identified three categories of health-care quality problems: underuse, overuse, and misuse (1–4). Underuse of effective therapies and misuse of services have received the most attention from quality improvement initiatives and patient safety efforts. However, recently, growing attention to an epidemic of overtreatment has been critically evaluated as problematic.

The term "overuse" in health care was introduced in 1991 in an editorial by Mark Chassin, as "the provision of health services when the risks outweigh their benefits" (5). The IOM first defined overuse in 1998 as the use of health-care resources and procedures in the absence of evidence that the service is beneficial (2). Overuse has been cited as a driver of the high cost of cancer in the United States (3, 4).

Overtreatment is a component of overuse defined as "treatment of conditions that will never cause symptoms, is futile or is excessive in complexity, duration, or cost when compared to accepted standards of care" (6). Overtreatment may seem innocuous in some cases (e.g., a patient has an extra blood test). In other cases (e.g., patients receiving chemotherapy or surgery that will not work for them), the harms are more apparent. Beyond the issue of cost, overtreatment exposes patients to the risks of adverse events from medications or procedures that they do not need.

In 2012, the American Board of Internal Medicine (ABIM), along with nine other specialty societies, released its Choosing Wisely campaign, focused on reducing overuse of specific medical tests or procedures in different health-care specialties. It includes an explicit goal of avoiding care that

is "unnecessary or whose harm may outweigh the benefits" (7). The recommendations provided by the Society for Gynecologic Oncology (SGO) are listed in **Table 1** (8). These SGO recommendations focus primarily on screening. Reducing overscreening and overtesting represents an important first step in controlling overuse. But these measures address low-hanging fruit – the most obvious or least remunerative examples of overused procedures.

As cancer treatment becomes increasingly expensive with the rapid development of precision medicine, eliminating overuse is crucial to a sustainable system of care. Easily identifiable targets of overuse in gynecologic cancers beyond those identified in the Choosing Wisely campaign exist. The purpose of this review is to explore strategies to reduce overtreatment in gynecologic cancers. This review will focus on the following specific examples selected by the authors as high priority areas where overtreatment can be curtailed: (1) the practice of lymphadenectomy and (2) postoperative radiation in early-stage endometrial cancer; (3) screening for recurrence in asymptomatic ovarian cancer patients; and (4) continuous chemotherapy for the treatment of ovarian cancer. Recommendations for reducing overtreatment are provided by the authors as opinions.

ENDOMETRIAL CANCER

Endometrial cancer is expected to be diagnosed in 60,050 women in the United States in 2016, making it the most common gynecologic malignancy (9). Fortunately, most patients (80%) are diagnosed with local disease and will survive their cancer diagnosis. In fact, the majority of 5-year deaths in this population are due to the medical comorbidities frequently linked with endometrial cancer, including older age, obesity, and diabetes (10). Initial treatment includes a hysterectomy with salpingo-oophorectomy with surgical staging. Patients who develop metastatic recurrent disease have a poor prognosis and treatment options are limited (11). Because of the difficulty predicting who is at risk for recurrence, adjuvant treatment following hysterectomy is broadly prescribed to many with the goal of preventing recurrence in a few patients.

TABLE 1 | The society for gynecologic oncology choosing wisely (8).

- **Do not screen low-risk women with CA-125 or ultrasound for ovarian cancer**
  - o CA-125 and ultrasound in low-risk, asymptomatic women have not led to diagnosis of ovarian cancer in earlier stages of disease or reduced ovarian cancer mortality. False-positive results of either test can lead to unnecessary procedures, which have risks of complication
- **Do not perform colposcopy in patients treated for cervical cancer with Pap tests of low-grade squamous intraepithelial lesion (LGSIL) or less**
  - o Colposcopy for low-grade abnormalities in this group does not detect recurrence unless there is a visible lesion and is not cost-effective
- **Do not perform Pap tests for surveillance of women with a history of endometrial cancer**
  - o Pap testing of the top of the vagina in women treated for endometrial cancer does not improve detection of local recurrence. False-positive Pap smears in this group can lead to unnecessary procedures, such as colposcopy and biopsy
- **Avoid routine imaging for cancer surveillance in women with gynecologic cancer, specifically ovarian, endometrial, cervical, vulvar, and vaginal cancer**
  - o Imaging in the absence of symptoms or rising tumor markers has shown low yield in detecting recurrence or impacting overall survival
- **Do not delay basic level palliative care for women with advanced or relapsed gynecologic cancer, and when appropriate, refer to specialty level palliative medicine**
  - o There is now an evidence-based consensus among physicians who care for cancer patients that palliative care improves symptom burden and quality of life. Palliative care empowers patients and physicians to work together to set appropriate goals for care and outcomes. Palliative care can and should be delivered in parallel with cancer directed therapies in appropriate patients

Although as a whole, clinical stage I endometrial cancer patients have a low risk for lymphatic metastasis, GOG 33 showed that some risk factors (grade, depth of myometrial invasion, and vascular space invasion) do correlate strongly with lymphatic metastasis (12). The primary role of surgical staging for endometrial cancer is to identify the small subset of patients with lymphatic metastasis to the pelvic lymph nodes as these are patients known to benefit from adjuvant therapy. Unfortunately, none of this information is reliably available pre- or even intraoperatively. The accuracy of preoperative tumor grade is poor, as 20–25% of cases that are grade 1 on biopsy will be upgraded after hysterectomy. Accuracy of depth of invasion at frozen section is similarly disappointing, especially when performed outside of high volume centers with experienced pathologists. A prospective, blinded study of the accuracy of frozen section revealed that tumor grade at frozen section correlated with final pathology in only 58% of cases, while depth of invasion correlated in 67% of patients. Overall, 28% of patients were upstaged from the intraoperative assessment to final pathology (13).

Surgical staging had been the norm for decades, its practice reinforced by retrospective studies showing a survival benefit in patients with high-risk features who underwent a systematic pelvic and para-aortic lymphadenectomy (14, 15). This surgical dogma has been questioned after two prospective randomized trials, evaluating that the value of lymph node dissection at the time of hysterectomy (ASTEC, CONSORT) failed to demonstrate a survival advantage with lymphadenectomy while confirming significant morbidity with the procedure (16, 17). The morbidity associated with lymph node dissection includes direct surgical morbidity (increased intraoperative time, greater blood loss, and risk of surgical complications) as well as the long-term consequences of lymphedema. Despite criticisms of these studies, including (1) a low-risk patient population with a low probability of nodal metastases and (2) the inconsistent application of information obtained from the nodal dissection to guide adjuvant therapy, these studies reflect many of the real world issues faced by clinicians caring for endometrial cancer patients.

Prospective studies examining the value of postoperative adjuvant treatment in patients with apparent early-stage disease but no lymphatic assessment have failed to demonstrate a survival benefit (11, 18–20). In the 1970s, a randomized prospective trial of postoperative whole pelvic radiation versus brachytherapy alone concluded that although radiation decreased recurrence rates, it had no effect on overall survival. More than 20 years of follow-up to this study revealed decreased long-term survival

and increased secondary malignancies following postoperative whole pelvic radiation (21). The finding that the reduction of locoregional recurrence after pelvic radiation was not associated with a survival advantage has been confirmed subsequently by PORTEC-1, GOG-99, and ASTEC (11, 17, 19). The PORTEC-2 trial showed that vaginal brachytherapy provides equivalent locoregional control when compared to whole pelvic radiation with fewer adverse effects and improved quality of life (18). Low-risk patients (Stage 1A and B, Grades 1 and 2) randomized to vaginal brachytherapy or observation have been shown to have similar recurrence risks (22). Despite flaws in many of these trials (e.g., underpowered for a survival outcome), adjuvant radiation is not recommended for women with low-risk disease (23).

Early-stage endometrial cancer patients who are observed after surgery, although overall more likely to recur, are more likely to have isolated vaginal recurrences than women treated with adjuvant radiation (19–21, 24). Salvage rates for isolated pelvic recurrences with modern radiation techniques have been shown to be high (24, 25).

Trends in the use of lymphadenectomy in women who underwent surgery for endometrioid adenocarcinoma of the endometrium in the United States were recently analyzed using the surveillance, epidemiology, and end results (SEER) cancer registry between 1998 and 2012. Investigators found that a decreased frequency of lymphadenectomy from 2007 to 2012 was not associated with a change in the proportion of women found to have lymphatic metastasis. Interestingly, a small increase in survival accompanied the decrease in lymphadenectomy (26).

The Identification of Endometrial Cancer Patients Who Can Safely Avoid Lymphadenectomy

Accurate identification of the small number of patients with lymphatic metastasis remains crucial as lymphadenectomy for these patients can have prognostic and possibly therapeutic value. When high-risk features are identified after hysterectomy only, clinicians must decide between returning to the operating room for a staging lymphadenectomy or basing treatment decisions on uterine factors, an approach that has a significant risk of resulting in overtreatment with postoperative adjuvant radiation as the majority of patients at "high risk" for lymphatic metastasis actually do not have metastatic disease (27).

Using a composite index of traditional risk factors for recurrence, investigators from the Mayo Clinic have identified a subgroup of patients at very low risk for lymph node metastasis. In a series of 328 patients treated at the Mayo Clinic with grade 1 or 2 endometrioid tumors, <2 cm in diameter and <50% myometrial invasion identified at time of intraoperative frozen section, the rate of nodal metastasis was 5% and 5-year survival was 97% (28). These criteria were further examined prospectively through a multi-institutional evaluation that noted a negative predictive value of 98.2% (29, 30). Broader utilization of these criteria could potentially eliminate unnecessary lymphadenectomies in women with endometrial cancer.

Sentinel lymph node biopsies (SLN) have been proposed as a surgical alternative to complete lymphadenectomy in patients with apparent early-stage endometrial cancer. The goal of SLN mapping is to accurately identify lymph node metastases while saving patients from the morbidity of complete lymphadenectomy. The utility of this technique as a strategy to reduce overtreatment has been firmly established in other disease sites (breast cancer and melanoma); however, the value and positive predictive value of SLN mapping in endometrial cancer has not been explored outside of single institution studies. Whether SLN biopsy can prevent the perioperative morbidity and long-term sequelae of lymphedema in this population without increasing recurrence rates and disease-related mortality is an important clinical question.

The Identification of Endometrial Cancer Patients Who Can Safely Avoid Adjuvant Radiation

The strongest argument for lymphadenectomy in early endometrial cancer is that women with a lymph node sampling may be able to safely avoid adjuvant radiation. Information obtained from lymph node dissection influences the prescription of postoperative adjuvant radiation. A report of 181 women, with a diagnosis of grade 1 endometrial cancer, who underwent staging lymphadenectomy found that 19% of the neoplasms were upgraded, 18% were upstaged, while adjuvant therapy was affected by the results of lymphadenectomy in 26% of women (31). Women without surgical staging received radiation at higher rates than those with information available regarding their lymph node status. The application of newer surgical algorithms (using Mayo criteria to select patients who need lymphadenectomy) and validation of the practice of SLN could potentially reduce overprescribing of adjuvant radiation without resorting to lymphadenectomies for all.

Recent advances in molecular technology may provide additional insight into the identification of patients with a good prognosis who may not require treatment beyond a hysterectomy. The Cancer Genome Atlas (TCGA) performed an integrated molecular analysis of 373 endometrial tumors and was able to define four groups based on genomic characterization of mutation profiles, and to furthermore demonstrate that these groups correlate with prognosis. One of these groups (POLE-mutant) carried an exceptionally good prognosis (32). Between 4 and 12% of endometrial cancers are POLE-mutated and this genetic abnormality does not necessarily map onto traditional histopathological categories (32–35). Updated molecular classifications of disease to predict biologic behavior are needed. An assay able to identify patients at low risk for recurrence would transform treatment for this disease.

OVARIAN CANCER

Ovarian cancer is the most lethal of the gynecologic cancers. In the United States in 2016, there will be an estimated 22,280 cases and 14,240 deaths related to this disease (9). Among women with stage III or IV ovarian cancer, 5-year survival is only 10–25% despite aggressive treatment with surgery and adjuvant chemotherapy. Despite high response rates to initial therapy, epithelial ovarian cancer ultimately recurs in most patients. The

poor prognosis associated with a diagnosis of epithelial ovarian cancer is due both to the advanced stage of disease at the time of diagnosis and the eventual development of chemotherapy-resistant disease. However, this disease is heterogeneous and there is considerable variability in survival even among patients diagnosed at an advanced stage (36). A reliable molecular signature identifying patients with a better or worse prognosis has not yet been identified.

Because of the high relapse rates, the follow-up of women treated for ovarian cancer represents a challenge for the gynecologic oncologist. Cancer surveillance following initial treatment and complete response is essentially screening for early relapse. In order for a screening test to be effective, effective treatment for the disease (in this case early relapse) must be available and the treatment of early relapse would have to be more effective than the treatment of late relapse. In the setting of platinum resistant disease, few therapeutic options prolong survival. In the setting of platinum-sensitive ovarian cancer, retreatment with platinum-based combination chemotherapy results in high complete response rates. As the platinum-free interval extends, the response rates to retreatment become even higher.

One of the harms of this screening for recurrent ovarian cancer is the development of a lead time bias (**Figure 1**). Early diagnosis of recurrent disease exposes the patient to additional chemotherapy without this improving overall survival and may limit treatment further into the disease course. Many women with ovarian cancer receive multiple imaging tests per year and lifelong chemotherapy once recurrent disease is diagnosed. Both imaging and continuous chemotherapy are of little value in changing survival from this disease but are commonly prescribed (37, 38).

The Utility of Following CA-125 Levels in Improving Survival from Ovarian Cancer

Cancer antigen 125 (CA-125) is a glycoprotein that is the current standard of care biomarker for ovarian cancer surveillance. More than 80% of women with advanced-stage ovarian cancer have an elevated level of CA-125 at the time of initial diagnosis. Periodic follow-up measurements of CA-125 levels after treatment for ovarian cancer allow the detection of recurrences months before symptoms or signs appear, since the CA-125 level generally increases 2–6 months before a recurrence is radiologically or clinically detectable (39). However, treatment for recurrence in asymptomatic women with an increased CA-125 level and a history of ovarian cancer has not been shown to alter survival. In a landmark study conducted by the European Organisation for Research and Treatment of Cancer (MRC OV05/EORTCC 55955), 529 women who experienced a complete clinical remission after undergoing initial treatment for ovarian cancer were randomized to undergo treatment for recurrence either (1) immediately after detection of a rise in the level of CA-125 or (2) after the onset of symptoms, regardless of the CA-125 level. No evidence of a survival benefit was found with early treatment for recurrence (27.1 versus 25.7 months) on the basis of an elevated CA-125 concentration. Women who were in the early group had earlier deterioration in quality of life versus women in the delayed treatment group (40). Criticisms of this study included enrollment of poor prognosis women, changes in second-line chemotherapy options for ovarian cancer, and low rates of secondary cytoreduction (41). A retrospective study of 121 patients undergoing secondary cytoreduction did suggest an advantage for patients whose recurrence was discovered through screening (42). This single institution study may have been biased by its retrospective nature and the tertiary care setting. Overall, there is no clear evidence that surveillance impacts survival compared to waiting for the presentation of symptoms (41, 43).

The Utility of Routine Imaging in Improving Survival from Ovarian Cancer

Expert recommendations include obtaining imaging in patients with a history of ovarian cancer only in women with

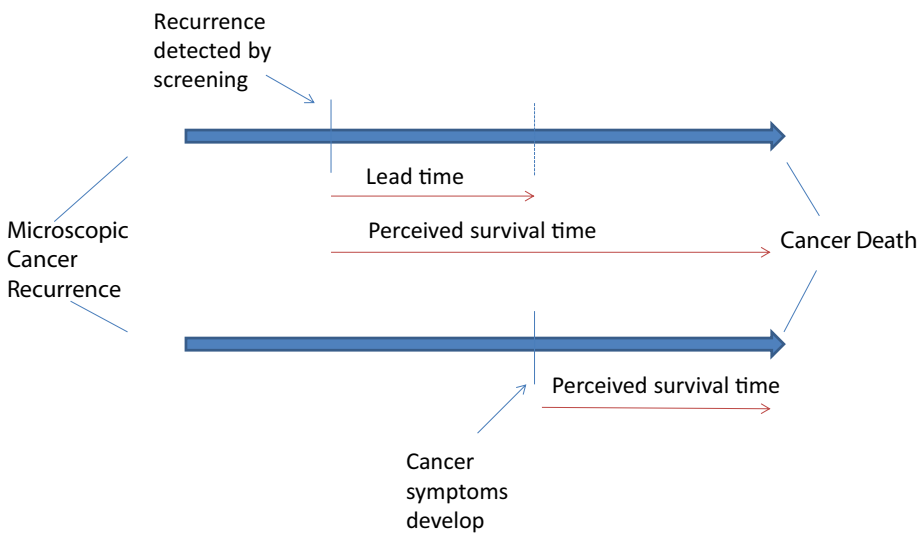

FIGURE 1 | Lead time bias that develops from early screening for cancer recurrence.

an increasing tumor marker or with symptoms worrisome for recurrence (41, 44). Computerized tomographic scans (CT) are currently the imaging modality of choice for the evaluation of suspected ovarian cancer recurrences. Given the lack of evidence that surveillance using the level of CA-125 present in blood samples prolongs survival, it is implausible that the early detection of recurrence through routine CT scanning could result in any significant increase in survival (40). These clinical limitations of CT make magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging with their added expense and potentially increased false-positive rates challenging to justify in the asymptomatic ovarian cancer patient.

Chemotherapy and the Treatment of Asymptomatic Disease

The majority of ovarian cancer patients will relapse within 5 years and, therefore, require salvage chemotherapy. Although improvements in chemotherapy have increased overall survival, recurrent ovarian cancer remains a lethal disease. Because salvage treatments are not curative, the goals of treatment in this setting are to extend survival through disease control and palliation of cancer symptoms. An emphasis on an individual patient's quality of life is crucial.

A 2006 study evaluated ovarian cancer survival with the SEER database for patients treated with chemotherapy by a medical oncologist or gynecologic oncologist. Although both groups of physicians are trained to provide medical treatment to ovarian cancer patients, substantial differences in the patterns of care emerged based on the patient's provider. During the first 5 years of care for ovarian cancer, patients treated by medical oncologists received more weeks of chemotherapy than patients treated by gynecologic oncologists (patient mean, 16.5 versus 12.1 weeks, respectively, $P < 0.0023$). This increase in chemotherapy administration translated to increased adverse events. Gynecologic oncology patients had fewer weeks that included chemotherapy-associated adverse events than medical oncology patients (patient mean, 8.9 versus 16.2 weeks, respectively, $P < 0.0001$). No survival advantage was achieved for patients receiving chemotherapy administered by a medical oncologist (37).

CONCLUSION

As we strive toward defining quality measures in health care in the United States, defining best practices for women with gynecologic cancer should be a priority. Further research in endometrial cancer should be focused on defining which women with this disease can safely avoid lymphadenectomy and post-hysterectomy radiation and providing evidence that postoperative surveillance is safe such that practitioners feel comfortable making this recommendation. Best practices for post-treatment surveillance in ovarian cancer patients should be individualized, taking into account the clinical benefit of second-line therapy, costs, morbidity and mortality of the surveillance methods, available treatment options, and patient preference.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Confronting the Care Delivery Challenges Arising from Precision Medicine

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Understanding the biology of cancer at the cellular and molecular levels, and the application of such knowledge to the patient, has opened new opportunities and uncovered new obstacles to quality cancer care delivery. Benefits include our ability to now understand that many, if not most, cancers are not one-size-fits-all. Cancers are a variety of diseases for which intervention may be very different. This approach is beginning to bear fruit in gynecologic cancers where we are investigating therapeutic optimization at a more focused level, that while not yet precision care, is perhaps much improved. Obstacles to quality care for patients come from many directions. These include incomplete understanding of the role of the mutant proteins in the cancers, the narrow spectrum of agents, broader mutational profiles in solid tumors, and sometimes overzealous application of the findings of genetic testing. This has been further compromised by the unbridled use of social media by all stakeholders in cancer care often without scientific qualification, where anecdote sometimes masquerades as a fact. The only current remedy is to wave the flag of caution, encourage all patients who undergo genetic testing, either germline or somatic, to do so with the oversight of genetic counselors and physician scientists knowledgeable in the pathways involved. This aspiration is accomplished with well-designed clinical trials that inform next steps in this complex and ever evolving process.

Keywords: precision medicine, biomarkers, targets, genetic testing, opportunities, obstacles

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INTRODUCTION

Cancer care delivery was once relatively simple due to the few available drugs, limited understanding of the complexity of the cancers, and less sophisticated diagnostic and therapeutic interventions. The exponential increase in knowledge brought about by microdissection of the genome, kinome, and other – omes, has yielded new classifications of cancers, classes of agents, different methods for dose determination, and increasing potential for personalization. This rapidly expanding knowledge creates the potential for diversity and inequality in cancer care.

Understanding the roles and limitations of these new resources narrows that treatment delivery gap. The harmonization of diagnostic approaches and expectations for each patient with a defined cancer histology and/or genomic subtype will assure the same care for all. Monitoring for treatment decisions should be consistent and driven by objective data, change in responsiveness, and/or toxicity parameters. Recognition of when the risk/benefit balance has shifted toward harm remains a critical element.

Optimization of cancer treatment in the molecular era is not always defined by the molecular make up of cancer. Characterization of the molecular biomarker utility across a type of cancer and then from the patient perspective needs to be coordinated. The charge to the molecular oncologist is to recognize when compelling data from high-level evidence identifies a molecular finding of therapeutic importance. In most cancers, this remains a goal. We have few validated biomarkers to guide us in women's cancers and an abundance of molecular noise to dampen. Molecular testing is often done for reasons that the patients do not understand, and the testing costs thousands of dollars, frequently yielding little guidance. Determining and validating selective targets, target-drug pairing, and best patient practices will take carefully designed studies with well considered correlative science, requiring patients, time, and support. Currently, other than the use of germline *BRCA1/2* mutation testing and Lynch Syndrome testing, application of molecular diagnostics to the broad gynecologic cancer population is premature.

BIOMARKERS: WHAT, WHEN, AND WHY

Biomarkers, Definition?

A biomarker generally refers to a measured characteristic, which may be used as an indicator of some biological state or condition. Biomarkers may be developed to address multiple purposes related to patient diagnosis and selection, or drug and treatment effect. Molecular diagnostics can be translocations, such as *BCR-ABL* for chronic myelogenous leukemia, expression of mutant proteins or inappropriate protein expression, such as p53 in many solid tumors, or loss of expression as with E-cadherin loss in lobular breast cancer.

Molecular biomarkers can be used for therapeutic selection. Amplification of *HER2* is both a diagnostic and selective biomarker. It helps classify a type of breast cancer, and its presence determines targeted therapy selection. Identification of specific mutations in lung cancer, such as *EGFR* mutations, drives selection of the therapeutic classes of targeted agents. Alternatively, broad sequencing in a discovery mode can be used to determine targetable molecular events on a case-by-case basis. This is the hypothesis underlying the NCI MATCH study (NCT02465060) and other basket studies.

Biomarkers also may be used as surrogates of clinical behavior, such as those readily measured in blood-like, CA-125 and PSA. These biomarkers may also be evaluated for prognostic and/or predictive potential. Prognostic biomarkers are those that dichotomize clinical outcomes, such as survival, in a therapy-agnostic fashion (**Figure 1A**). They are most often defined based upon correlative findings. Clinical biomarkers used commonly as prognostic directors in women's cancers include stage, grade, age, lymphovascular space invasion, and number of positive lymph nodes (1).

Predictive biomarkers are most elusive and potentially most valuable (2, 3). They dichotomize outcomes in a therapy-specific fashion (**Figure 1B**). HER2, a diagnostic and selection biomarker, is both prognostic and predictive, shifting the full cohort outcome and biomarker positive patients in the upper set of curves (**Figure 1C**) (4, 5). HER-2^{AMP} breast cancer patients had a worse prognosis when given the same treatment as their HER-2 non-amplified counterparts. The introduction of HER-2 targeted therapy has changed that poor prognosis. Now, HER-2^{AMP} is a biomarker predictive of responsiveness to HER-2 targeted agents.

Integral vs. Integrated Trial Biomarkers

Rigorous biomarker development is important. It requires qualification, optimization, and validation at levels of pre-analytic and analytical methods. Standard operating procedures for the collection and processing of patient-derived materials, pre-analytic methodologies, assure the collection of high-quality specimens. What samples, how they are taken, how and when they are processed, and the what/how/when of storage are critical pre-analytical variables (6). Quality control of reliability, reproducibility, variance, and cut-off determination are key analytical variables (7, 8).

Biomarkers that are required for the execution of a trial and/or the application of an agent are integral to the therapeutic direction. Integral biomarkers require the tightest pre-analytical and analytical standards, and if involved in patient care, must be done in appropriately certified laboratories. Integrated biomarkers are those that are included in clinical trials in hypothesis-directed objectives to be executed in a controlled, optimized fashion, to validate them for future integral application. Integral and integrated biomarkers use assay methodologies that are well past exploration and discovery and are moving toward anticipated use or standard of care. Understanding where a molecular biomarker is in development is critical to its proper application to the patient treatment setting.

Fit-for-Purpose Biomarkers

The complexity of biomarker selection underscores the importance of using biomarkers that are fit-for-purpose (FFP). A FFP biomarker is defined by its intended use and by the biomarker assay method performance (2). The intended use or purpose of the biomarker or biomarker assay data is described in many ways, including pharmacokinetic, pharmacodynamic, diagnostic, exploratory, safety, enrollment, or companion diagnostic. A FFP biomarker is categorized as (a) integral, used for patient or treatment selection, (b) integrated, used to established treatment or disease state effects, or (c) exploratory, used descriptively or for screening for effects that are unestablished or poorly described. The stringency of the proposed assay method validation is defined and determined by the biomarker category, risk–benefit to the patient, and invasiveness. Biomarker assay method performance must be reliable and reproducible, and the assay must have well-defined performance characteristics. Performance metrics are qualitative and quantitative and include measures of sensitivity, specificity, accuracy, precision/robustness, stability, reference intervals/standards and cut-points (dynamic range), calibrators, range of quantification, dilutional linearity, sample re-analysis, interference, and normal signal

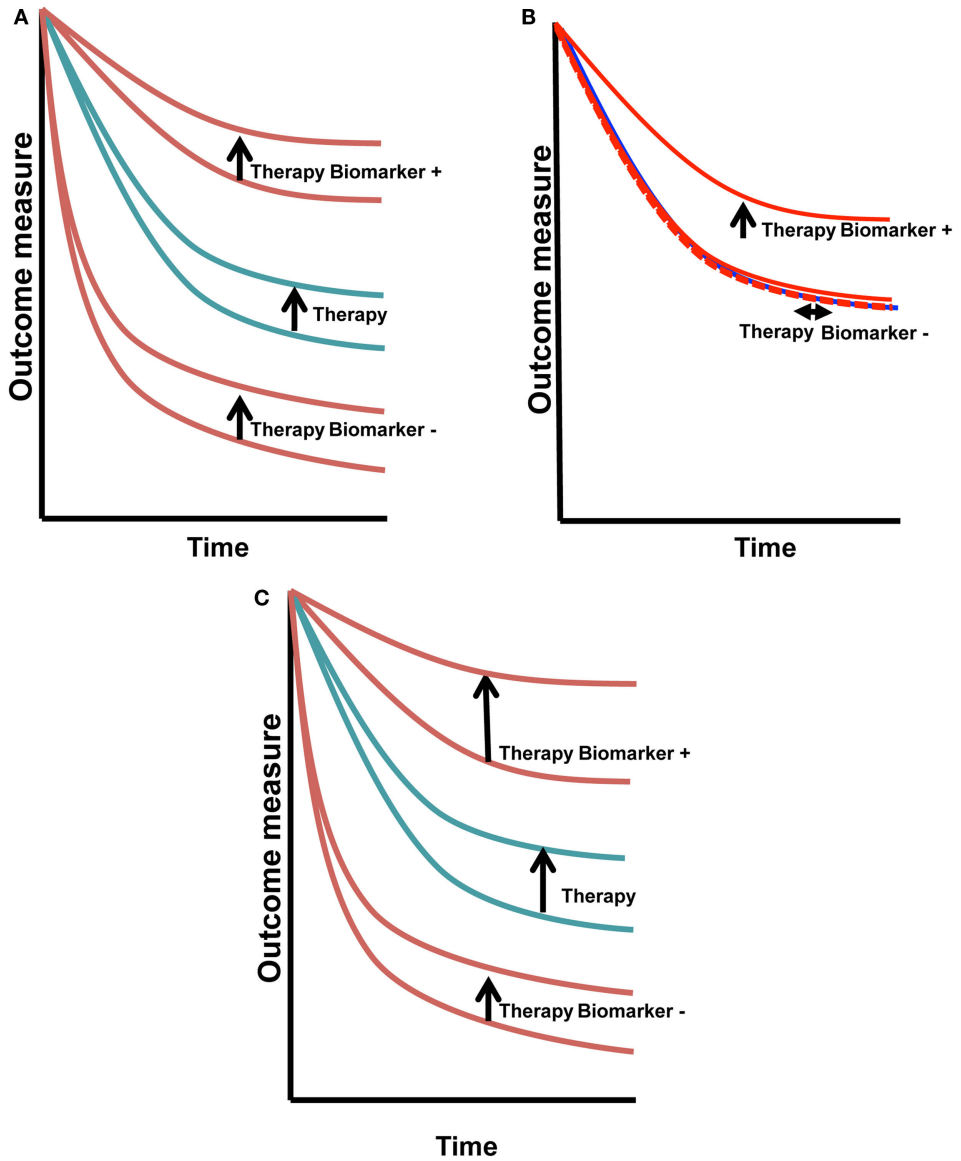

FIGURE 1 | Predictive vs. prognostic biomarkers. Prognostic biomarkers **(A)** have similar change in outcome with therapy that is independent of the biomarker status. Predictive biomarkers **(B)** have a treatment/outcome interaction, seen in this example as improvement with treatment in biomarker$^+$ cases (vertical arrow), with absence of change in the biomarker$^-$ cases (horizontal arrow). Biomarkers that may be both prognostic and predictive **(C)** will shift the biomarker$^+$ curve the same or greater if both the prognostic and predictive effects are positive. If one is positive and the other is negative, the outcome may cancel. This is a more complex situation to dissect.

distribution. Methodology performance evaluation is iterative and is updated throughout the life cycle of the biomarker development (9).

The circumstances under which biomarker testing is applied should be considered in the context of standard testing issues when planning a clinical trial. Each trial should have a biomarker prioritization plan. Parallel development of drugs and biomarkers is the key to rapid and purposeful progress. Many prognostic, but few predictive, biomarkers are under development. Such development is found in the translational literature and in clinical trial design where such questions are included.

OPTIMIZING MOLECULAR CANCER CARE DELIVERY FOR THE PATIENT

When Is It Precision Treatment or Scientific Experiment?

Optimal use of diagnostic and therapeutic resources requires understanding when there is potential for reliable data or when it is a shot in the dark. Few biomarkers have been validated in gynecologic cancers. They include the serum biomarkers for germ cell tumors (βHCG and αFP) (10), recurrent epithelial ovarian cancer (CA-125 and HE4) (11–14), endometrial cancer (HE4) (15),

granulosa cell tumors (inhibin) (16), and the molecular markers of germline or somatic *BRCA1 or BRCA2* mutation (1, 17–19).

Driver molecular events have been identified and validated in some sarcomas and solid tumors. Drivers are molecular events that, based upon preclinical modeling and clinical testing, initiate, promote, and/or maintain malignancy in an obligatory fashion. Specific inhibition of driver(s) in patients results in dramatic clinical response. For example, the *bcr-abl* translocation results in constitutive activation of abl kinase and drives chronic myelogenous leukemia. Its inhibition with imatinib, dasatinib, and others is the gold standard example to define driver function (20). As impressive as these events are in preclinical models and in patients, to date, the only curative driver events have been identified in leukemias.

The most common drivers identified cause gain-of-function oncogenic behaviors, commonly by translocation, mutation, or occasionally by amplification. The regions in oncogenes that result in unfettered activation are few and are "hot spot" mutations for which focused screening can be done, or are identifiable breakpoints at translocations causing an activation event that can be readily identified. Similarly, oncogenic mutations, such as those seen in *c-kit* and *PDGFR* in gastrointestinal stromal tumors (21, 22) and translocations, such as the driving *ALK* translocation in non-small cell lung cancers (23), likewise, cause constitutive kinase or receptor activity. Inhibition of oncogenic signaling pathways by small molecule inhibitors results in impressive objective clinical effects (24, 25).

Inhibition of tumor suppressor genes is another mechanism through which carcinogenic behaviors are unmasked. Loss-of-function of tumor suppressor genes occurs with one of several events, such as mutational introduction of a stop codon that prevents transcription and translation of an active protein or by mutation that inactivates or alters function of the translated protein. These events are seen in p53 in ovarian and endometrial cancers. Unlike the hotspot mutational foci seen in oncogenic gain-of-function mutations or translocations, tumor suppressor gene mutations and rearrangements can and do occur all along the gene with "hot spots" that may identify population founder events. The more common gain-of-function p53 mutation is one where the mutation abrogates normal p53 checkpoint activity allowing cells to move through the cell cycle without stopping to repair the DNA damage. Protein is not lost and is seen as strong and broad staining of p53 by immunohistochemistry. The loss-of-function events, where p53 protein is lost, also have been identified in gynecologic cancers (26), and the early data suggest that there may be biological differences caused by the two mutational events (27). Yet, there are no validated specific or selective therapeutic opportunities related to p53 mutations. Thus, while serving a diagnostic and prognostic purpose, p53 has no targeted therapeutic direction or predictive value.

*BRCA*1 and *BRCA*2 are tumor suppressor genes. Homozygous genomic injury with resultant loss of both functional alleles has strong biologic effect in reduction of homologous recombination double-stranded DNA repair (28). Germline monoallelic loss predisposes to breast and ovarian cancers yielding a very high lifetime risk and has been used to trigger cancer prevention approaches. Recently, PARP inhibitors, a drug class within the broad category of DNA repair inhibitors, have been shown to be more active in women with germline loss (29). *BRCA* mutations have thus been validated as predictive biomarkers in this setting. *BRCA* mutation testing has been approved by the US FDA as a companion diagnostic for selection for treatment with olaparib; it is a predictive and selective biomarker approved as related specifically to treatment with the PARP inhibitor, olaparib, for women in fourth or later ovarian cancer recurrence. Despite inclusion in the EMA approval of olaparib, the role of somatic BRCA mutation remains unclear and has not been accepted by the US FDA. Clarification of homozygous mutation vs. single somatic mutation and issues of gene dosage should be addressed.

When Is Molecular Testing Reasonable for Standard of Care Oncologic Intervention?

A strong family history alone does not predict accurately the full spectrum of women with *BRCA* mutation-associated ovarian cancer. Thus, NCCN and SGO recommend testing all women with high-grade serous ovarian cancer. This can have implications for the patient's family if she is found to harbor a deleterious germline mutation, found in approximately 17% of the newly diagnosed high-grade serous ovarian cancer patients (30). Lack of mutation has not been shown to be of biologic value. Knowledge of *BRCA* status may have impact upon cancer care for investigational uses, as defined by clinical trial entry criteria, but in the US does not affect treatment opportunities until fourth treatment line. The effect on the patient and her family is also of importance and is addressed elsewhere in this Research Topic.

Risk panel testing, whole exome and genome testing, and testing of oncogene panels are done as "standard of care" in some centers and often requested in order to find something actionable. Panel testing is the examination of a series of potentially important risk genes, such as the BROCA panel defined by Swisher and colleagues (31, 32). It includes the Lynch Syndrome genes and other genes with low frequency, but deleterious germline mutations, including *PALB2*, *RAD51*c, and *RAD51d*. Mutations in these genes may be linked to the risk of ovarian and other cancers, a prognostic event, but there is no validated predictive function (31). There are no data that exome or whole genome sequencing is medically useful or cost-effective for gynecologic cancer patients. Too often, this testing is presented to or by the patient as an expectation, related to receipt of care. The facts and foibles are not presented in depth, and often no or minimal informed consent is done, since many of these are commercially available. This includes not fully informing the patient about the financial implication and the support or lack thereof by their insurance coverage. The number of truly actionable events, where there are validated clinical outcomes linked to genomic findings, are exceptionally rare in gynecologic cancers and do not inform patient care. Such testing should be done in the context of a clinical trial, such as the NCI MATCH (NCT02465060).

Opportunities and Obstacles

Molecular characterization of gynecologic and other cancers created a great opportunity for learning about the behavior of the cancer, its heterogeneity, how subclones outgrow during

treatment, and to identify therapeutic opportunities (**Table 1**). These prospects may have little benefit to the individual patient but in aggregate may provide key information that, when mined, can yield important new insights. This was demonstrated by the remarkable progress occurring after broader characterization of *BRCA* mutation carriers. Those advances resulted in identification of the precursor fallopian tube lesion for ovarian cancer, an understanding of the importance of different mechanisms of DNA repair, and the advancement of several new classes of DNA repair inhibitory agents.

The further understanding of molecular aspects of cancer has resulted in novel trial designs and statistical models. Trial designs, categorizing therapy based upon common molecular events, such as NCI MATCH (NCT02465060), are examining tissue for molecular events. It then seeks to match the molecular event to a drug that may target the molecular event. This study recognizes that the role of the molecular event in a given cancer is unknown. This is a direction to refer women with more rare ovarian cancers for which trials are not available and phase 1 options may be limited.

Several studies have been published with similar target-matching approaches. The SHIVA investigators found that the use of molecularly targeted agents outside their indications does not improve outcome over physician's choice, underscoring the requirement for understanding the biology and selection opportunities within cancer/drug pairing (33). Schwaederle and colleagues (34) showed clinical benefits in the arm in which patients were matched to therapeutics by molecular targets over the arm with standard of care treatment. However, it did not present the cancer breakdown of the participating patients, preventing readers from determining if the positive results may have been driven by an overabundance of cancers with proven targets, such as non-small cell lung cancer subsets. Another study evaluated the role of the use of selection biomarkers in clinical trials of FDA-approved agents (35). This study showed improvement with the application of selection biomarkers where there was a validated biomarker for the targeted agent. These conflicting observations raise caution to the blanket application of costly sequencing. An alternative is the examination of exceptional responders (36). Finding mutational events and not being able to determine the role of those molecular changes can result in misdirection of therapy and potentially harm the patient clinically and economically, and importantly, can dash their hope by lack of success.

TABLE 1 | Obstacles and opportunities of molecular testing in gynecologic cancers.

Opportunities	Obstacles
Advance understanding of cancer(s) • Identify novel drivers and facilitators • Examine heterogeneity • Dissect cause of molecular events	Intrinsic cancer elements • Unclear functional status of mutation • Heterogeneity • Tumor–microenvironment interactions • Molecular divergence • Activation of secondary pathways
Knowledge on a per-patient basis for therapeutic selection	Selection approaches may miss optimal personal opportunities
Translate science to therapeutic opportunities	Mechanisms of resistance and risk of negating effects of subsequent targeted agents
Drive novel trial designs and statistical models	Cost: patient time (from work, travel, etc), assay costs, and physician and counseling costs Low clinical trial participation

The explosion in understanding about the molecular basis of cancer, especially in women's cancers, and in new agents, provides an important opportunity for patient education. The physician can frame the progress in genomics against the background of new agent availability. This can lead to a more informed joint decision as to whether referral to a screening/treating trial, such as MATCH, or for testing is appropriate for the patient at her point in her disease.

Heterogeneity provides some insight into the paucity of cures with targeted therapies. A great obstacle to application of personalized molecular medicine at this time appears to be cancers themselves. Solid tumors have some, or many, molecular events, often of uncertain importance, making targeted therapy more difficult to select. Discerning driver mutations from facilitating mutations from passenger mutations with no biologic consequence remains empiric. It is often further complicated by secondary mutations in many cases. *PI3K* mutations are a case in point. Almost all epithelial solid tumors have some form of PI3K pathway mutation or dysfunction (37, 38). PI3K inhibitors have been uniformly disappointing in solid tumors, while being approved for use in lymphomas where there are no PI3K mutations, but there is strong pathway activation. The next obstacle, a consequence of the molecular variability seen in most solid tumors, is intratumoral heterogeneity. Sequencing over disparate geographic areas has demonstrated intratumor molecular heterogeneity and allowed determination of temporal and spatial clonality (39, 40). It has demonstrated that divergence can be an early event.

CONCLUSION

The promise of personalized molecular medicine has been long in being recognized, although clear progress is evident. Gynecologic cancers are complex, and focused attention to their genomics, biology, and local tumor microenvironment has yielded important clues to new therapeutic directions. While few clear drivers have been identified, selection parameters, including DNA repair dysfunction, are seen with the role of germline BRCA mutations and Lynch syndrome biology. The major opportunity and challenge ahead is to develop and validate the tools necessary to optimize the application of biomarkers and targeted agents to rapidly and efficiently improve cancer care delivery to women with gynecologic cancers.

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