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REVIEW
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A Review of Cancer Genetics and Genomics Studies in Africa

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Cancer is the second leading cause of death globally and is projected to overtake infectious disease as the leading cause of mortality in Africa within the next two decades. Cancer is a group of genomic diseases that presents with intra- and inter-population unique phenotypes, with Black populations having the burden of morbidity and mortality for most types. At large, the prevention and treatment of cancers have been propelled by the understanding of the genetic make-up of the disease of mostly non-African populations. By the same token, there is a wide knowledge gap in understanding the underlying genetic causes of, and genomic alterations associated with, cancer among black Africans. Accordingly, we performed a review of the literature to survey existing studies on cancer genetics/genomics and curated findings pertaining to publications across multiple cancer types conducted on African populations. We used PubMed MeSH terms to retrieve the relevant publications from 1990 to December 2019. The metadata of these publications were extracted using R text mining packages: RISmed and Pubmed.mineR. The data showed that only 0.329% of cancer publications globally were on Africa, and only 0.016% were on cancer genetics/genomics from Africa. Although the most prevalent cancers in Africa are cancers of the breast, cervix, uterus, and prostate, publications representing breast, colorectal, liver, and blood cancers were the most frequent in our review. The most frequently reported cancer genes were *BRCA1*, *BRCA2*, and *TP53*. Next, the genes reported in the reviewed publications' abstracts were extracted and annotated into three gene ontology classes. Genes in the *cellular component* class were mostly associated with *cell part and organelle part*, while those in *biological process* and *molecular function* classes were mainly associated with cell process, biological regulation, and binding, and catalytic activity, respectively. Overall, this review highlights the paucity of research on cancer genomics on African populations, identified gaps, and discussed the need for concerted efforts to encourage more research on cancer genomics in Africa.

Keywords: cancer, genetics, genomics, Africa, molecular biology

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INTRODUCTION

Cancer is the second leading cause of death globally (1). In Africa, cancer incidence and mortality continue to grow rapidly. According to the 2018 Globocan data, new cancer cases and cancer deaths in Africa were estimated at 1,049,800 and 700,800, respectively (2). In 2018, women in East Africa had the highest cumulative risk of dying from cancer globally. The burden of cancer in Africa is increasing, and this burden is expected to increase by 60% by the year 2030. To lower this projected increase in cancer burden, population-relevant biological studies and the identification of innate risk factors among African populations are needed (3–5).

As cancer is a genetic disease, scientific studies investigating its causes, diagnosis, and treatment in developing countries need to focus more on genetics and genomics. The African or Black population is not a homogenous group and, as such, necessitates the need for genomic/genetic studies to reflect the diverse African populations. The population history of Africa shows that the people of Africa are the most genetically and phenotypically diverse population (6, 7). The peopling history of Africa has been described by Campbell et al. and Tucci & Akey (8, 9), and their reviews showed that African ethnic groups and tribes are genetically heterogeneous. Hence, there is likely a critical contribution of the underlying within-group genetic differences to the disparity in cancer prognosis seen among Blacks (10). Therefore, cancer genetics/genomics studies are expected to significantly impact the understanding of the risk, susceptibility, diagnosis, and treatment of this disease.

The genomic heterogeneity of human populations was driven by ancient migration and heterogeneous adaptive pressures on the human genome, particularly on the African Continent (11, 12). These evolutionary events resulted in the split of human populations into five distinct groups: southern Khoe-San, northern Khoe-San, central African hunter-gatherers, West Africans, and East Africans, out of which a subset migrated out of Africa and is now recognized as the out-of-Africa population (11, 12). Therefore, the African continent could be considered to harbor the repository of human genomic diversity and serves as the resource reference for understanding the role of genomics in human health equity. This repository is further deepened by the present-day North African populations enriched with the genetic pool of the out-of-Africa's Euro-Asian populations. Still, Africa's contribution to global genetic and genomics information is grossly disproportionate to its population's diversity and size. For example, very few African populations were included in the HapMap and 1000Genome projects (13). This is a serious shortcoming for a group of people that represent over 90% of human genomic diversity. A recent review of genome-wide association studies (GWAS) showed that Africans (including African Americans) only represent 2.4% of individuals included in all GWAS studies (14).

The proper understanding of genetics and genomics among African populations will expectantly improve prevention, diagnosis, and treatment outcomes of cancer. Although recent evidence shows that the burden of cancer is in Africa, there remains a huge deficit in requisite skills and infrastructure required to carry out the necessary research studies to alleviate this knowledge gap, requiring still non-African nations to fill this gap (15).

Accordingly, in this review, we discuss both genetics and genomics study findings across multiple cancer types in African populations. The goal here is to demonstrate the existing knowledge and to crucially identify the gaps that should be filled in order to address the cancer burden across Africa.

METHODS

The peer-reviewed publications included in this review were extracted from PubMed and covered the period between January 1990 and December 2019, as shown in the flow chart in **Figure 1**. Since PubMed Medical Subject Heading (MeSH) terms involve synonym control, it yields more precise and inclusive search results (16). Our literature search approach, therefore, utilized an integration of MeSH terms that incorporated "the disease" (neoplasm), 54 African countries, and combinations of study parameters ('gene or protein or molecular biology or mutation or genetics or genomics'). After extracting African cancer papers, we next filtered those to include only papers pertaining to cancer molecular biology (protein or nucleic acid). Cancer molecular biology papers were then further filtered using "genetic* OR genomic* OR mutation*[MeSH Terms]." The final criteria were that the studies must utilize biospecimens of African origin. Two authors (SOR and OAR) manually verified these publications to ensure the accuracy of terms.

For the purpose of data extraction, the metadata and abstract of each publication returned from our search were collected in a single corpus and subjected to text-mining using the R packages RISmed (17) and Pubmed.mineR (18). The publications returned were analyzed in R to identify the cancer types/sites associated with each publication, as described by Acharya et al. (19). Furthermore, the R package "PubmedmineR" was used for obtaining the names and frequency of occurrence of genes denoted in "Human Genome Nomenclature Committee" (HGNC) symbols (20). For this purpose, we considered the genes reported in the abstract as the genes associated with the most prominent findings of the publications. Next, these genes were pulled and subjected to gene ontology functional profiling for three gene ontology classes ("molecular function", "biological process", and "cellular component") using "goProfiles" (21).

RESULTS

The total numbers of publications returned by our search on the topics of cancer globally, as well as cancer, cancer molecular biology, and cancer genetics/genomics within Africa between 1990 and December 2019, are shown in **Figure 1**. Out of nearly two and half million publications on cancer globally, only 7,697 (0.329%) papers were returned by our search on cancer in Africa, with only 1,456 (0.061%) related to molecular biology (protein or nucleic acid). Of these publications, only 375 articles were found using the search terms "genetic, genomics, mutations".

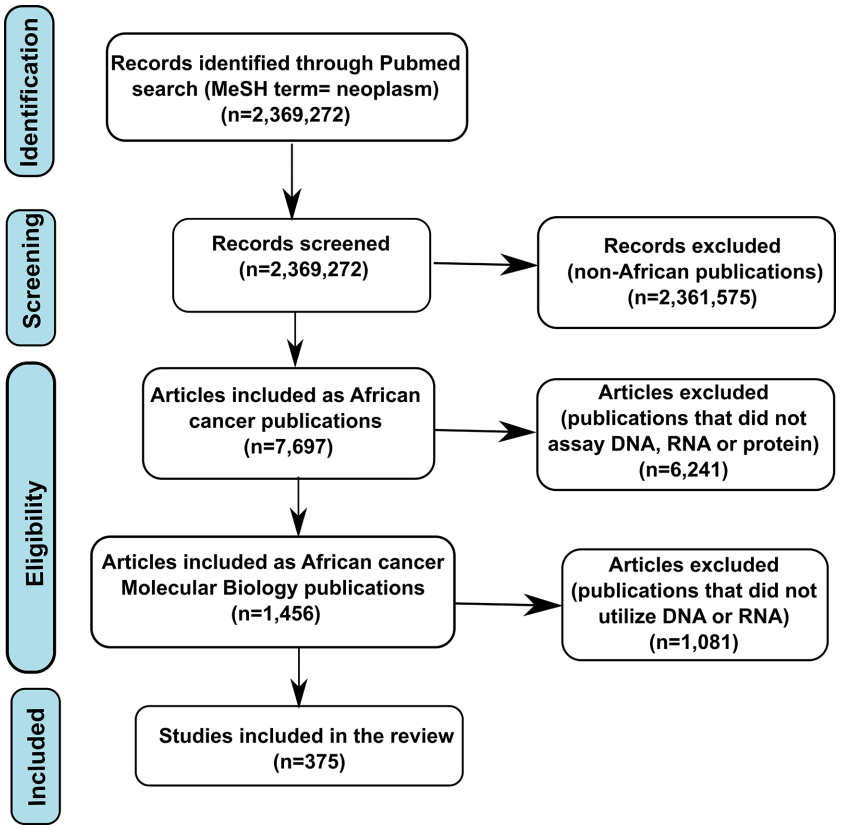

FIGURE 1 | Flow diagram of the literature search strategy.

Among all cancer publications pertaining to Africa, the cancer sites with the highest number of published studies represented cancers of the cervix, breast, liver, head/neck, and colorectal while, lung, brain, bladder, ovarian, and uterine cancers were the least frequently reported on (**Figure 2A**). For publications related to cancer molecular biology in Africa, breast, liver, colorectal, blood, and prostate cancer were the most frequent. In contrast, cancers of the brain, stomach, lung, skin, and uterine cancer had the fewest publications (**Figure 2B**). Most papers reporting cancer genetics or genomics reported on breast, colorectal, liver, blood, and ovarian cancer, with the fewest cancer genetics or genomics studies on the brain, stomach, lung, skin, and uterine cancers (**Figure 2C**).

There were also disparities in the publications by country, as illustrated in **Figures 3A–C**. Nigeria had the most papers on cancer overall, followed by South Africa, Egypt, Tunisia, Morocco, and Kenya (**Figure 3A**). For cancer molecular biology papers, Egypt took the lead, followed by Tunisia, South Africa, and then Nigeria (**Figure 3B**). Tunisia, however, returned the most search results for cancer genetics/genomics papers followed by Egypt, South Africa, and Morocco (**Figure 3C**). Overall, only seven African countries contributed at least 10 cancer genetics/genomics publications, while 22 African countries returned no search results on cancer genetics/genomics studies. The search results show clear evidence of regional differences in publishing capacity, with North Africa and South Africa leading in cancer research.

Next, we focused specifically on the list of 375 genetics/genomics publications for gene curation and review. We did this to identify the functional contributions of these studies to the understanding of biological processes associated with carcinogenesis, using functional correlations comparison (22). A total of 152 genes in the abstracts of 375 publications on cancer genomics were extracted and further annotated into the following gene ontology classes: *cellular component, biological process, and molecular function* (**Figures 4A–C**). In the *cellular component* class, the genes studied were mostly associated with cell part, organelle, organelle part, and cell membrane. In contrast, the genes in the biological process were mainly associated with cell process, biological regulation, response to stimulus, and positive regulation of the biological process. The *molecular function* ontology genes were mostly associated with binding, catalytic activity, molecular function regulator, molecular function transducer activity, and transcription regulation in the molecular function class, which are dysregulated in cancer. The most studied genes in the publications were *BRCA1*, *BRCA2*, *TP53*, *EGFR*, and *MLH1* (**Table 1**), indicating a dearth of data on the plethora of other

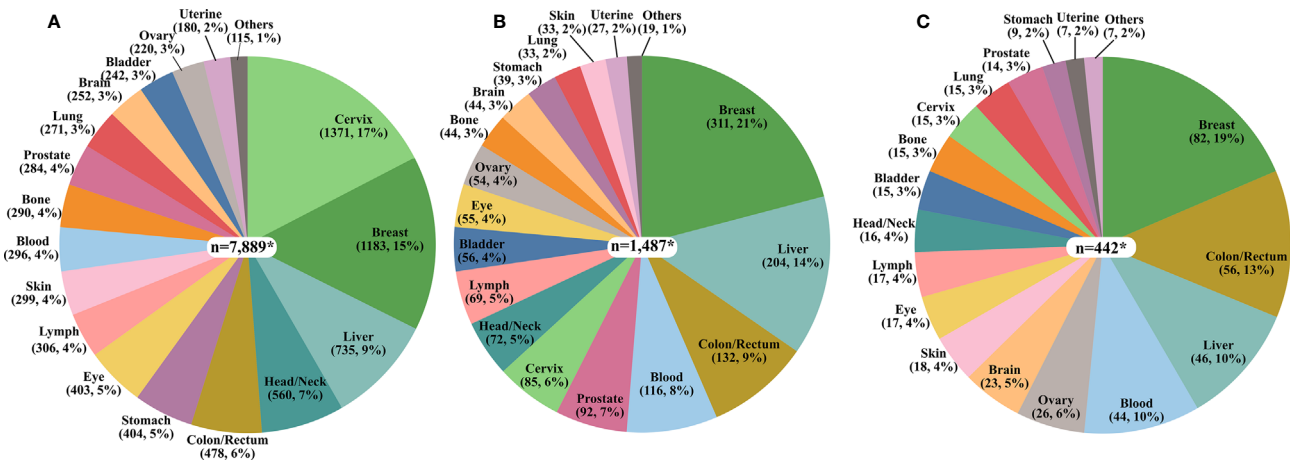

FIGURE 2 | The proportion of the number of publications on each cancer type. **(A)** Cancer in Africa (n=7,697) **(B)** Cancer Molecular Biology in Africa (n=1,456), and **(C)** Cancer Genetics/Genomics in Africa (n=375). *The total values presented in the pie charts are greater than the sum of publications in each category due to the multiplicity of cancer sites for some publications as exemplified by studies on breast/ovary and blood/lymph.

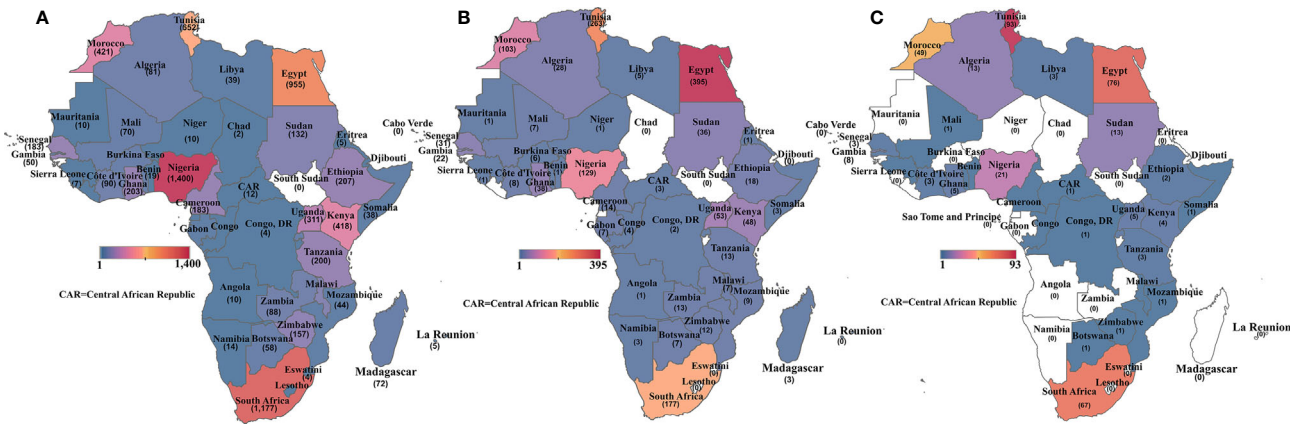

FIGURE 3 | Heat map showing the number of publications retrieved for **(A)** all cancer publications per African country; **(B)** cancer molecular biology publications per African country and **(C)** cancer genetics/genomics publications per African country. Countries without any publication in each category are shaded in white.

critical cancer-associated genes. Next, we reviewed some of the key findings reported across the 375 genomics papers for each of the major and most frequently published cancer types below.

Breast/Ovarian Cancer

Breast cancer has continued to be the leading cause of cancer morbidity and mortality in Africa, with an incidence and mortality rate of 37.9 and 17.2 per 100000, respectively, according to GLOBOCAN 2018 data (2). Breast cancer's prominence in Africa dates back to around 3000BC in the ancient Egyptian medical text - the Edwin Smith Papyrus, the oldest cancer record (23, 24). Not surprisingly, breast cancer had the highest number (n=82, 19%) of peer-reviewed cancer genetics/genomics publications in Africa. With the current understanding of cancer as a genomic disease and the unique phenotype that breast cancer presents in the people of African ancestry, attempts to address its burden require rigorous genomics investigations.

Together with cancer of the ovary, breast cancer risk is greatly increased in women with inherited mutation(s) in tumor suppressor genes (25). Not surprisingly, the earliest publications on breast and ovarian cancers in African populations focused on understanding the contribution of variations in the tumor suppressor genes *BRCA1/2* and *TP53*, particularly in North African populations of Morocco, Tunisia, Egypt, and Sudan (26–40). While these findings hold immense benefits for those populations, their *BRCA* variants are not dissimilar to those present in the out-of-Africa populations.

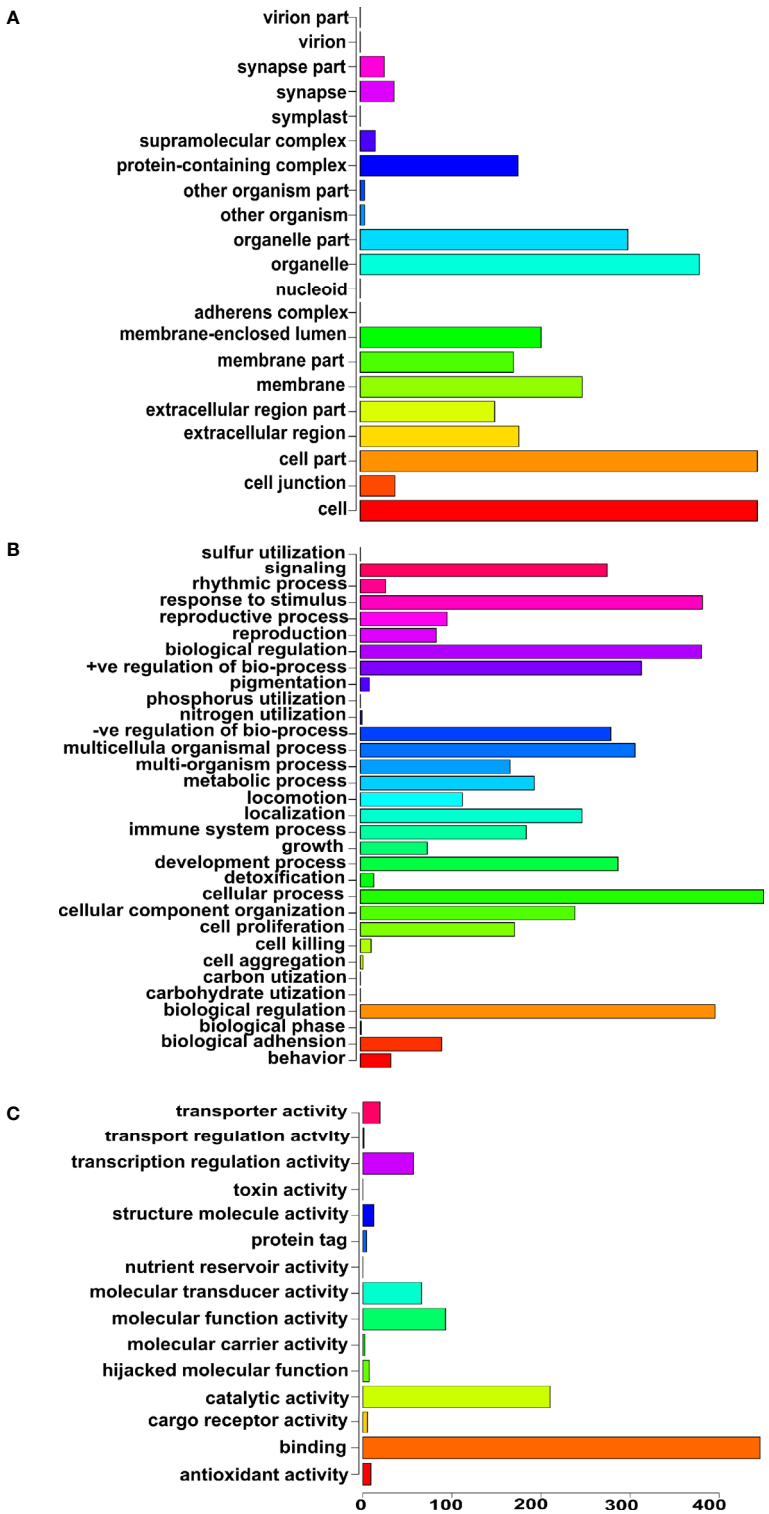

FIGURE 4 | Gene ontology of the genes reported in the abstracts of publications on cancer genomics in Africa. **(A)** Cellular component ontology, **(B)** Biological process ontology, and **(C)** Molecular function ontology.

TABLE 1 | List of top 20 genes reported in the abstracts of publications on cancer genetics and genomics in Africa.

	Gene symbol	Genes	Frequency
1	*BRCA1*	breast cancer 1, early onset	164
2	*BRCA2*	breast cancer 2, early onset	108
3	*TP53*	tumor protein p53	73
4	*EGFR*	epidermal growth factor receptor	53
5	*MLH1*	mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)	41
6	*KRAS*	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	39
7	*BRAF*	v-raf murine sarcoma viral oncogene homolog B1	30
8	*XPA*	xeroderma pigmentosum, complementation group A	29
9	*RET*	ret proto-oncogene	22
10	*NPM1*	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	21
11	*NLRP7*	NLR family, pyrin domain containing 7	20
12	*APC*	adenomatous polyposis coli	19
13	*JAK2*	Janus kinase 2	19
14	*MSH2*	mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)	19
15	*ABCB1*	ATP-binding cassette, sub-family B (MDR/TAP), member 1	16
16	*GSTT1*	glutathione S-transferase theta 1	16
17	*MGMT*	O-6-methylguanine-DNA methyltransferase	15
18	*RB1*	retinoblastoma 1	15
19	*WT1*	Wilms tumor 1	15
20	*MDM2*	MDM2 oncogene, E3 ubiquitin protein ligase	14

This, therefore, limits the translational impact of such findings to controlling breast/ovarian cancer in the Sub-Saharan African populations.

Furthermore, the major epidemiological implication of *BRCA* mutations lies in identifying specific founder mutation(s) within each population, with the view of using it as a predictive molecular risk marker and treatment recommendation. For instance, advances in understanding the role of *BRCA* proteins in tumorigenesis have now led to improved therapeutic choices with the availability of PARP inhibitors for breast cancer patients with germline mutations (41). Also, the identification of founder *BRCA* gene mutations in populations like Ashkenazi-Jewish (Hungarian and Russian), Polish, Norwegian and Icelandic people has resulted in improved low-cost genetic testing and the determination of high-risk individuals for breast and ovarian cancers (42, 43). Therefore, these have made it imperative for the founder mutations of the *BRCA* gene within Africa populations to be identified and included in breast cancer screening, diagnosis, and treatment.

In an attempt to consider *BRCA* contributions to breast cancer in Africa, Rebbeck et al. (44) published a global distribution of *BRCA1* and *BRCA2* germline mutations by including women from Nigeria and South Africa. However, the extent to which their subjects represent the ethnic and genetic diversity in these countries is unclear. They did note that the mutations observed in African American families were of African origin because they are unlike the mutations seen in out-of-African ethnic groups (44–46). This study of Rebbeck et al. (44) was part of the Consortium of Investigators of Modifiers of *BRCA1/2* investigations, which only included the nation of South Africa (http://cimba.ccge.medschl.cam.ac.uk/cimba-groups/study-groups/). A more detailed study of Zheng et al. (47) on Nigerian women established that up to 20% of inherited invasive breast cancer cases in Nigeria are associated with inherited mutations in *BRCA1*, *BRCA2*, *PALB2*, or *TP53*. Their findings on *BRCA1* and *BRCA2* built on the earlier report of Fackenthal et al. (48) that Nigerian breast cancer patients have a very high frequency of *BRCA1* and *BRCA2* mutations. These mutations were reported by Pitt et al. (49) to be associated with greater structural variation and aggressive biology in Nigerian women with HR + /HER2 − tumors. Similar findings were reported by Pegoraro et al. (50) in Black South Africans with ovarian epithelial malignancies.

Recently, Mahfoudh et al. (51) showed that the 5382insC *BRCA1* mutation contributes to the development of triple-negative breast cancer (TNBC) in Tunisia. The higher mortality of breast cancer in women of West African ancestry is due in part to higher levels of TNBC (compared to whites), which is associated with the poorest prognosis of all breast cancer subtypes. Hence, *BRCA* screening in Africa could help identify women who can benefit from *PARP* inhibitors leading to improved clinical outcomes. In South Africa, Reeves et al. (52) characterized *BRCA1* mutations in breast and/or ovarian cancer to identify founder mutations in Afrikaner families. However, this population is also of European ancestry, and the mutations that were identified were similar to those reported in the Netherlands and in Ashkenazi Jews (53). They also reported that variants of *PALB2*, a partner and localizer of *BRCA2* was also associated with the early onset of breast cancer in some South African patients (53). *PALB2* functions as a scaffold between *BRCA1* and *BRCA2*. Similar *PALB2* mutations have previously been identified in women of European ancestry but not in women with Nigerian ancestry, as reported by Sluiter et al. (54).

The first publication on *BRCA* mutations in the indigenous Sub-Saharan African population was by Zhang et al. (55), who identified an ancient *BRCA1* mutation (Y101X) in Yoruba (Nigeria, West Africa) breast cancer patients. The team further reported a non-pathogenic novel exon 21 deletion of *BRCA1* (c. 5277 + 480_5332+672del) in Nigeria in addition to a novel deleterious *BRCA1* mutation (c. 1949_1950delTA) in a woman from Senegal (West Africa) (56). Another novel founder, *BRCA2*

mutation, was identified by var der Merwe et al. (53) in the Bantu-speaking Xhosa population (South Africa). Other studies have identified new *BRCA* mutations and their contribution to early-onset and sporadic breast and/or ovarian cancer in Arabic speaking countries (57) of Egypt (58), Tunisia (51, 59–66), Algeria (67–69), Morocco (70–72), and Sudan (73, 74), in addition to Senegal (75), Mauritius (76) and South Africa (50, 77–79) in the Sub-Saharan region.

Additional studies on *BRCA* genes have expanded to identifying the population-based mutation frequency and screening/genetic testing in the Democratic Republic of the Congo (80), Morocco (81), Tunisia (82, 83), Algeria (84, 85), familial studies in Morocco (86, 87), and large genomic rearrangement in Egypt (88, 89). Of these, the contribution of *BRCA* mutations to male breast cancer was reported only in the Moroccan study by Guaoua et al. (86). A mutation in the *TP53* gene often accompanies *BRCA* mutations in breast and ovarian cancers, making the mutations in these DNA repair genes relevant in therapeutic interventions (90, 91). The publications on *TP53* mutation have focused on its expression in breast cancer and the contribution of its polymorphism, particularly codon 72 to breast cancer (28, 31, 33, 36, 92–94), as well as to its interaction with *MDM2* 344T>A polymorphism in response to chemotherapy of breast cancer in Tunisia (95). Other DNA repair genes that have been studied in Africa include *XRCC1* and XPD in Egypt (96, 97). Overall, even though it is one of the most studied genes in African cancer research, there remains a very small number of publications on *BRCA* mutations in the indigenous African population, clearly showing a knowledge gap on a hereditary gene critical in managing incidence and clinical outcomes in breast cancer.

Exogenous factors that drive DNA damage include viruses and xenobiotics. The presence of these agents and genetic alterations that mediate the ensuing host-response can promote carcinogenesis. The first reports of virus-associated breast cancer in Africa were by Levine et al. (98) and Hachana et al. (99), who reported the presence of a human breast carcinoma virus (a virus similar to mouse mammary tumor virus) in 74% of tumors in Tunisia. These were the only two studies that reported this virus in Africa. Studies have also shown an association of the hepatitis C virus in Egypt (100) and Human papillomavirus (HPV) in Rwanda (101) to breast cancer progression. However, the most reported virus linked to breast cancer in Africa is the Epstein-Barr virus (EBV), with studies published in Algeria (102), Eritrea (103), Egypt (104), and Sudan (105). EBV was the first identified human oncogenic virus that was detected in Uganda in 1964 by Denis Parsons Burkitt (106–108) and its molecular pathogenesis has been reviewed by Lawson et al. (109). The virus is responsible for many cancers across the continent, and the host genomic factors that facilitate tumorigenesis are described below.

The detoxification of carcinogenic chemical entities is primarily catalyzed by cytochrome P450 (phase I) and a host of phase II xenobiotic-metabolizing enzymes. Polymorphisms in these genes dictate, in large part, the effect of xenobiotics on the biological system. Such polymorphisms have been reported in *CYP1A1* and *CYP1B1* in Nigeria and Egypt (110, 111), *CYP2D6* in South Africa (112), and *CYP1A2* in Tunisia (113). Furthermore, as hormone-responsive cancers, these cytochrome P450 genes play critical roles in estrogen metabolism and the response of the tumor to endocrine therapy. For genes coding for phase II xenobiotics metabolizing enzymes, the deletion of *GSTT1* and *GSTM1* were reported by Khedhaier (114) to predict the early onset and prognosis of breast cancer among Tunisian women. The number of TA repeats in the promoter of low activity *UGT1A1* was reported to be protective against breast cancer in pre-menopausal Nigerian women (115, 116). Similarly, the association of polymorphisms in paraoxonase, cyclooxygenase, glyoxalase, and glutathione peroxidase genes with breast cancer were reported in Egypt and Rwanda (117–120).

Inflammation is a major hallmark of cancer, and it is known to contribute to aggressive tumor biology. This makes understanding the variations in immuno-oncogenic genes important in understanding the population biology of cancer in Africa. Mestiri et al. (121, 122) reported that polymorphisms in *TNF-α* and *TNFRII* increase the susceptibility to breast cancer in Tunisian women, with *TNFRII* -196R prevalent in premenopausal women. Conversely, *FASL* (rs763110) was associated with a good prognosis in the same population (123). However, *HLA-DQB1* and *HLA-G* +3142C>G (rs1063320) polymorphisms were related to increased breast cancer susceptibility (124, 125). Pathogenic polymorphisms of other inflammatory genes like *NRF2*, *IL1α*, *IL1β*, *IL6*, *IL8*, and *CXCR2* have also been identified in Tunisian and Egyptian breast cancer patients (126–130).

Recent evidence suggests that inflammation-driven cancer in Blacks is influenced by vitamin D levels (131, 132). To establish the association of vitamin D variants and related genes with breast cancer, El-Shorbagy et al. (133), Abd-Elsala et al. (134) and Shaker & Senousy (135) showed that polymorphisms in the vitamin D receptor (*VDR*) increases the risk of breast cancer in Egyptian women who carry the ATT haplotype. The risk of developing breast cancer due to these mutations was elevated in women who also carry *RANKL* (rs9533156), *OPG* (rs2073617), and *CHI3L1* (rs4950928) (135). Similar studies have also reported the risk allele in Ethiopian women as *VDR* rs2228570 (FokI) (136) but the study of Wang et al. (137) did not identify variants in vitamin D related genes as risk factors for breast cancer in Nigerian women that were used as the ancestral population for African American women. This genome-wide association study, however, identified *TYRP1* (rs41302073), a melanin synthesis regulatory gene, as a significant risk allele for breast cancer in their dataset that included African American and Barbadian women. Furthermore, the authors also used the same dataset to identify *WWCI* as an important susceptibility locus in the Hippo pathway for breast cancer (138).

Polymorphisms in the angiogenesis-associated genes have also been identified in breast cancer in African populations and include the *LEP*, *LEPR*, *VEGF*, and *MMP2*. Leptin and *LEPR* Q223R (rs1137101) were identified as risk factors for breast cancer in Egyptian and Nigerian women (139–141)

while leptin alone was notably reported as a key driver of breast cancer progression through the induction of *JAK/STAT3*, *ERK1/2*, and estrogen pathways in obese Egyptian women (142). Furthermore, variants of *VEGF* and *MMPs*, which induce the upregulation of these proteins, were reported as risk factors in North African countries of Morocco, Egypt, and Tunisia (143–148). Other overexpressed angiogenic proteins reported are *EGFR* in Tunisia (149) and *IGFBP2* and *IGFBP5* in Nigerian women (150). The authors proposed these angiogenic proteins as druggable targets in breast cancer treatment. Another therapeutic pathway that has been studied is the *PIK3/AKT* pathway. Jouali et al. (151) reported *PIK3CA* hotspot mutations in 13% of triple-negative breast cancer cases in Morocco. They suggested that this pathway could be of therapeutic importance for triple-negative breast cancer in Morocco.

Cancer is a polygenic disease, and scientific investigation to understand breast cancer's population biology, therefore, cannot be simplified to a single genetic variant. Hence, techniques to investigate multiple genes at a time such as with next generation sequencing are now being utilized to understand the genetic risk factors of breast cancer in Africa. To that effect, genome-wide studies (GWAS) published primarily on breast cancer in African populations include GWAS in Tunisia and South Africa (152–154) and whole-exome sequencing in Tunisia and Egypt (155–157). In the Tunisian population, Shan et al. (154) and Hamdi et al. (152) identified rs1219648, rs2981582, rs8051542, rs889312, and rs889312 as breast cancer susceptibility single nucleotide polymorphisms (SNPs), with rs9911630 as the SNP with the strongest effect on the expression of *BRCA1* and two long non-coding RNAs (NBR2 and LINC008854). The genome-wide copy number alteration analysis of breast cancer in South African women (153) identified the amplification in Xp22.3 and 6p21-p25, and other regions that affect known cancer genes like *CCND1*, *CDKN1A*, *MDM2*, *TP53*, and *SMAD2*. Meanwhile, the whole-exome sequencing study by Hamdi et al. (152) and Riahi et al. (156) linked breast cancer in Tunisian women to alterations in *MMS19*, *DNAH3*, *POLK*, *KATβ6*, and *RCC1* in *BRCA1/2* mutation-negative patients with familial breast cancer. A similar study in Egypt also found other novel genetic variants responsible for familial breast cancer. These genetic variants are different from those linked to DNA damage repair (like *BRCA1* and *BRCA2*) but are linked to other functional genes like *NBPF10*, *ZNF750*, *CHTI5*, *NPIPB11*, and *PHIP*, that are involved in RNA binding, transcriptional regulation, extracellular matrix, a structural protein, and signal transduction, respectively.

The contribution of epigenetic factors to risk and prognosis of breast cancer reported in Africa included the roles of tissue microRNA, circulating free mRNA, circulating long non-coding RNA (158–163) as well as DNA methylation status of breast cancer susceptibility genes like *APC*, *ERα*, *RASSFIA*, *UCHL1*, *COX-2*, and *FHIT* (161, 164–167) in breast tumor across Africa.

Prostate Cancer

Prostate cancer continues to be the leading cause of cancer morbidity and mortality among African men (168, 169). Although genetics is a major risk factor for this disease, there are only a few publications on prostate cancer genomics in Africa. In this subsection, we review 14 papers that were relevant to prostate cancer out of the list of 375 papers extracted. Prostate cancer presents with an aggressive phenotype among men of African descent, and like breast cancer, it is a hormone-responsive tumor. Consequently, early studies on this disease identified androgen's influence in the control of normal prostate growth and, in its transformation into adenocarcinoma, a phenomenon called the "androgen hypothesis" (170, 171). Therefore, peer-reviewed publications on prostate cancer genetics in African populations have reported genetic variants that contribute to elevated circulating androgens, including androgen reduced clearance and upregulated activity of androgen receptor. These include the polymorphisms in cytochrome P450 genes like *CYP3A4*, *CYP3A5*, *CYP1A1*, *CYP17* in Morocco, Tunisia, Nigeria, South Africa, and Senegal (172–176). Besides, alterations in CAG and GGN repeats in the androgen receptor gene have been reported as risk factors in North Africa, Ivory Coast, and Nigeria (177, 178). Unlike the North African populations, prostate cancer in Sub-Saharan African populations and North African Berbers were associated with high frequencies of low size alleles (CAG under 18 repeats, and GGC under 15 repeats) (178). Other reported genetic variations that increase African populations' susceptibility to prostate cancer include *GSTM1*, *GSTT1*, UDP-glucuronosyltransferase, and sulfotransferase in Tunisia and Algeria (179–182).

A deeper understanding of the disease's polygenic risk was elucidated by four studies that have investigated the genome-wide genetic variations in prostate cancer across Africa. These included GWAS of prostate cancer in Tunisia, Ghana, and Uganda (183–185), as well as a whole-genome sequencing of six individuals in South Africa (186). It is interesting to note that these four studies did not identify any common high-risk prostate cancer variants. The Tunisian study identified three regions (on chromosomes 9, 17, and 22) containing 14 significant SNPs, three of which are shared with Caucasian populations (185). The Ghanaian study of Cook et al. (184) identified 30 most significant SNPs distributed across chromosomes 1, 2, 3, 5, 6, 7, 8, 9, 10, 13, and 20.

Meanwhile, the Ugandan study identified risk alleles on chromosomes 1, 6, 11, 13, 14, and 17 (183). Although the Ugandan and Ghanaian populations shared cytoband 6p21.32 in common, the nucleotide positions and risk alleles were still different. This chromosome position codes for *HLA-DQB1*, which has been reported to be important for the adaptation of African ancestral populations to the African rainforest environment. These studies further add to the existing evidence of the heterogeneity of African populations (12) and that cancers in these populations may have a different biology. These findings provide further evidence for the need to disaggregate the Black population by genetic lineage in studying the contributions of genomics to racial disparities of diseases like prostate cancer. Importantly, it is yet to be revealed whether these differences influence the disease phenotype and disparity in outcome.

The most commonly reported genomic alteration that drives prostate tumorigenesis is *TMRPSS2-ERG* fusion, and this androgen-upregulating fusion is known to correlate with higher grades of the disease. Although men of African ancestry are known to present with higher disease grade, only three studies have examined the *TMRPSS2-ERG* fusion on the Continent (187–189). This fusion often results from either a chromosomal translocation or an interstitial deletion, and these studies reported rates that were less than 20% in Ghanaian and Black South African patients (187–189).

Liver Cancer

According to the 2018 GLOBOCAN data, hepatocellular carcinoma accounted for 8.4 cases per 100,000 and 8.3 deaths per 100,000 globally (2) and it is the 4th most common cancer in Africa. We retrieved 46 publications that studied liver cancer genetics/genomics in Africa. Several of these studies investigated the contribution of the hepatitis virus and mycotoxins to this malignancy. These biotic and abiotic agents represent the major causes of this disease on the continent (190, 191). Hence, a preponderance of publications on liver cancer in Africa focused on understanding the contribution of mutation and expression of *TP53*, and other tumor suppressors like *TP73*, *RB*, *KLF6*, and *CTNNB1*, to liver carcinogenesis (190, 192–207), particularly in Senegal, Gambia, Nigeria, South Africa, Egypt, and Morocco. These studies identified the mutation in codon 249 of *TP53* as a genetic risk factor for developing hepatocellular carcinoma following exposure to either the hepatitis virus or mycotoxins (see Lin et al. (208) for detailed mechanism). In Morocco, *MDM2* 309 T>G was associated with liver cancer (209, 210). These mutations are known to upregulate this oncogene's expression, which in turn binds p53 and prevents its tumor suppression function (209) resulting in increased genomic instability as demonstrated by loss of heterozygosity in chromosome 4-q13 in Black South Africans (211).

The development of hepatocellular carcinoma is often preceded by chronic inflammation of the liver. In Africa, hepatic inflammation is exacerbated by high-prevent co-morbid conditions like non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and liver cirrhosiss. For instance, the prevalence of NAFLD in Nigeria, Ethiopia, and South Africa has been reported to be 68.8%, 73%, and 87%, respectively (212).

Despite the pervasiveness of liver cancer across Africa, only the Egyptian and Tunisian populations have been studied for the contribution of variation in inflammation-related genes to this disease. These studies reported mutations in *IL3R*, *IL17A*, *IL8*, *IL1*, *IL16*, *IL12*, *IL27*, and *TNF-*α as risk factors for hepatitis and hepatocellular carcinoma (213–219).

Other authors have focused on the development of biomarkers for liver cancer, using epigenetic factors like microRNAs. These include serum Mir-224, Mir-215, Mir-143, Mir-122, Mir-199a, and Mir-16 (220, 221). Specifically, Mir-122 and Mir-222 levels were reported by Motawi et al. (222) as a discriminating biomarker for distinguishing liver injury from liver cancer. This group further reported that LncRNA *HULC* rs7763881 and *MALAT* rs619586 were associated with decreased susceptibility of Egyptian hepatitis virus-persistent carriers to liver cancer (223).

Mycotoxicosis, with concomitant early-life protein malnutrition, is an important driver of liver cancer in Africa (224–226). One group of enzymes that are involved in detoxifying mycotoxins are the glutathione-S-transferases ($\mu, \theta, \pi, \alpha, \sigma$). Hence, individuals who do not express all the enzymes due to homozygous deletion are more susceptible to myco-carcinogens (227). Overall, two studies have identified the deletion of *GSTM1* and *GSTT1* haplotypes as risk factors for aflatoxin-associated hepatocellular carcinoma (228, 229) in Africa.

The last group of genes that have been studied on hepatocellular carcinoma in Africa are those involved in angiogenesis, including *VEGF*, *MMP*, *RASSF1A*, and *RECK*. In Egypt, Samamoudy et al. (230) reported that patients with *MMP9* (rs3918242) are at high risk of developing liver cancer while *RECK* (rs12814325) (231) could account for the disease progression and metastasis.

Cervical Cancer

Cervical cancer continues to be responsible for the highest cancer mortality in Africa, accounting for 2,000,000 deaths in 2018 (2), and its incidence rates continue to increase in most Sub-Saharan African countries (232). However, studies on cervical cancer genetics/genomics only represented 3% of the publications we retrieved. Similar to liver cancer, cervical cancer is viral-related and primarily caused by Human Papillomavirus (HPV). Several reviews have discussed the burden, distribution, and contribution of HPV serotypes to cervical cancer in Africa (233–235). Despite the burden of HPV in Africa, only a small proportion of women that are infected develop cervical cancer (236, 237). It is, therefore, essential to understand the genetic factors that contribute to the risk of progression from HPV infection to cervical cancer across Africa.

One of such genetic factors that increase susceptibility to HPV-associated cervical carcinogenesis is the *TP53* R72P mutation (238), which was reported in Gabon, Senegal, Sudan, Morocco, and South Africa; and this risk increases when combined with the chromosomal allelic loss of *RB* or with aberrant methylation of *DAPK1*, *RARB*, *TWIST1*, and *CDH13* (79, 239–244). Furthermore, aberrant methylation of these genes was proposed by Feng et al. (245) to be useful in Senegal for the screening of cervical cancer, either alone or in combination with cytology. The importance of this homozygous arginine polymorphism at codon 72 of *TP53* in determining genetic susceptibility of a population has been shown in Israeli Jewish women who have been reported to have reduced susceptibility to HPV-associated cervical cancer (246).

The variations in genes involved in inflammatory and apoptotic response pathways have also been reported to increase African women's susceptibility to cervical cancer (247). The reported polymorphisms in Africa include those of *TLR 2/3/4/9* and *IL1/10/15* genes in Tunisia and -308 promoter polymorphism of *TNF-*α in South Africa (248–250). Meanwhile, polymorphisms in *FASR*-670A and *CASP8*-652 were associated with a reduced risk of developing cervical cancer in South African women (251).

Colorectal Cancer

Colorectal cancer is the 5th most common cancer in Africa and accounted for 550,000 deaths in 2018 (2). We retrieved 56 publications on colorectal cancer genetics/genomics from Nigeria, Ghana, South Africa, Algeria, Tunisia, Morocco, and Egypt. The findings in these publications included: (1) the identification of I130K *APC* polymorphism in the indigenous Black population in South Africa and Tunisia to development of familial adenomatous polyposis coli (252–255), (2) the presence of mutations in the *MUTYH*, *MLH1*, and *MSH2* gene in patients with colorectal cancer and attenuated polyposis in Algeria, Egypt, Morocco, Tunisia, and South Africa (256–266), (3) the burden of *KRAS* and *BRAF* mutations in colorectal cases in Morroco, Nigeria, Ghana, Egypt and Tunisia (267–275) and (4) the level of microsatellite instability in South African, Nigerian, Ghanian, Tunisian, and Moroccan colorectal cancer patients (259, 271, 274, 276–281). Other studies have also explored the contribution of epigenetic changes to colorectal cancer carcinogenesis in Africa (278, 282–285). For example, the methylation of *UCH1* and *p14ARF* genes were reported to drive colorectal cancer in the presence of *TP53* mutation in Tunisia (282, 283, 286, 287). Other studies on the North African populations reported the influence of polymorphisms in telomere and mitochondrial D-loop region on the clinicopathological characteristics of the colorectal cancers among their patients (288, 289). Hence, the dearth of data on the genomics of this disease makes it difficult to explain the increase in the level of sporadic colorectal cancers reported in African countries, despite the difference in lifestyle and dietary habits. Profiling of these genes, including the use of targeted next-generation sequencing, in the screening and clinical management of this disease is essential in reducing its burden (255, 290).

Lung Cancer

Across Africa, lung cancer ranks 6th, with about 550,000 cases in 2018 (2). However, the burden of this disease is on the North African countries and South Africa (2). This burden reflects the pattern of tobacco smoking reported through national surveys (291). Lung cancer genetics/genomics studies have also largely been conducted on the North African populations of Tunisia and Egypt. These studies investigated the role of angiogenic pathway genes like *EGFR* and *MMP-3* in lung carcinogenesis (292–297). The expression of *EGFR* was associated with poor prognosis, and the frequency of the mutations observed in Tunisian and Moroccan patients was similar to those of Europeans (294, 296, 298). However, Dhieh et al. (292) found that abnormal p53 expression in these patient populations was more frequent than in Europeans. Similarly, a nonsense mutation (Arg-196-Term) in exon 6 of *TP53* was identified in the small cell lung cancer from gold miners in South Africa (299).

Cigarette and air pollution are major sources of lung carcinogens; hence, studies have reported polymorphisms in *CYP1A1*, *CYP1A2*, *CYP2F1*, *CYP2A6*2*, and *CYP2A6*9* (300–305) in lung cancer patients in North Africa. These polymorphisms alter the detoxification rate of toxicants, and individuals who carry the slow metabolizer variants have an increased risk of lung cancer (300). For example, Hussein et al. (302) concluded that Egyptian smokers with *CYP1A1* m1 (rs4646903) and *CYP1A1* m2 (rs1048943) are more likely to develop squamous cell carcinoma. Furthermore, lung carcinogens are highly inflammatory and studies in Tunisia, for example, identified alterations in inflammatory genes-*TNF-α*, *IL8*, *IL17A*, *IL17F*, *CCR2*, and VDR *Fok1* (rs2228570) and *ApaI* (rs7975232) that predispose to lung cancer (306–310).

There were additional studies that used epigenetic techniques to develop diagnostic or prognostic markers for non-small cell lung cancer in Egypt. These included the study of Haroun et al. (311) that identified *FHIT* methylation and that of Hetta et al. (312) which reported circulating microRNA-17 and microRNA-22 as potential biomarkers for early detection of lung cancer.

Bladder Cancer

Chronic inflammation with attendant oxidative stress induced by *Schistosomia haematobium* infection remains a major cause of bladder cancer in Africa (313–315), with squamous cell carcinoma being the most common (316, 317). Schistosomiasis (or bilharzia) is a neglected tropical disease that is widespread across Africa (318). This cancer is the 10th most prevalent cancer in Africa and accounted for 240,000 death in 2018. Studies on its genetics/genomics represented about 3% of the publications that we reviewed.

Its pathogenesis involves the bladder infection by *S. haemotobium*, which induces the formation of carcinogenic N-nitrosamine that contributes to squamous cell carcinogenesis (319), particularly in individuals with *TP53* mutation (320). In addition, mutations in genes associated with inflammation and detoxification of carcinogenesis are critical risk factors. One of which is the polymorphisms in *CYP2D6* and *CYP1A1* that have been studied in Egypt and Tunisia (321–323) and that of *CYP2D*1A*, which was found to increase the risk and clinicopathological outcome of both transitional and squamous cell carcinomas in Egypt (322). Similar findings were reported in the same North African countries for individuals with *GST* null genotypes and *NAT*5* (341T>C) (324–331).

The neoplastic transformation and progression of bladder cancer are enhanced through oxidative stress-induced genomic instability and chromosomal aberrations, which particularly involve the loss of heterozygosity on chromosomes 8 and 9 (332–338). These aberrations, coupled with p53 and p16 loss, have been reported in both bilharzial and non-bilharzial bladder cancer in Egypt and Tunisia (36, 332, 339–343).

The pattern of CpG island hypermethylation was studied by Gustierrez et al. (344) and they showed that the Schistosoma-associated tumors in Egyptian patients had higher hypermethylation of genes like E-cadherin, DAP-kinase, *TP14*, *TP15*, *TP16*, *APC*, *GSTP1*, and *TP73*. Other authors have further proposed using these unique epigenetic modifications for the early diagnosis of bladder cancer by utilizing plasma circulating microRNA and urinary DNA methylation profile (345, 346).

It is important to note that pesticides have also been implicated in bladder tumorigenesis (347, 348) through

oxidative stress and *KRAS* mutation in Egyptian occupationally-exposed individuals (347).

Other Solid Tumors

Studies in South Africa, Egypt, Sudan, and Tunisia identified the EBV as the major cause of head and neck cancer (349–354). The genetic risk factors that have been reported include *TP53* mutations in Sudan and Egypt (355–357), *XRCC1*, *TNF-α*, *IL10* promoter, *CYP1A1*, *CYP2D6*, and *NAT2* polymorphisms in Tunisia (358–361) as well as genome-wide aberrations associated with chromosomes 2p, 3p, 5q, and 18q and microsatelite instabilities (362–364) and mutations in the mitochondrial D-Loop region and Cytochrome b gene (365).

The genomic studies on the cancer of the brain, kidney, pancreas, and other organs are still emerging with very limited publications (366–378). The emphasis of these publications on the polymorphisms of genes associated with inflammatory response is an indication of the importance of this biological process to the neoplastic transformation of normal tissue and the progression of the malignancy. In addition, studies on retinoblastoma concentrated on identifying the constitutional mutations in *RB* within the North African populations (379–382) while publications on esophageal and gastric cancers focused on identifying the role of *RAS* genes mutations as drivers of genomic instability (383–386).

Lymph and Hematological Malignancies

The most prevalent lymphoma in Africa is Burkitt lymphoma. Its pattern and geographical spread are similar to that of malaria and ancient human migration on the continent (387–392). This aggressive pediatric B-cell non-Hodgkin lymphoma is caused by the EBV, which induces genomic instability in the B-cell that results in hyperproliferation (393, 394) and it is associated with unique *TP53* mutations that are clustered between codons 213 to 248 (395–397).

Other studies on lymphoma include: (1) the role of *TP73* and *FOXP3* in the pathogenesis of reactive lymphoid hyperplasia and diffuse B-cell lymphoma, as well as the contribution of *HLA-G* polymorphism to non-Hodgkin lymphoma in Egypt (398–400), (2) susceptibility of individuals with A/A genotype of *TNF* promoter (-308A/G) to non-Hodgkins lymphoma in Tunisia (401) and Egypt (402) and the identification of *HLA-B*18*, *DRB1*03*, *DRB1*07*, and *DQB1*02* as lymphoma susceptibility loci in Algerian children (403).

Studies from Egypt, Tunisia, and Morocco have identified the susceptibility or prognostic implications of mutations in *FLT3-ITD*, *NPM-1*, *KIT*, *NPM1*, *HFE*, *DNMT3A*, *TERT*, and *NRAS* in hematological malignancies (404–410). *NRAS* G12D and *NRAS* G13C mutations were reported in Nigerian leukemia patients Anyanwu et al. (411).

DISCUSSION

In order to provide an overview of research progress in African cancer genomics with the view of identifying the critical gaps, we searched and reviewed publications on cancer genetics and genomics in Africa. The 375 publications on cancer genetics/genomics retrieved on PubMed represented only 0.016% of total publications on cancer globally.

According to the 2018 GLOBOCAN data on cancer in Africa, the most frequently diagnosed cancers were breast, cervix, prostate, liver, and colorectum, while the leading causes of cancer deaths were from cancers of the cervix, breast, prostate, liver, and colorectum (2). However, of the top ten frequently diagnosed cancers and the leading cause of cancer deaths in Africa, only breast, colorectal, liver, and ovarian cancers were proportionately represented in cancer genetics/genomics studies returned from search terms.

Overall, Africans are grossly underrepresented in cancer genomics and molecular biology research globally. For example, research on prostate cancer in African men or breast cancer in African women, both leading causes of death in Africa, are still understudied compared to cancers in their non-Black and white counterparts (412).

Although Africa seems to be on the right track in terms of focusing on some of the top cancers, researchers and funding agencies, need to elevate and prioritize genetics and genomics research on cancers that remain hugely underrepresented or unrepresented in the literature for which there is a significant burden in Africa. These include cancers of the lung, ovary, stomach, bladder, prostate, and non-Hodgkin lymphoma, which are among the leading ten causes of death but remain understudied in the literature. Filling this research gap is essential to improving awareness, prevention, diagnosis, and treatment outcomes for people affected by cancer across the continent.

It is also worth noting that most studies on cancer in Africa are clustered to a few regions, mainly North Africa, Nigeria, Ghana, and South Africa. Most of the continent lacks any appreciable data, is often excluded from research efforts, and is devoid of the infrastructure and resources needed to contribute to cancer genomics/genetics discoveries.

It is important to reiterate that this review was based on publications that were indexed in Pubmed only. This is because Pubmed is considered as the most reputable index for biomedical publications, and the data we have retrieved are a good representation of the spectrum and scope of this review. It is also possible that our search did not retrieve some studies that included African populations, and this could be because those studies were not focused on African countries or groups but have used them for comparative purposes, thereby making the data obscure and less prominent in their findings. The use of MeSH terms ensured that relevant publications were extracted from Pubmed.

CONCLUSION AND FUTURE DIRECTIONS

As presented in this review, the preponderance of the peer-reviewed publications on cancer genomics in Africa was on the North Africa populations. Hence, there is a need for a concerted effort to address the gaps in the contribution of genomic variance and alterations to cancer in Sub-Saharan African populations.

Recently, Durvasula and Sankararaman (413) reported the presence of ghost archaic introgression into the genome of Sub-Saharan Africa populations, and some of this introgression included regions involved in carcinogenesis. This and the details presented in this review lay credence to the inadequacy of the use of predominantly Caucasian genomics data for cancer control in Africa. The use of personalized medicine and targeted therapy in cancer management rely on understanding the genomics of the population. Hence, there is a need to step up cancer genomics studies for Africa to benefit from medical advances. Also, because Africa is the root of humanity, understanding the genetic basis of this disease in Africans will contribute to improving cancer health equity globally.

In addition, scientific investigations on cancer racial disparity have largely considered the Black race as a homogenous group. However, the evidence is now emerging that there are within-group differences in cancer risk among Blacks (414). This review also clearly demonstrated the need to disaggregate Africa in cancer studies. To reduce cancer disparity and achieve equity in treatment outcomes, cancer genetics and genomics studies in African should endeavor to stratify populations by their ancestry roots, tribes, or languages rather than countries. This is imperative to identifying population-relevant genetic variants since African countries are geopolitical constructs that bear no relationship with the biological relatedness of the people that are clustered together in those countries.

Furthermore, every genomic study requires a reference to make an appropriate inference, but African populations are presently inadequately represented in the current reference genomes. To address this unmet need, Shermanet et al. (415) recently published a pan-African reference genome. The African Pan Genome sequences they assembled revealed that up to 10% of the genome will be missed by any efforts relying only on GRCh38 to study human variation. Yet, it is important to note that their study only included representative samples (5%) from Ibadan, Nigeria, and may not be a true "Pan African Genome" and may best represent the West African human population, which the Yoruba people belong to. Further research efforts are, therefore, needed to assemble more African reference genomes, which should be based on the genetic divergence of human populations in Africa.

AUTHOR CONTRIBUTIONS

BS conceived, designed, and supervised the review. SR and OR collected and analyzed the data. BS, SR, and OR wrote the manuscript. All authors contributed to the article and approved the submitted version.

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