# SOCIAL INEQUITIES IN CANCER

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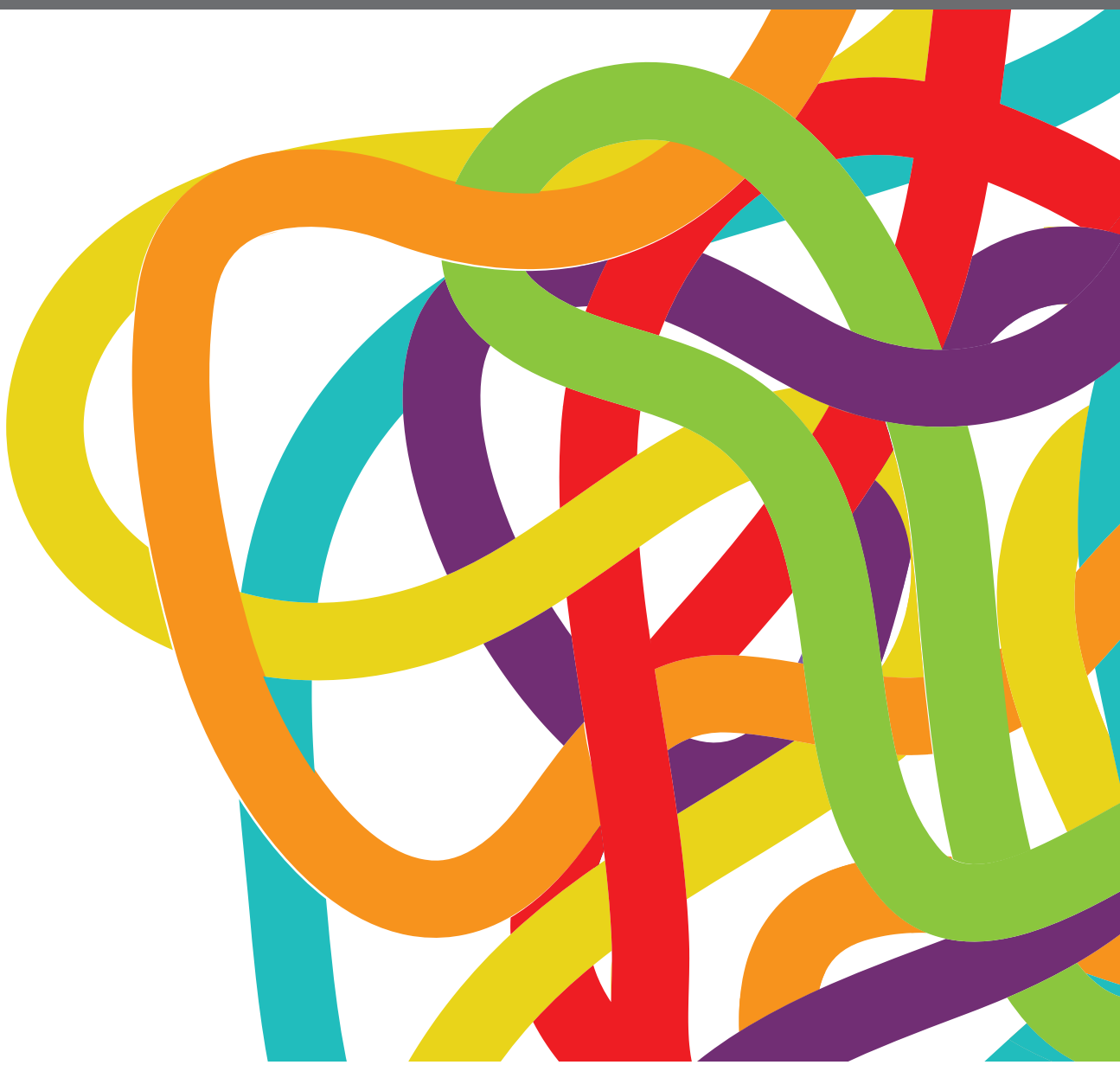

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# SOCIAL INEQUITIES IN CANCER

Topic Editors:
**Dana Hashim,** Icahn School of Medicine at Mount Sinai, United States
**Friederike Erdmann,** Danish Cancer Society, Denmark; International Agency for Research on Cancer, France; Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Germany
**Hajo Zeeb,** Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH & University of Bremen, Germany

"Social Inequities in Cancer" is a compendium of articles that identify barriers and metrics on the topic of modifiable and unnecessary cancer inequalities. Social inequities have long been recognised as a strong contributing factor in health and cancer inequalities for the past several decades. Despite progress in cancer treatment, cancer incidence, mortality and survival vary markedly between and within countries. Globalisation, greater life expectancy, emerging analytical technologies, and the scalability of big data have revolutionized the vantage point from which social inequities can be studied. The focus of these articles is inequalities as they relate to cancer, with the inequalities ranging from the community to the global scale.



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EDITORIAL
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# Editorial: Social Inequities in Cancer

*Dana Hashim*[1]*, *Friederike Erdmann*[2,3,4] *and Hajo Zeeb*[4,5]

[1] Department of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY, United States, [2] Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark, [3] Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France, [4] Department of Prevention and Evaluation, Leibniz-Institute for Prevention Research and Epidemiology-BIPS GmbH, Bremen, Germany, [5] Health Sciences Bremen, University of Bremen, Bremen, Germany

**Keywords: social inequalities, socioeconomic status, global health, social inequities, cancer epidemiology, cancer disparities, social epidemiology**

## Editorial on the Research Topic

## Social Inequities in Cancer

Social inequalities and equities are very closely related, but with important differences. In cancer epidemiology, social inequalities refer to differences in socioeconomic position (SEP) related to statistical differences in incidence, mortality, and survival rates between populations. Social inequities may be the cause of social inequalities. Social inequities are systemic, unnecessary, unjust, and avoidable barriers that prevent segments of the population from achieving optimal health (1). Geographical, economic, societal, and cultural aspects of inequity interact to construct circumstances in which these subgroups are, to varying degrees, excluded or included. As populations navigate the cancer care continuum of cancer prevention, detection/diagnosis, and management/treatment (2), ingrained social inequities lead to cancer incidence, mortality, and/or survival disparities (3–5). Social inequities have been recognized in numerous studies as a strong predictor of morbidity and premature mortality worldwide (6) and contribute to cancer inequalities within countries and between countries (7). Although reductions in cancer burden are achievable by reducing social and economic inequities, socioeconomic factors and their role in cancer causation and outcomes are often not targeted in public health strategies.

The field of "social epidemiology" is distinguished by its focus on the conditions of the environment in which population subgroups grow, work, and live, encompassing the cumulative impact of these factors—the social determinants—, as a whole, on health, and disease outcomes (7, 8). The study of social inequities in cancer prevention strategies is a field of active research, e.g., with a recent publication identifying low social class based on occupational title as having a positive relationship with cancer mortality (4) as well as the recent incorporation of a socio-demographic index (SDI) to annual Global Burden of Disease reporting to stratify disease burden (9–11).

It must be acknowledged that targeting social inequities to improve public health requires attention to concepts and methods conducive to illuminating links between our physiology and social, political, and economic systems (12). Several studies in this current topical issue focus on analyses of cancer incidence, mortality, and survival by measures of socioeconomic status using Baysian models, area-based socioeconomic indices (Carstairs, Theil T), human development index (HDI), and a childhood/adolescent SEP based on parents' ownership of a car. The goal of this research topic is to draw attention to several aspects of social inequities, including identifying unequal distributions of cancer in social groups, health care system research, specific risks among less-studied ethnic groups including life course models, and cancer survival inequities.

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***Edited and reviewed by:***
*Imtiaz Ahmad Siddiqui, University of Colorado Anschutz Medical Campus, United States*

***Correspondence:**
*Dana Hashim*
*dana.hashim@mssm.edu*

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## UNEQUAL DISTRIBUTION OF CANCER IN SOCIAL GROUPS

Kamath et al. provide an in-depth account of social disparities in liver cancer frequency, risk factors as well as preventive services in New York City, known for its mixed ethnic and social composition. Their study is an excellent example of using multiple existing data sources in order to shed light on cancer related-disparities at neighborhood level, with concomitant illustration using geographical mapping.

Germany has a large immigrant population, established since the 1960s and recently expanded in the wake of large refugee movements. The "Aussiedler" (resettlers) are a unique population consisting of ethnic Germans formerly residing in the ex-USSR. Kaucher et al. report on two large administrative data-based-cohorts and show that initially elevated frequencies of stomach and lung cancer (among men) converge to the risk among the majority population, whereas mortality remains largely unchanged. Analyses of colorectal, prostate, and female breast cancer incidence rates reveal patterns favoring the migrant population. Unfortunately, there are no data on relevant life-style and other risk factors in this study and ethnicity was used as a proxy for SEP.

Using an area-based measure of social deprivation, Hoebel et al. study the socially unequal distribution of cancer risk in Germany. They largely confirm international results, also in terms of reverse gradients for malignant melanoma, breast and thyroid cancer. Their analysis provides insights into both absolute and relative inequalities and indicate that overall, there are larger social inequalities in cancer among men compared to women. However, site-specific analyses differentiate this picture to some extent.

Cervical cancer remains at the top of important cancers for many less developed countries. Santamaría-Ulloa and Valverde-Manzanares provide an account of existing social differences in cervical cancer incidence in Costa Rica. The economic dimension of the index used is a compound measure of residential electricity consumption and residential access to internet and the Theil T index used to quantify inequality on a district level. Higher incidence rates are found to be related to a lower uptake of cervical cancer screening, and rates differ substantially across socioeconomic regions within Costa Rica.

On the global level, Fidler and Bray use the HDI as composite metric to study global cancer frequencies. They outline HDI stratification as an important approach providing guidance for the development and implementation of cancer control plans worldwide. A notable characteristic of the HDI is the fact that it combines social (education), health (life expectancy), and economic (gross national income) data at country level. Further discussion is warranted regarding how the HDI compares to the SDI used in the Global Burden of Disease studies.

## LIFE COURSE, GENETIC-ETHNIC ISSUES

Little is known about prostate cancer risk factors, although blacks have a much higher rate than whites. Madathil et al. investigate the relationship between lifelong SEP and prostate cancer in a French-speaking Canadian population using a Bayesian life course exposure model. Measures of SEP during childhood/adolescence include parents' ownership of a car and father's longest occupation, while the subject's first and longest occupations indicate early- and late-adulthood SEP. Lower SEP over the life course is associated with higher PCa incidence, with evidence for sensitive time periods.

Brovkina et al. focus on hereditary breast and ovarian cancer syndrome (HBOS) among Tatars, one of the largest ethnic minority groups in Russia. It was previously reported that the BRCA mutation, while frequent for the Slavic population, has not been found in Tatar women with hereditary breast cancer. This study demonstrates a predisposition for the *CDK12*c.1047-2A>G nucleotide variant in HBOCS in patients of Tatar ethnicity and identifies *CDK12* as a novel gene involved in HBOCS susceptibility.

## HEALTH CARE SYSTEMS AND CANCER RESEARCH

The study by Alavi et al. is the first to focus on public versus private rehabilitation centers in Iran. Private rehabilitation centers were rated higher in communication, basic amenities and autonomy compared to public centers. Using the Blinder-Oaxaca decomposition model, perceived social class explain 76% of the inequality in autonomy in choosing between public and private rehabilitation center.

With a broad perspective on potentials for cancer research, the review by Drake et al. outlines the methods by which funding schemes, scientists, genome consortia, and policy makers can play a role to ensure cancer research is generalizable and beneficial to patients in both high- and low-income countries. This includes higher representation of low-to-middle income countries in large molecular and genomic studies, focus on cost-effective approaches to precision medicine, and an overall pooling of data and resources to foster the mechanistic understanding of cancer on a global level.

## SURVIVAL AND SOCIAL FACTORS

Survival rates have substantially improved over the last decades for most cancer sites. Nonetheless, not all patients benefit from these advances. It has been consistently observed that socioeconomically disadvantaged cancer patients have worse survival than patients

from socioeconomically advantaged groups and, in some countries, this socioeconomic gap has widened over time.

Ingarfield et al. assess the change in social inequality in the survival of patients with head and neck cancer between short-, mid-, and long-term survival in Scotland. Findings show a clear gradients in overall, disease-specific and net survival across socioeconomic groups (measured by area-based Carstairs 2001 index). Further analyses with full adjustment reveal that the survival inequalities can be largely explained by differences in multiple factors, including patient, tumor, and treatment.

Finke et al. conduct a systematic review and meta-analysis synthesizing current knowledge on socioeconomic differences in lung cancer survival with a particular focus on differences by measurements of socioeconomic status used (individual-level vs. ecological grouping). Findings from the meta-analyses indicate a poorer prognosis among lower income patients. While no evidence for associations between individual education or occupation and lung cancer survival are observed, studies using an area-based socioeconomic measure show lower survival for lower socioeconomic groups. Of note, only eight of the 94 reviewed individual studies account for smoking status in their analysis.

Evidence is accumulating that for childhood cancer, socioeconomic and social factors also impact survival. Mogensen et al. review the most recent publications on social and socioeconomic factors and childhood cancer survival in high-income countries and find the evidence to be heterogeneous. Some studies observe no survival differences between children by socioeconomic background, while several studies indicated a social gradient with higher mortality among children from families of lower SES. Mogensen et al. note that knowledge on underlying mechanisms for social inequalities in survival is lacking.

Social inequities affect all aspects of cancer, from research to health care systems, from disparities in incidence to treatment outcome, and life after cancer. It is also a topic that has recently become high priority with the increasing burden of cancer worldwide. As a result of improving survival rates (13), the number of cancer survivors is continuously increasing. Access to health information and globalization are also introducing a wider range of social groups to screening, diagnostic, and treatment services as well as exposing disparities in access to health services. The public health relevance of social inequities is substantially increasing and will continue to be an important consideration to explain observed differences in cancer incidence, mortality, and survivorship—even in the near future.

While the studies presented in this twelve-article collection cannot comprehensively cover a topic of expanding breadth and depth, the new research questions raised in the individual articles highlight the knowledge gaps, socioeconomic metrics, and analytical techniques on the subject of social inequities. In doing so, this collection contributes to identifying opportunities in reducing social inequality gaps and, therefore, overall cancer burden, by providing an evidence-based foundation to build on public health research aimed at reducing the social inequity in cancer.

## AUTHOR CONTRIBUTIONS

DH conceived the draft and wrote the manuscript. FE and HZ contributed to the manuscript text and editing. HZ supervised the manuscript writing process. All authors provided critical feedback and helped shape the direction of the manuscript.

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# Liver Cancer Disparities in New York City: A Neighborhood View of Risk and Harm Reduction Factors

*Geetanjali R. Kamath[1,2,3], Emanuela Taioli[1,2,3], Natalia N. Egorova[3], Josep M. Llovet[4,5,6], Ponni V. Perumalswami[7], Jeffrey J. Weiss[8], Myron Schwartz[9], Stanley Ewala[10] and Nina A. Bickell[2,3,8]**

[1] Institute for Translational Epidemiology, New York, NY, United States, [2] Tisch Cancer Institute, New York, NY, United States, [3] Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [4] Mount Sinai Liver Cancer Program, Divisions of Liver Diseases, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY, United States, [5] Liver Cancer Translational Research Laboratory, BCLC, Liver Unit, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Institut d'Investigacions Biomèdiques August Pi iSunyer (IDIBAPS), University of Barcelona, Barcelona, Catalonia, Spain, [6] Institució Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia, Spain, [7] Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [8] Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [9] Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [10] Icahn School of Medicine at Mount Sinai, New York, NY, United States

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**Edited by:**
*Friederike Erdmann, Danish Cancer Society, Denmark*

**Reviewed by:**
*Jerry Polesel, Centro di Riferimento Oncologico di Aviano (IRCCS), Italy*
*Mary H. Ward, National Cancer Institute (NCI), United States*

***Correspondence:**
*Nina A. Bickell*
*nina.bickell@mssm.edu*

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**Introduction:** Liver cancer is the fastest increasing cancer in the United States and is one of the leading causes of cancer-related death in New York City (NYC), with wide disparities among neighborhoods. The purpose of this cross-sectional study was to describe liver cancer incidence by neighborhood and examine its association with risk factors. This information can inform preventive and treatment interventions.

**Materials and methods:** Publicly available data were collected on adult NYC residents ($n$ = 6,407,022). Age-adjusted data on liver and intrahepatic bile duct cancer came from the New York State Cancer Registry (1) (2007–2011 average annual incidence); and the NYC Vital Statistics Bureau (2015, mortality). Data on liver cancer risk factors (2012–2015) were sourced from the New York City Department of Health and Mental Hygiene: (1) Community Health Survey, (2) A1C registry, and (3) NYC Health Department Hepatitis surveillance data. They included prevalence of obesity, diabetes, diabetic control, alcohol-related hospitalizations or emergency department visits, hepatitis B and C rates, hepatitis B vaccine coverage, and injecting drug use.

**Results:** Liver cancer incidence in NYC was strongly associated with neighborhood poverty after adjusting for race/ethnicity ($\beta = 0.0217$, $p = 0.013$); and with infection risk scores ($\beta = 0.0389$, 95% CI = 0.0088–0.069, $p = 0.011$), particularly in the poorest neighborhoods ($\beta = 0.1207$, 95% CI = 0.0147–0.2267, $p = 0.026$). Some neighborhoods with high hepatitis rates do not have a proportionate number of hepatitis prevention services.

**Conclusion:** High liver cancer incidence is strongly associated with infection risk factors in NYC. There are gaps in hepatitis prevention services like syringe exchange and vaccination that should be addressed. The role of alcohol and metabolic risk factors on liver cancer in NYC warrants further study.

**Keywords: hepatocellular carcinoma, chronic hepatitis, health-care disparities, low-income populations, vaccinations, cancer screening**

## INTRODUCTION

Cancer of the liver and intrahepatic bile ducts (liver cancer) is a public health problem in the United States (US). Since 1980, its nationwide incidence rate has tripled, and its mortality rate has doubled, outpacing the increase in any other cancer (2). Only 31% of those with localized liver cancer survive 5 years past diagnosis. The 5-year survival rate for regional and distant liver cancer is even poorer at 11 and 3%, respectively (2). Several studies have succeeded in reducing liver cancer incidence, most effectively through hepatitis B vaccination, and to an extent through antiviral therapy for hepatitis B and C (3). Although liver cancer prognosis can be improved by early detection and treatment during its long subclinical course, this is a challenge since liver cancer is usually asymptomatic in its early stages (3, 4). Currently, no guidelines currently exist for routine liver cancer screening in people of average risk; however, people at higher risk due to cirrhosis and/or chronic hepatitis B infection may benefit from screening with ultrasound exams, with or without alpha-fetoprotein blood tests, twice a year (5).

In New York City (NYC), liver cancer is the fifth leading cause of cancer-related death among men and seventh among women (1). The 2010–2014 age-adjusted liver cancer incidence rate in NYC was 12 per 100,000 residents, higher than the US (7.8) and New York State (NYS) (8.6) (1, 6). The age-adjusted mortality rate per 100,000 was also higher at 7.7 compared with the US (6.3) and NYS (6.1) (1, 6). Certain neighborhoods have incidence rates of 16–22.2 per 100,000, comparable to Asia, West Africa, and Central/South America (7).

New York City is a microcosm of the global population due to its unique demographics, high percentage of foreign-born inhabitants, and diversity of country of origin. Although a recent review examined racial/ethnic liver cancer disparities in the US (8), it has not been studied on a local level. A study of cancer incidence in NYC and three of its neighborhoods (East Harlem, Central Harlem, and Upper East Side) found that neighborhood was associated with incidence of all cancers, including liver cancer (9). To understand the basis for NYC disparities in liver cancer incidence and mortality, it is crucial to identify high-risk subpopulations, the risk factors most strongly associated with liver cancer, and how they are distributed in the city. The information can help inform preventive and treatment interventions for communities that require them the most.

## MATERIALS AND METHODS

### Data Collection

Data were collected from the pool of adult (≥18 years) NYC residents ($n$ = 6,407,022 per the 2010 US Census) at the neighborhood level, and defined neighborhood borders using NYC United Hospital Fund (UHF) codes. Originally, the UHF divided NYC into 42 distinct neighborhoods by combining adjoining zip codes areas with similar characteristics, meant to approximate NYC Community Planning Districts. To increase statistical power, these were later collapsed into 34 neighborhoods (10).

#### Primary Outcomes

Cancer data for NYC included age-adjusted incidence and mortality rates per 100,000 residents from the NYS Cancer Registry (1). The average incidence rate was calculated from the number of residents diagnosed with liver and/or intrahepatic bile duct cancer over 2007–2011, divided by the corresponding age-specific intercensal population estimates (from the NYS Department of Health). Age adjustment was based on the US Census 2000 standard population. Mortality rate estimates for 2015 were obtained from the NYC Department of Health and Mental Hygiene (NYCDOHMH) using the online interactive tool, Epiquery (11). Crude mortality rates are presented for neighborhoods with small numbers and/or unreliable age-adjusted estimates. For all outcomes, the most recent available estimates at the neighborhood level are presented.

#### Sociodemographics

Data on gender and race/ethnicity were collected from the 2010 US Census, and neighborhood-specific distributions were extracted using Epiquery. Data on poverty were obtained from the American Community Survey conducted by the US Census Bureau (12). Poverty was defined as the % of people reporting annual incomes below the federal poverty threshold during 2010–2014 ($11,139–$12,071 for one person). Data on insurance coverage were obtained from the Community Health Survey (CHS), an annual telephone survey conducted among NYC residents ≥18 years by the NYCDOHMH (13). We report the % of people who had no type of health insurance coverage.

#### Risk Factors for Liver Cancer

Viral hepatitis data are derived from surveillance reports filed by the Bureau of Communicable Disease (14). They include confirmed or probable cases of chronic hepatitis B and C reported to the Health Department by health-care providers and laboratories meeting the definitions by the Centers for Disease Control/Council of State and Territorial Epidemiologists' (positive hepatitis B surface antigen, hepatitis B e-antigen, and hepatitis B nucleic acid test; enzyme-linked immunosorbent assay antibody test with a high signal-to-cutoff value; recombinant immunoblot assay; and RNA test for hepatitis C).

Prevalence of self-reported current smoking (proportion of people who reported smoking cigarettes daily or on some days as of the interview day), injecting drug use (% of people who reported having used a needle to inject non-prescription drugs at least once), obesity (body mass index ≥30 kg/m$^2$), diabetes (% of people who reported ever being told by a health-care professional that they have diabetes), and physical activity (% of adults who reported in the past 30 days: (1) exercising (running, calisthenics, golf, gardening, or walking, other than at their regular job) and (2) walking/bicycling >10 blocks for transportation) were obtained *via* the CHS (13). Diabetes control was measured by data from the NYC A1C Registry. We report the % of diabetic adults (history of ≥2 glycosylated hemoglobin, or A1C, test values ≥ 6.5%) who received medical care in 2012, with their last A1C measurement ≥9% (15).

As a proxy for alcohol use, clinical data on the number of patients who were hospitalized or visited an emergency department

(ED) during 2014 were abstracted from the mandatory NYS hospital discharge abstract database (16), using the ICD-9 codes 291.0–291.5, 291.8, 291.9, 303.00–303.93, 305.00–305.03, 357.5, 425.5, 535.3, 571.1–4, 571.5, 571.9, 572.3, 577.1 (diagnoses of alcohol-related morbidity) (17), and of alcohol poisoning (790.3, 980, E860) (18). Only one hospitalization/ED visit per patient was counted. Approval to collect data under exempt status was obtained from Mount Sinai's Institutional Review Board.

### Preventive Services

Data on the availability of preventive services providing hepatitis B or C testing and treatment, hepatitis B vaccination, and syringe exchange facilities were collected from the NYC Health Map website (19), which lists names and addresses of clinics by service type. The number of services in each UHF neighborhood was obtained by matching address zip codes. The % of NYC residents who reported ever having received at least 1 dose of the hepatitis B vaccine and ever getting tested for hepatitis C was obtained from the CHS.

## Statistical Analyses

Descriptive data are presented for the entire city, and each neighborhood in the form of tables and density maps prepared using ArcGIS Desktop (version 10.3.1; ESRI, Redlands, CA). Predictors were weighted risk scores calculated for three domains of modifiable liver cancer risk factors: (1) metabolic (obesity, diabetes, and proportion of A1C $\geq$ 9%); (2) alcohol-related morbidity (hospitalizations, ED visits); and (3) infections (rates of newly reported hepatitis B and C cases, hepatitis B vaccination coverage, and self-reported injecting drug use). Each continuous item was given an ordinal score based on tertiles, quartiles, or a specific cutoff. For each item, neighborhoods received a prevalence score from 1 to 3 based on increasing tertiles (quartiles 1–4 for hepatitis B). Hepatitis B vaccine coverage was reverse scored to reflect a protective effect. Due to the distribution, a cutoff of <1% and ≥1% was used to score injecting drug use prevalence category as 1 or 2. Each item was also assigned a correlation score from 1 to 3 based on the strength of its correlation with liver cancer incidence (Pearson's $r \leq 0.3$, $0.3 < r < 0.5$, $r \geq 5$). Prevalence scores were multiplied by the correlation scores to obtain item scores, which were summed up to produce a risk score for each domain.

Spatial autocorrelation of liver cancer incidence was assessed using Moran's global index (Moran's *I* statistic) (20). A sensitivity analysis was conducted to evaluate the effect of spatial dependence by comparing linear regression models with and without a spatial lag term. The spatial lag model was run by adding a spatial weights matrix as an independent variable with weights based on inverse distances between neighborhood centroid coordinates. All spatial analyses were conducted using the spatial software GeoDa version 1.12.1.129.

The relationship between liver cancer incidence and each predictor was assessed in unadjusted and adjusted generalized linear regression models, with neighborhood as the unit of analysis ($n = 34$) (SAS Proprietary Software 9.4, TS1M1). All models met the assumptions for the specified Poisson distribution (21). Stratified analyses by prevalence of neighborhood poverty were conducted. Point estimates, 95% Wald confidence intervals, and *p*-values for the regression coefficient β were evaluated at a statistical significance level of $\alpha = 0.05$ (two-sided hypothesis test).

# RESULTS

New York City's racial and ethnic composition includes 33% non-Hispanic White, 29% Hispanic, 23% African-American, 13% Asian or Pacific Islander, and 3% other races. Half of NYC residents (53%) are female, 21% live in poverty, and 13% are uninsured. There was considerable variation in the distribution of demographic characteristics according to neighborhood (**Table 1**).

## Liver Cancer Statistics

During 2007–2011, there was an average of 921.4 cases of liver and intrahepatic bile duct cancer in NYC annually. The age-adjusted incidence rates were highest in the Bronx [South Bronx (22.3), Fordham/Bronx Park (15), and Pelham/Throgs Neck (13.7)]; Manhattan [Union Square and Lower Manhattan (15.9), Central Harlem (15.8), East Harlem (15.7), and Washington Heights/Inwood (13.3)], and Brooklyn [Sunset Park (16.7)] (**Figure 1**). Mortality rates follow similar geographic distribution, with the highest mortality rates in Sunset Park (12.6), Fordham/Bronx Park (12.1), South Bronx (11.6), Union Square and Lower Manhattan (11.5), Pelham/Throgs Neck (11), and Central Harlem (9.2). Two neighborhoods showed high mortality rates despite relatively lower incidence: Williamsburg/Bushwick in Brooklyn (10.6) and Ridgewood/Forest Hills in Queens (9.1).

## Liver Cancer Risk Factors

The distribution of individual liver cancer risk factors is presented in **Table 2**. Obesity was less prevalent in NYC (24%) compared with the US average (≈38%) (4) but varied widely from 8% in the Upper West Side to 37% in East New York. East Harlem had the highest prevalence of self-reported diabetes (23%) and poor glycemic control (21%). A high proportion of poorly controlled diabetes was also observed in East New York, Bedford–Stuyvesant/Crown Heights, Williamsburg/Bushwick, the South Bronx, and Fordham/Bronx Park. There was relatively less variation in self-reported physical activity. East Harlem had the highest prevalence of self-reported injecting drug use at 4.7%, followed by Upper West Side (2.1%), and the South Bronx (1.8%). Cigarette smoking was most prevalent in Greenpoint (21%), Long Island City/Astoria, and Ridgewood/Forest Hills (19%). Finally, the mean and range of composite scores for the three modifiable risk factor domains (metabolic, alcohol, and infection) are presented in **Table 3**. Alcohol risk scores were moderately correlated with metabolic and infection risk scores; however, results of statistical tolerance tests did not indicate a significant threat of multicollinearity on the model estimates (22).

## Association Between Distribution of Liver Cancer Incidence and Risk Factor Scores

Neighborhood-level data on poverty and Hispanic ethnicity were associated with high liver cancer incidence ($\beta = 0.0277$, $p < 0.0001$, and $\beta = 0.0113$, $p < 0.0001$), even after adjustment

**TABLE 1** | Distribution of sociodemographic characteristics according to neighborhood.

| Neighborhood | % Male[a] | Race/ethnicity (% of population)[a] | | | | | % Living in poverty[b] | % Uninsured[c] |
|---|---|---|---|---|---|---|---|---|
| | | White | Black | Hispanic | Asian/Pacific Islander | Other | | |
| Kingsbridge/Riverdale | 45.0 | 42.5 | 11.1 | 39.8 | 4.7 | 1.9 | 16.1 | 2.7 |
| The Northeast Bronx | 44.7 | 11.1 | 58.8 | 24.4 | 2.8 | 2.9 | 15.4 | 10.3 |
| Fordham/Bronx Park | 47.4 | 8.7 | 24.8 | 59.6 | 5.0 | 2.0 | 32.9 | 18 |
| Pelham/Throgs Neck | 47.0 | 20.4 | 20.7 | 49.7 | 6.6 | 2.7 | 23.2 | 11.8 |
| South Bronx[d] | 46.9 | 1.5 | 29.5 | 66.5 | 1.0 | 1.4 | 41.2 | 11.9 |
| Greenpoint | 49.5 | 68.1 | 2.9 | 23.0 | 4.1 | 1.9 | 26.5 | 8.6 |
| Downtown Brooklyn/Heights/Slope | 47.1 | 56.6 | 15.5 | 18.1 | 6.5 | 3.3 | 16.4 | 10.3 |
| Bedford–Stuyvesant/Crown Heights | 44.8 | 11.2 | 71.4 | 13.1 | 1.9 | 2.5 | 27.2 | 11.4 |
| East New York/New Lots | 46.1 | 1.9 | 51.2 | 38.8 | 4.7 | 3.4 | 33.4 | 3.8 |
| Sunset Park | 51.4 | 15.8 | 2.3 | 44.6 | 35.7 | 1.6 | 31.1 | 27.4 |
| Borough Park | 49.4 | 61.0 | 4.3 | 12.8 | 20.0 | 1.8 | 26.9 | 16.0 |
| Flatbush | 45.0 | 11.9 | 72.4 | 10.9 | 2.3 | 2.4 | 18.6 | 14.3 |
| Canarsie and Flatlands | 44.4 | 24.1 | 61.4 | 8.9 | 3.5 | 2.1 | 13.3 | 8.5 |
| Bay Ridge/Bensonhurst | 48.5 | 60.3 | 1.1 | 13.4 | 23.4 | 1.8 | 16.0 | 13.2 |
| Coney Island | 47.2 | 64.7 | 6.6 | 11.7 | 15.4 | 1.6 | 20.4 | 11.3 |
| Williamsburg/Bushwick | 48.5 | 14.6 | 30.4 | 48.7 | 4.5 | 1.8 | 31.5 | 10.4 |
| Washington Heights/Inwood | 48.0 | 15.9 | 12.0 | 68.0 | 2.5 | 1.7 | 25.4 | 18.7 |
| Central Harlem | 45.6 | 13.9 | 54.6 | 24.2 | 4.3 | 2.9 | 29.8 | 5.3 |
| East Harlem | 47.1 | 11.7 | 29.0 | 51.7 | 5.6 | 2.0 | 32.9 | 14.7 |
| Upper West Side | 45.8 | 67.2 | 7.5 | 14.9 | 7.9 | 2.5 | 11.6 | 7.8 |
| Upper East Side–Gramercy[d] | 45.0 | 75.5 | 3.4 | 7.4 | 11.5 | 2.2 | 8.4 | 7.8 |
| Chelsea Village[d] | 50.4 | 66.0 | 4.0 | 10.6 | 16.6 | 2.8 | 11.0 | 12.2 |
| Union Sq–Lower Manhattan[d] | 48.1 | 45.7 | 6.8 | 10.0 | 50.4 | 8.0 | 16.1 | 5.2 |
| Long Island City/Astoria | 49.4 | 46.9 | 6.1 | 27.1 | 16.6 | 3.3 | 16.7 | 9.6 |
| West Queens | 51.9 | 16.1 | 5.9 | 51.4 | 24.5 | 2.1 | 19.2 | 29.0 |
| Flushing/Clearview | 47.7 | 31.3 | 2.1 | 16.2 | 48.4 | 1.9 | 15.2 | 12.8 |
| Bayside-Fresh Meadows[d] | 47.5 | 44.0 | 5.2 | 12.2 | 36.2 | 2.3 | 11.6 | 7.5 |
| Ridgewood/Forest Hills | 47.7 | 54.5 | 2.0 | 26.1 | 15.5 | 2.0 | 13.1 | 17.6 |
| Southwest Queens | 49.0 | 22.6 | 12.4 | 32.7 | 20.2 | 12.1 | 14.3 | 9.5 |
| Jamaica | 46.7 | 7.1 | 53.9 | 18.0 | 14.5 | 6.5 | 16.0 | 19.6 |
| Southeast Queens | 46.4 | 13.6 | 54.9 | 11.8 | 14.7 | 5.1 | 7.6 | 9.5 |
| The Rockaways | 47.0 | 35.2 | 38.8 | 21.0 | 2.3 | 2.7 | 20.2 | 8.4 |
| Northern Staten Island[d] | 48.5 | 40.2 | 21.0 | 28.9 | 7.5 | 2.4 | 20.4 | 10.1 |
| Southern Staten Island[d] | 48.4 | 76.0 | 2.5 | 11.1 | 8.8 | 1.5 | 7.7 | 4.1 |
| NYC | 47.5 | 33.3 | 22.8 | 28.6 | 12.6 | 2.7 | 20.6 | 12.6 |

[a]*United States Census, 2010.*

[b]*American Community Survey, percentage with annual income below 100% of federal poverty threshold, 2010–2014.*

[c]*New York City (NYC) Department of Health and Mental Hygiene. Epiquery: NYC Interactive Health Data System—[Community Health Survey 2015] [08/28/2017]. http://nyc.gov/health/epiquery.*

[d]*Gender, race, and poverty data for combined neighborhoods are averages of constituent UHF 42 neighborhoods.*

*All percentages are age-adjusted using the 2010 US Census standard population.*

for White race and Hispanic ethnicity ($\beta = 0.0217$, $p = 0.013$). A higher proportion of foreign-born residents was correlated with higher rates of hepatitis B ($r = 0.48$, $p = 0.0037$).

Among the three modifiable risk factor domains, infection was the strongest predictor of liver cancer incidence, with an expected increase of 5.3% in incidence when the infection risk score increased by 1 ($p < 0.0001$), followed by alcohol-related morbidity (4.8% increase, $p = 0.001$) (**Table 3**). Metabolic risk score was also weakly but positively associated with liver cancer incidence (3% increase, $p = 0.052$). We conducted formal testing by including interaction terms between poverty tertiles and each of the three risk scores (metabolic, alcohol, and infection), and observed lack of statistical interaction. When stratified by tertiles of poverty prevalence, infection score was most strongly associated with liver cancer incidence at the high poverty level (10% increase, $p = 0.027$). Similarly, infection risk score was most strongly associated with liver cancer incidence (4% increase, $p = 0.011$), especially at the high poverty level (12.8% increase, $p = 0.026$), in models that adjusted for metabolic and alcohol risk score.

## Spatial Autocorrelation Sensitivity Analysis

The Moran's $I$ test indicated the presence of a significant positive spatial autocorrelation for the outcome, liver cancer incidence ($I = 0.28$, $p = 0.005$). Comparison of ordinary least squares regression and a spatial lag model found no meaningful effect of spatial autocorrelation on model estimates (Table S1 in Supplementary Material).

## Preventive Services

The number of centers offering preventive services are 80, 89, and 28, respectively, for hepatitis B testing, treatment, and vaccination; 127 and 128, respectively, for hepatitis C testing and treatment; 23 syringe exchange programs (SEPs), with multiple additional

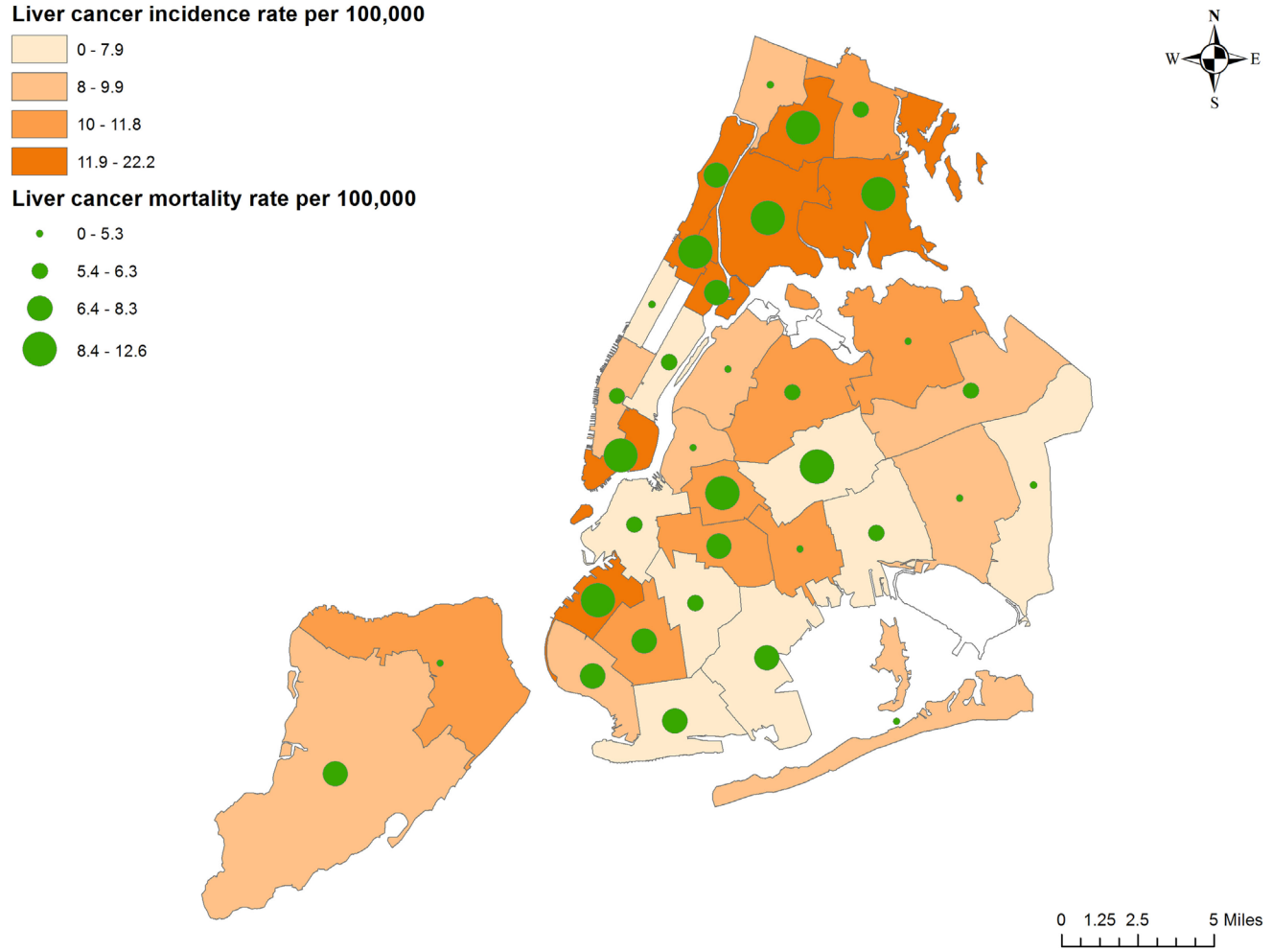


**FIGURE 1** | Liver cancer incidence and mortality rates according to neighborhood.

distribution locations, and hundreds of Expanded Syringe Access Program locations throughout NYC. Their availability in relation to hepatitis burden is depicted in **Figures 2** and **3**.

## DISCUSSION

To the best of our knowledge, this is the first study to describe liver cancer incidence and the distribution of its underlying risk factors at a neighborhood level in NYC. In addition, this is the first study to assess the availability of hepatitis prevention and treatment services in the context of disease burden.

Results indicate that not only does NYC have higher rates of liver cancer incidence and mortality compared with NY State and the rest of the US but also large disparities exist among city neighborhoods, with incidence rates in some neighborhoods as high as those in China and West Africa (7). The most striking finding was the strong relationship between poverty, liver cancer, and its risk factors, even after adjusting for other demographics and risk factor scores. Of the three modifiable risk factor domains, infection was most strongly and consistently associated with liver cancer incidence. Rates of newly reported chronic hepatitis B and C in NYC show a gradual rise since 2013 (9, 10). This could be partially attributed to improved surveillance and test sensitivity and updated US Department of Health guidelines for Hepatitis C testing in "baby boomers" (23). However, recent changes in drug use patterns could explain the rise in both hepatitis B and C rates. The National Institute of Drug Abuse reported that the % of drug reports identified as heroin, a common injectable drug, increased from 10.4% in 2012 to 11.6% in 2013 in NYC, along with a decrease in the average age at admission to substance abuse treatment (24).

Recent immigration patterns may also contribute toward the observed increase in hepatitis B. Between 2000 and 2011, NYC has seen a 4% increase in foreign-born residents (25). Neighborhoods with the highest gains (≥5,000 people) include East and Central Harlem, Lower Manhattan, parts of the South Bronx, Sunset Park, etc. (25). The same neighborhoods have seen high immigration from three countries with high prevalence of hepatitis B (China: 5.49%, Dominican Republic: 4.09%, and

**TABLE 2** | Distribution of behavioral liver cancer risk factors according to neighborhood.

| Neighborhood | Prevalence of risk factor (% of population)[h] | | | | | | | | | In the highest quartile[g] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Current smoking[a] | IDU[b] | Exercise[a] | Walked/ biked[a] | Obesity[a] | Diabetes[a] | A1C ≥ 9%[c,d] | ≥1 HBV vaccine dose[e] | Ever HCV tested[f] | |
| Kingsbridge/Riverdale | 8.3 | 0 | 83.4 | 73.9 | 33.3 | 8.7 | 15.1 | 51.7 | 28.3 | |
| The Northeast Bronx | 12.3 | 0 | 72.4 | 78.7 | 28.2 | 10.1 | 17.5 | 58.0 | 54.1 | |
| Fordham/Bronx Park | 10.4 | 1.39 | 71.2 | 80.0 | 28.6 | 18.4 | 20.2 | 47.8 | 46.3 | LC, M, I, P |
| Pelham/Throgs Neck | 16.5 | 0.79 | 73.2 | 76.3 | 29.9 | 11.9 | 19.2 | 51.1 | 42.8 | LC |
| South Bronx[e] | 17.0 | 1.76 | 70.4 | 82.1 | 34.4 | 20.2 | 20.7 | 47.1 | 52.4 | LC, M, A, I, P |
| Greenpoint | 20.7 | 0 | 77.9 | 85.1 | 26.2 | 9.4 | 16.2 | 37.8 | 41.0 | |
| Downtown Brooklyn/Heights/ Slope | 13.5 | 0.64 | 81.2 | 92.0 | 16.1 | 4.6 | 17.1 | 60.7 | 36.1 | |
| Bedford–Stuyvesant/Crown Heights | 17.9 | 0.23 | 72.8 | 78.1 | 36.3 | 13.6 | 21.1 | 53.7 | 57.2 | A, P |
| East New York/New Lots | 12.3 | 0.19 | 72.3 | 73.5 | 37.1 | 21.7 | 21.5 | 50.1 | 46.5 | M, A, P |
| Sunset Park | 15.3 | 1.51 | 67.1 | 93.1 | 23.6 | 12.1 | 15.6 | 32.9 | 33.4 | LC, I, P |
| Borough Park | 15.1 | 0.48 | 69.8 | 77.8 | 16.3 | 8.8 | 13.4 | 45.3 | 26.7 | I |
| Flatbush | 9.4 | 1.03 | 72.9 | 82.0 | 35.6 | 13.7 | 19.6 | 51.1 | 47.3 | |
| Canarsie and Flatlands | 8.0 | 0 | 76.4 | 75.1 | 29.1 | 13.9 | 18.2 | 45.0 | 43.8 | |
| Bay Ridge/Bensonhurst | 15.2 | 0.85 | 73.0 | 83.5 | 21.2 | 10.3 | 12.4 | 33.5 | 30.9 | I |
| Coney Island | 18.4 | 0.93 | 68.4 | 82.6 | 26.8 | 13.7 | 12.5 | 39.9 | 36.2 | I |
| Williamsburg/Bushwick | 18.0 | 1.52 | 69.7 | 79.9 | 25.9 | 15.0 | 21.2 | 42.6 | 46.7 | M, A, I, P |
| Washington Heights/Inwood | 12.0 | 0.44 | 76.8 | 81.2 | 25.8 | 14.1 | 18.6 | 38.0 | 41.9 | LC, M |
| Central Harlem | 12.8 | 0.21 | 74.2 | 81.1 | 31.4 | 13.7 | 19.6 | 40.7 | 45.9 | LC, I, P |
| East Harlem | 16.8 | 4.66 | 65.9 | 83.6 | 27 | 23.1 | 20.7 | 57.3 | 58.3 | LC, M, A, I, P |
| Upper West Side | 13.0 | 2.07 | 91.1 | 90.8 | 7.8 | 6.9 | 14.2 | 63.4 | 37.4 | |
| Upper East Side-Gramercy[e] | 10.2 | 0.4 | 87.6 | 92.1 | 12.5 | 4.1 | 11.3 | 47.6 | 37.4 | |
| Chelsea Village[e] | 13.2 | 0.6 | 84.2 | 91.3 | 9.3 | 4.8 | 13.1 | 60.6 | 52.1 | I |
| Union Sq–Lower Manhattan[e] | 17.0 | 0.19 | 79.8 | 88.4 | 7.9 | 9.3 | 13.3 | 49.9 | 43.9 | LC, A, I |
| Long Island City/Astoria | 19.1 | 0.51 | 80.2 | 85.5 | 25.1 | 9.8 | 15.4 | 42.7 | 29.4 | |
| West Queens | 17.8 | 0.27 | 73.6 | 89.4 | 21.1 | 9.6 | 16.0 | 35.5 | 30.3 | I |
| Flushing/Clearview | 11.5 | 0.25 | 67.7 | 79.2 | 17.2 | 10.7 | 11.3 | 45.1 | 43.3 | |
| Bayside-Fresh Meadows[e] | 9.1 | 0.17 | 75.1 | 78.4 | 19.1 | 14.2 | 10.4 | 53.3 | 30.9 | |
| Ridgewood/Forest Hills | 18.8 | 0 | 70.5 | 83.8 | 17.5 | 5.1 | 13.0 | 40.9 | 36.7 | |
| Southwest Queens | 12.8 | 1.38 | 67.3 | 72.6 | 28.6 | 20.4 | 17.6 | 42.8 | 37.6 | |
| Jamaica | 6.7 | 0.05 | 67.1 | 79.8 | 30.8 | 13.6 | 17.3 | 40.2 | 44.5 | |
| Southeast Queens | 11.0 | 0 | 74.2 | 69.1 | 26.0 | 12.2 | 16.7 | 54.0 | 45.5 | |
| The Rockaways | 16.0 | 0.85 | 69.5 | 77.3 | 34.1 | 13.9 | 18.4 | 41.0 | 53.4 | M, A |
| Northern Staten Island[e] | 17.5 | 0 | 78.5 | 74.2 | 23.7 | 9.0 | 17.9 | 45.2 | 41.1 | |
| Southern Staten Island[e] | 17.5 | 0.37 | 79.3 | 65.5 | 24.6 | 6.2 | 12.4 | 47.9 | 33.1 | |
| NYC | 14.3 | 0.66 | 74.5 | 81.6 | 24.1 | 11.6 | 17.0 | 46.6 | 41.4 | |

*LC, liver and bile duct cancer incidence rate; M, metabolic risk factor score; A, alcohol risk factor score; I, infection risk factor score; P, poverty.*

*[a]New York City (NYC) Department of Health and Mental Hygiene. Epiquery: NYC Interactive Health Data System—[Community Health Survey (CHS) 2015] [08/29/2017]. http://nyc.gov/health/epiquery.*

*[b]Injecting drug use: NYC Department of Health and Mental Hygiene. CHS [2012]; public use dataset accessed on 09/08/2017.*

*[c]NYC A1C Registry, 2012; rates based on registrants reported with likely diabetes (based on a history of ≥2 A1C test values ≥ 6.5%).*

*[d]NYC residents ages ≥18 years; rates are per 100,000 adults and are age-adjusted to 2000 Census (July 2013 NYSDH population estimates).*

*[e]A1C registry data for combined neighborhoods are averages of constituent UHF 42 neighborhoods.*

*[f]NYC Department of Health and Mental Hygiene. Epiquery: NYC Interactive Health Data System—[CHS 2012] [09/08/2017]. http://nyc.gov/health/epiquery.*

*[g]NYC Department of Health and Mental Hygiene. Epiquery: NYC Interactive Health Data System—[CHS 2013] [09/08/2017]. http://nyc.gov/health/epiquery.*

*[h]All percentages are age-adjusted using the 2010 US Census standard population.*

Jamaica: 3.76%) (26), mirroring their own high hepatitis B rates. Chinese-born immigrants in NYC were found to have high seroprevalence of hepatitis B and increased risk for liver cancer (27). Another study found hepatitis B prevalence of 9.6% among a sample of African-born participants residing mostly in Central Harlem and the South Bronx (28). Immigrant health is an important public health issue in a diverse city like NYC. Most liver cancer risk factors are preventable, but due to poverty or other issues, health policies may not have the desired effect. Ongoing surveillance for hepatitis and effective and timely culturally and linguistically competent prevention and treatment may be the key to preventing progression to liver cirrhosis and liver cancer in NYC residents. The population of certain areas in Harlem and Bronx is ideal for exploring preventive public health strategies, and implementing surveillance programs.

Preventive and treatment services for hepatitis are available throughout the city, but not all neighborhoods with high hepatitis rates have a proportionate number of required services. We observed that high hepatitis B rates were correlated with lower vaccine coverage and lower proportion of free vaccination

**TABLE 3** | Association between liver cancer incidence and risk factor scores.

| Risk factor domain | Scores, mean (range) | Unadjusted model | | | | Adjusted model[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | β | 95% CI | % Change[b] | *p* | β | 95% CI | % Change[b] | *p* |
| **Overall population** | | | | | | | | | |
| Metabolic score | 9.8 (5–15) | 0.0292 | −0.0002 to 0.0587 | 3.0 | 0.052 | 0.0001 | −0.0345 to 0.0348 | 0.0 | 0.995 |
| Alcohol score | 9.9 (5–15) | 0.0465 | 0.0195 to 0.0735 | 4.8 | 0.001 | 0.025 | −0.0112 to 0.0613 | 2.5 | 0.176 |
| Infection score | 15.3 (8–24) | 0.0513 | 0.0256 to 0.077 | 5.3 | <0.0001 | 0.0389 | 0.0088 to 0.069 | 4.0 | 0.011 |
| **By poverty level** | | | | | | | | | |
| **High poverty** | | | | | | | | | |
| Metabolic score | 12.4 (5–15) | 0.0211 | −0.0371 to 0.0792 | 2.1 | 0.478 | −0.0862 | −0.2697 to 0.0973 | −8.3 | 0.357 |
| Alcohol score | 13.1 (5–15) | 0.0186 | −0.041 to 0.0782 | 1.9 | 0.541 | 0.0816 | −0.0949 to 0.2582 | 8.5 | 0.365 |
| Infection score | 19.2 (16–28) | 0.095 | 0.0109 to 0.179 | 10.0 | 0.027 | 0.1207 | 0.0147 to 0.2267 | 12.8 | 0.026 |
| **Medium poverty** | | | | | | | | | |
| Metabolic score | 9.5 (5–15) | −0.0131 | −0.0675 to 0.0413 | −1.3 | 0.637 | −0.0235 | −0.079 to 0.032 | −2.3 | 0.407 |
| Alcohol score | 10.0 (5–15) | 0.0272 | −0.0224 to 0.0768 | 2.8 | 0.283 | 0.0332 | −0.019 to 0.0854 | 3.4 | 0.213 |
| Infection score | 14.9 (8–22) | 0.008 | −0.0332 to 0.0492 | 0.8 | 0.705 | 0.0018 | −0.0401 to 0.0437 | 0.2 | 0.932 |
| **Low poverty** | | | | | | | | | |
| Metabolic score | 8.0 (5–13) | −0.015 | −0.084 to 0.0539 | −1.5 | 0.700 | −0.0075 | −0.0785 to 0.0635 | −0.7 | 0.836 |
| Alcohol score | 7.0 (5–12) | 0.0106 | −0.0611 to 0.0823 | 1.1 | 0.773 | −0.0181 | −0.1002 to 0.064 | −1.8 | 0.666 |
| Infection score | 12.6 (8–18) | 0.0504 | −0.022 to 0.1228 | 5.2 | 0.172 | 0.0578 | −0.0263 to 0.1419 | 6.0 | 0.178 |

[a]*All adjusted models include the following variables: metabolic score, alcohol score, and infection score.*
[b]*Percentage change in incidence of liver cancer per unit increase in risk score: calculated as* $(e^{\beta} - 1) \times 100$.

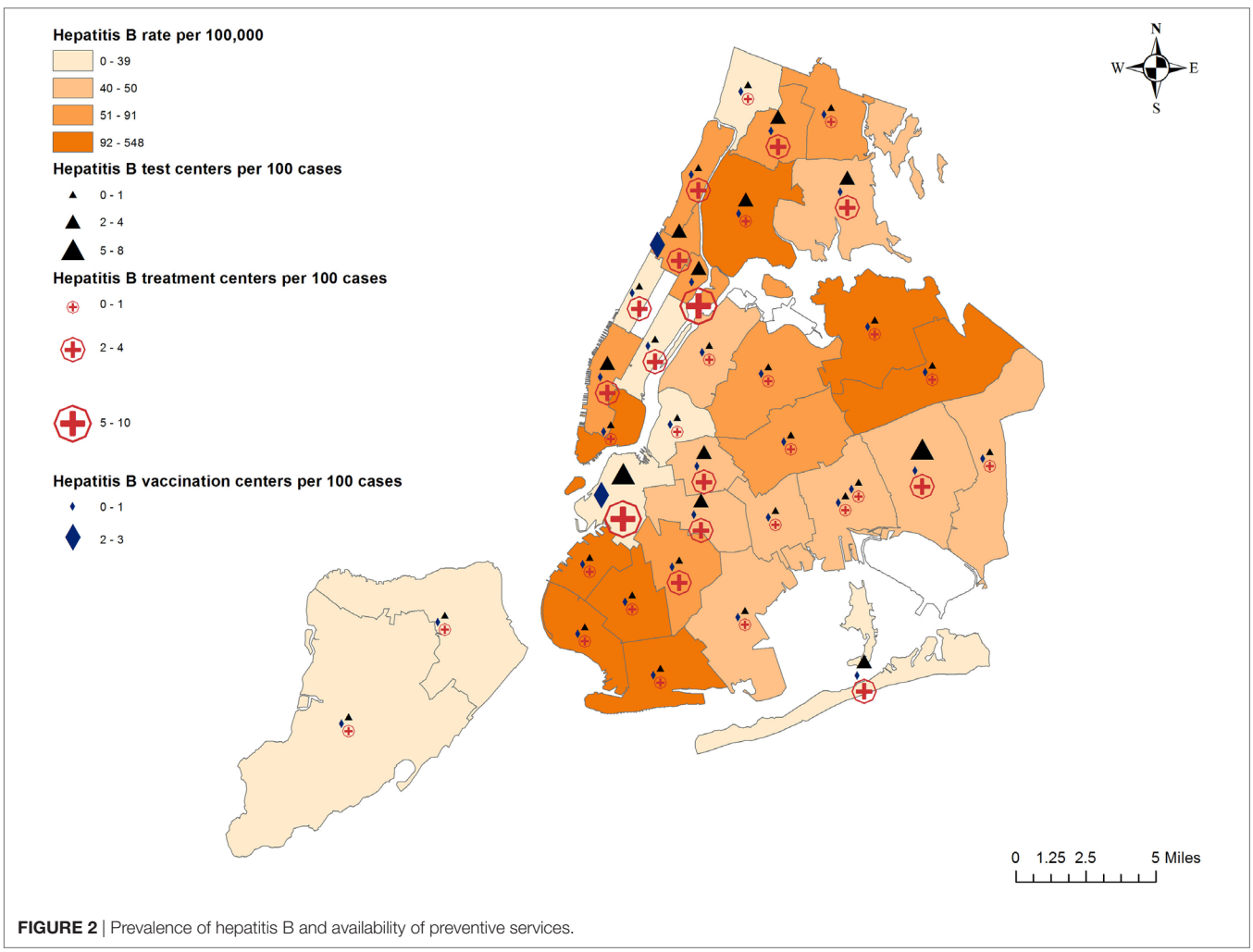


**FIGURE 2** | Prevalence of hepatitis B and availability of preventive services.

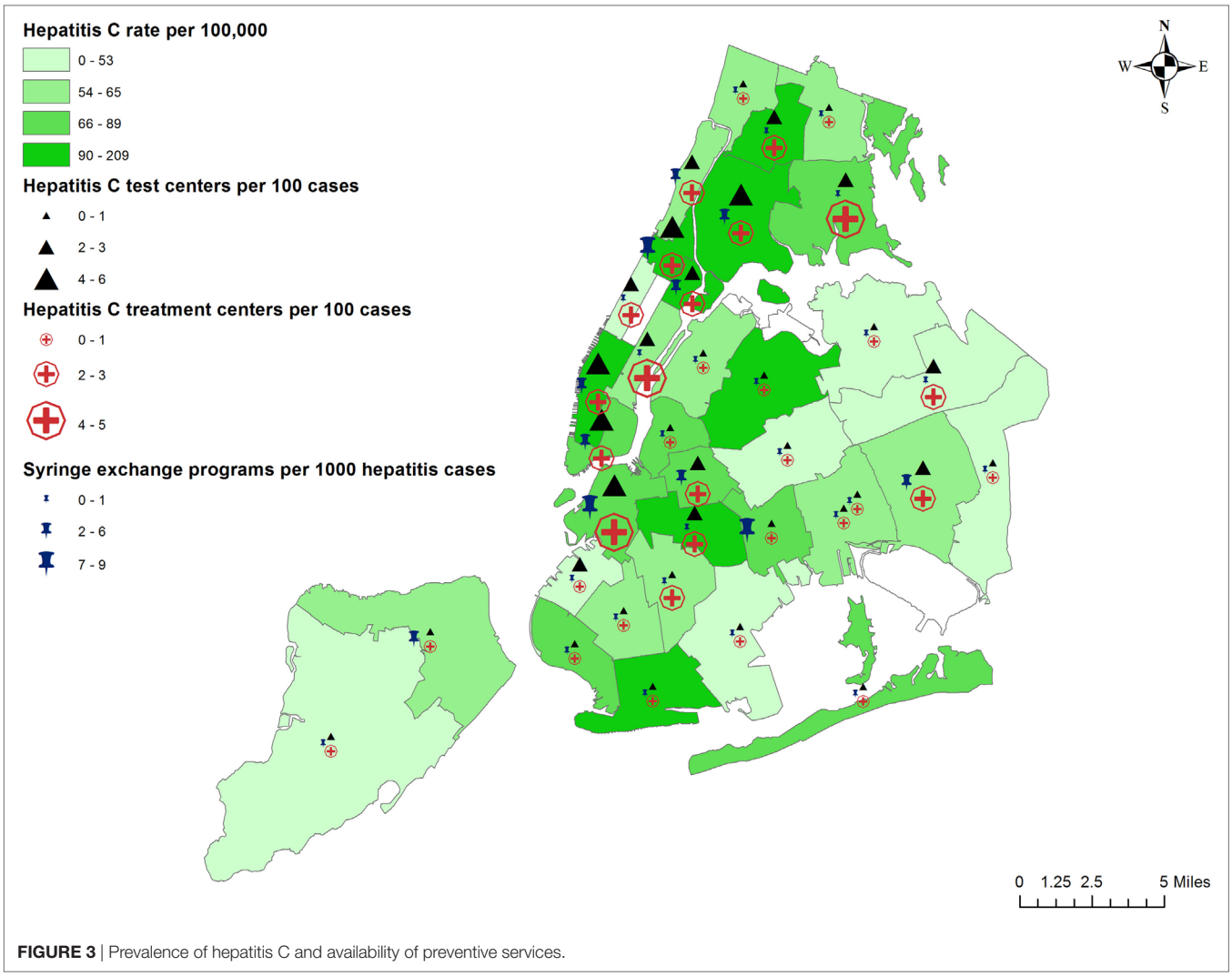


**FIGURE 3** | Prevalence of hepatitis C and availability of preventive services.

centers. Lower insurance coverage was also strongly correlated with lower vaccine coverage. Hepatitis B vaccination can cost $120–$370 without insurance, plus consultation/professional administration fees. This is largely unaffordable for less affluent, uninsured people. Non-monetary factors such as having a vaccinated acquaintance, perceived risk of disease, perceived vaccine safety, and provider recommendation may also influence patients' choice to receive the hepatitis B vaccine (29). Therefore, a multi-pronged intervention is required to increase hepatitis B vaccine coverage in NYC, addressing disease-specific knowledge, access, affordability, and psychosocial factors.

While hepatitis C-related services were found to be more numerous, some neighborhoods appear to have fewer than 1 SEP per 1,000 hepatitis cases (Fordham–Bronx Park and Bedford–Stuyvesant–Crown Heights), while others (Coney Island and West Queens) have fewer than one hepatitis C testing and treatment centers per 100 hepatitis C cases. Although residents in poorer neighborhoods were more likely to get tested for hepatitis C, there is no information on how many of those who tested positive cleared the virus or received treatment. Without insurance, hepatitis C drugs for a 12-week course can cost between $39,600 and $94,500 (30, 31). Even with insurance, arranging for prior authorization of hepatitis C treatment is often time consuming and a barrier to patients starting treatment, e.g., most NYS insurance providers require a prescription to be written by or in consultation with a specialist (32). Hepatitis C treatment for those who cannot obtain health insurance is provided by the NYS Hepatitis C Patient Assistance Program HepCAP (33). However, many of them are not eligible for HepCAP, highlighting important gaps in current hepatitis C management.

This study has some limitations: as an ecological study based on the most recently available data, the neighborhood-level associations may not reflect individual risk of liver cancer; thus the results should be interpreted in a geographical context only. Surveillance data for hepatitis B and C may include people that no longer have active infection, and therefore these should not be considered incidence or prevalence rates, but simply the number of newly reported cases. Hepatitis may also be underdiagnosed due to the passive nature of surveillance data, since active testing is more costly and resource intense. Study power to detect significant associations could be restricted by small sample size ($n = 34$). Age, sex, and racial/ethnic diversity are other potential

source of variation; however, due to the non-individual nature of the data and multiple race indicators, it was not possible to adjust for these variables. Alcohol risk scores were moderately correlated with metabolic and infection risk scores; however, results of statistical tolerance tests did not indicate a significant threat of multicollinearity on the model estimates. The NYC Health Map website does not provide data on private medical offices which may provide vaccinations and/or treatment whose information is not publicly available. Finally, we did not have data on homeless or incarcerated populations, who have an even higher risk of hepatitis C (34). However, this is the first study that attempts to quantify the relative role of infection, metabolic factors, and alcohol in HCC risk in a diverse environment such as NYC and highlights current gaps in hepatitis prevention services like syringe exchange and vaccination, that can be addressed by the expansion of existing services. The role of alcohol and metabolic risk factors on liver cancer in NYC warrants further study.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Program for the Protection of Human Subjects Office (PPHS), Icahn School of Medicine at Mount Sinai. The protocol was approved (under exempt status) by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai. A consent waiver was obtained since the data were de-identified, publicly available data.

## AUTHOR CONTRIBUTIONS

GK, ET, and NB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design; study supervision: ET and NB. Acquisition, analysis, or interpretation of data: GK, NE, and SE. Drafting of the manuscript: GK, ET, NB, PP, JW, and MS. Critical revision of the manuscript for important intellectual content: GK, ET, NB, NE, PP, JW, MS, JL, and SE. Statistical analysis: GK.

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# Cancer Incidence and Mortality Among Ethnic German Migrants From the Former Soviet Union

*Simone Kaucher*[1], *Hiltraud Kajüter*[2], *Heiko Becher*[1,3†] *and Volker Winkler*[1*†]

[1] *Unit of Epidemiology and Biostatistics, Institute of Public Health, University Hospital Heidelberg, Heidelberg, Germany,* [2] *Epidemiological Cancer Registry of North Rhine-Westphalia, Münster, Germany,* [3] *Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Germany is a country known for immigration. In 2015, 21% of the general population in Germany consisted of individuals with a migration background. This article focuses on cancer-specific incidence and mortality among one of the biggest migrant groups in Germany: the resettlers. Resettlers are ethnic Germans who mainly immigrated from the Russian federation and other countries of the former Soviet Union after its collapse in 1989. We investigated differences between resettlers and the general German population, regarding (i) incidence and mortality of malignant neoplasms, (ii) time trends of the corresponding incidence and mortality, and (iii) cancer stage at diagnosis. We provide data from two resettler cohorts covering an observation time of 20 years: one cohort on cancer incidence ($N = 32,972$), and another cohort on mortality ($N = 59,390$). Cancer-specific standardized incidence ratios (SIR) and standardized mortality ratios (SMR) for all malignant neoplasms combined and the most common cancer-sites were calculated between resettlers and the general German population. Time trend analyses using Poisson regression were performed to investigate the developments of SIRs and SMRs. To investigate differences in stage at diagnosis, logistic regression was performed, calculating Odds Ratios for condensed cancer stages. We observed higher incidence and mortality of stomach cancer [SIR (men) 1.62, 95%CI 1.17–2.19; SMR (men) 1.62, 95%CI 1.31–2.01; SIR (women) 1.32, 95%CI 0.86–1.94; SMR (women) 1.52, 95%CI 1.19–1.93] and higher mortality of lung cancer [SMR (men) 1.34, 95%CI 1.20–1.50] among resettlers compared to the general German population, but lower incidence and mortality of colorectal (both sexes), lung (women), prostate and female breast cancer. However, time trend analyses showed converging incidence risks of cause-specific incidence over time, whereas differences of mortality did not show changes over time. Results from logistic regression suggest that resettler men were more often diagnosed with advanced cancer stages compared to the Münster population. Our findings suggest that risk factor patterns of the most common cancer-sites among resettlers are similar to those observed within the Russian population. Such increases in prostate, colorectal and breast cancer incidence may be the consequence of improved detection measures, and/or the adaptation of resettlers to the German lifestyle.

**Keywords: incidence, mortality, migrants, Germany, former soviet union, cohort study, cancer**

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*Claudia Santos-Hövener,*
*Robert Koch Institut, Germany*

***Correspondence:**
*Volker Winkler*
*v.winkler@uni-heidelberg.de*

*These authors have contributed equally to this work*

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## INTRODUCTION

In 2015, there were an estimated number of 247.5 million migrants worldwide (1). Research on migrants is important, since it contributes to the knowledge of disease etiology and also reveals differences in the health status between migrants and host populations. Differences in health status are often linked to different exposures in the migrant country of origin (2, 3), to the migration process itself (4) and to integration in the host country (5). Migrants are often a vulnerable group and have a lower socioeconomic status compared to the host population. Consequently, migrants often may have higher risks of diseases that are related to their living and working environment (6). Migrants may seek health care in an altered manner relative to the German population due to their different perceptions of risk, health, and disease combined with poor language skills (7).

Previous research regarding cancer risk among migrants showed heterogeneous results dependent upon cancer-site of interest, country of origin, and host country. In general, it was observed that migrants from non-Western countries showed a higher risk of infectious-related cancer-sites than the host populations of Western European countries, including stomach, liver and cervix uteri cancer. On the contrary, a lower risk of cancer-sites related to a Western lifestyle was observed, including breast and colorectal cancer (8). These results reflect findings from studies in the US and in Australia, which also found a lower breast cancer risk and a higher incidence risk of stomach and liver cancer among migrants compared to host populations (9–11). Furthermore, it was observed that breast cancer risk of non-Western migrants increased with duration of stay and increasing acculturation (9).

Germany has long been a country of immigration (4). In 2015, 21% of the general population in Germany reported to having a migration background. An individual was classified as having a migration background if they or at least one parent immigrated to Germany from their country of origin (12). The two biggest migrant groups in Germany originate from Turkey and the former Soviet Union (FSU). During the early 1960s many Turkish people migrated to Germany for work. However, migrants from the FSU are a unique group of ethnic Germans (resettlers: in German: (Spät-) Aussiedler), whose ancestors emigrated to the Russian empire in the 18th and 19th centuries. After World War II, resettlers were allowed to immigrate to Germany, obtaining German citizenship upon arrival. Consequently, after the collapse of the Soviet Union, many ethnic German migrants immigrated from the FSU (13, 14). To avoid (self-) segregation of incoming resettlers, the German government passed the law of residence assignment in 1989. After arrival, resettlers were usually assigned to their first place of residence based on regional population density and economic performance of the federal state. Although resettlers were obliged to live in this assigned place of residence for at least 2 years (since 2005 3 years) (15), a few exceptions to this rule were permitted. In some circumstances people immigrating to Germany were allowed to resettle closer to family members already living in the country, rather than being assigned to a city by the German government.

Since the late 1980s the FSU has been undergoing massive social changes. These changes have in turn led to a dramatic decrease in life expectancy and overall mortality crisis. In the Russian federation between 1987 and 1994, mortality for all major causes of death (except for cancer) increased (16). This mortality development was very similar to that observed in Kazakhstan and in Ukraine. In 2006, age-adjusted mortality was still high with about 1,300 deaths per 100,000 people compared to 650 per 100,000 people in Germany (17). **Table 1** compares age-adjusted estimated incidence and mortality rates of the most common cancer-sites between Germany, the Russian federation and Kazakhstan in 2012 and shows incidence/mortality ratios for each country, indicating survival after cancer diagnosis (18).

Given the high burden of lung cancer among males and stomach cancer among both sexes in resettler country of origin, this article focuses on cancer-specific incidence and mortality among resettlers in comparison to the general German population. Furthermore, the development of cancer incidence and mortality will be investigated over 20 years after immigration to Germany and cancer stage at diagnosis will be compared between resettlers and the Münster population.

**TABLE 1 |** Estimated age-adjusted incidence and mortality rates (adjusted to Segi) per 100,000 and incidence/mortality ratios for all malignant neoplasms and the most common cancer-sites in Germany, the Russian federation and Kazakhstan in 2012 (18).

| Cancer-site | Germany (incidence/ mortality) ratio | Russian federation (incidence/ mortality) ratio | Kazakhstan (incidence/ mortality) ratio |
|---|---|---|---|
| **MEN** | | | |
| All malignant neoplasms* | 323.7/122.1<br>2.65 | 245.8/176.3<br>1.39 | 282.2/202.5<br>1.39 |
| Stomach | 10.7/5.7<br>1.88 | 24.5/20.6<br>1.19 | 35.2/30.3<br>1.16 |
| Colorectal | 39.7/13.1<br>3.03 | 30.0/19.9<br>1.51 | 29.1/16.9<br>1.72 |
| Lung | 38.8/31.3<br>1.24 | 51.4/47.1<br>1.09 | 59.2/54.5<br>1.09 |
| Prostate | 77.3/10.4<br>7.43 | 30.1/12.4<br>2.43 | 14.9/8.6<br>1.73 |
| **WOMEN** | | | |
| All malignant neoplasms* | 252.5/83.4<br>3.03 | 187.1/91.3<br>2.05 | 216.7/104.8<br>2.07 |
| Stomach | 5.4/3.1<br>1.74 | 10.8/8.7<br>1.24 | 12.8/10.5<br>1.22 |
| Colorectal | 23.3/8.1<br>2.88 | 21.8/12.6<br>1.73 | 19.4/10.7<br>1.81 |
| Lung | 17.9/14.5<br>1.23 | 6.8/5.6<br>1.21 | 8.1/7.2<br>1.13 |
| Breast | 91.8/15.5<br>5.92 | 45.6/17.2<br>2.65 | 63.0/18.0<br>3.50 |

*Without non-melanoma skin cancer (ICD-10: C44 diagnoses).*

# MATERIALS AND METHODS

## Cancer Incidence

To investigate cancer incidence among resettlers, a registry-based cohort was established in the administrative district of Münster [part of the federal state North Rhine-Westphalia (NRW)], called the AMIN cohort (Aussiedler in Münster - Incidence cohort study). The cohort consists of a sample of all resettlers who were assigned to the study area between 1990 and 2001.

Cancer cases of this cohort were assessed by the federal cancer registry of NRW. The cancer registry performed a pseudonymized record linkage by using encrypted personal identifiers instead of plaintext data (19, 20). Additionally, issues arising from name changes were addressed by utilizing information on common changes from previous studies on ethnic German migrants. Data was collected on the incidence of all cancer cases in the administrative district of Münster between 1994 and 2013, and it was documented whether or not the individual was a cohort member. The study was restricted to histologically confirmed primary malignant tumors (excluding non-melanoma skin cancer). Cancer site-specific analyses were performed for the most common cancer-sites among the resettler cohort (stomach, colorectal, lung, female breast, and prostate cancer).

Since vital status could not be assessed with the follow-up procedure used for the AMOR cohort (described below), person-time was estimated based on an approach for cohorts with an incomplete follow-up (21). In brief, person-time of each individual was first calculated between date of immigration and date of diagnosis or 31st of December 2013 (end of follow-up). In a second step, the person-time estimation procedure used information on out-migration and on non-cancer mortality from the AMOR cohort (described below). Sensitivity analyses were additionally performed to control for possible biases resulting from these assumptions.

## Cancer Mortality

Mortality was investigated by combining three registry-based cohort studies on resettlers immigrating between 1990 and 2005, called AMOR studies (Aussiedler Mortality cohort studies). These cohort studies collected data from different regions in Germany: the federal state of NRW (22), the federal state of the Saarland (23) and the region of Augsburg in the federal state of Bavaria (24). Mortality follow-up was performed until 31st of December 2009. Local registry offices provided information on the vital status of each cohort member (alive, deceased). If the status was deceased, cause of death was either retrieved from local health authorities as anonymized death certificates or from regional statistical offices, using ICD codes. A detailed description of the cohorts, the follow-up procedure and the study characteristics, as well as detailed analyses on mortality of the pooled AMOR cohort can be found elsewhere (25).

Person-time was calculated for each individual in one of three ways: either between the date of immigration and the date of death, the date of out-migration or the 31st of December 2009 (end of follow-up). In case of a missing date of event or loss to follow-up, the midpoint between the last known contact and 31st of December 2009 was used as the end of observation. Applying a SAS macro, person-years were calculated to the exact day (26).

To compare resettler cancer mortality to the general German population, the WHO mortality database was used to calculate mortality rates for standardization. Thus, the rates for comparison included observed deaths of the cohort (17).

## Statistical Analyses

For all malignant neoplasms combined and the most common cancer-sites, standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) with exact 95% confidence intervals (95%CI) were calculated. Expected numbers of cancer diagnoses were calculated using incidence rates of the Münster population excluding the resettler cohort and the estimated person-years from the AMIN cohort. Expected numbers of cancer deaths were calculated using mortality rates of the general German population from the WHO mortality database.

Time trends of cancer incidence were analyzed by modeling SIRs with Poisson regression using the observed number as the dependent and year [defined as "calendar year – 1993" (1: 1994, . . . , 20: 2013)] as the independent variable. The offset was the logarithm of the expected number. Time trends of cancer mortality were modeled accordingly, except defining year as "calendar year – 1989" (1:1990, . . . , 20:2009).

Cancer stage at diagnosis was categorized in condensed stages as local or advanced based on the T Classification system (T information: tumor size). This system applies cancer-site specific rules of the European Network of cancer registries (ENCR) in order to classify cancer stage (27). For sensitivity analysis the NM Classification system for condensed stage was used (28), which uses information on regional lymph nodes (N) and distant metastasis (M) for each tumor for classification. In the analyses, stomach, colorectal, lung, breast, and prostate cancer were investigated as combined cancer-sites. Since staging classifications differ by cancer-sites and cannot be applied for all cancer-sites (e.g., lymphomas or brain tumors), the analysis was restricted to the most common cancer-sites. **Table 2** presents the different classification systems for the observed cancer-sites.

Logistic regression was used to assess the association between advanced stage at cancer diagnosis and resettler status (yes/no). Condensed stage was the dependent variable and resettler status the independent variable while adjusting for age at diagnosis and year of diagnosis [again defined as "calendar year – 1993" (1: 1994, . . . , 20: 2013)]. As the main model encompassed a complete case analysis, unknown stages were excluded from the analysis. Additionally, sensitivity models were performed: all unknown stages were assumed to be either (I) local stage or (II) advanced stage.

All statistical analyses were performed separated by sex using SAS Version 9.4.

# RESULTS

## Descriptive Results

**Table 3** compares the study characteristics of the AMIN and the AMOR cohorts. The AMIN cohort was estimated to accumulate

**TABLE 2 |** Condensed classification systems to categorize stages into local, advanced, and unknown stages.

| | T Classification[a] | | NM Classification[b] | |
|---|---|---|---|---|
| **Stage** | **T status *(for stomach, colorectal, lung & prostate cancer)*** | **T status *(for breast cancer)*** | **N status** | **M status** |
| Local | T1-T2 | T1-T3 | N0<br>N0 | M0<br>Unknown |
| Advanced | T3-T4 | T4 | N1-N3<br>N1-N3<br>any N | M0<br>Unknown<br>M1 |
| Unknown | Unknown | Unknown | Unknown<br>Unknown | M0<br>Unknown |

[a]*Cancer-site specific classification.*
[b]*Same classification system for the five investigated cancer-sites.*

**TABLE 3 |** Study characteristics of the AMIN and the AMOR cohort.

| **Characteristics** | **AMIN cohort** | | **AMOR cohort** | |
|---|---|---|---|---|
| | ***N*** | **%** | ***N*** | **%** |
| **NUMBER OF INDIVIDUALS** | | | | |
| Total | 32,972 | 100.0 | 59,390 | 100.0 |
| Men | 16,033 | 48.6 | 28,744 | 48.4 |
| Women | 16,939 | 51.4 | 30,646 | 51.6 |
| **PERSON-YEARS** | | | | |
| Total | 483,371 | 100.0 | 797,264 | 100.0 |
| Men | 234,124 | 48.4 | 384,404 | 48.2 |
| Women | 249,247 | 51.6 | 412,860 | 51.8 |
| **IMMIGRATION PERIOD** | | | | |
| 1990-1992 | 9,363 | 28.4 | 17,367 | 29.2 |
| 1993-1995 | 9,863 | 29.9 | 18,637 | 31.4 |
| 1996+ | 13,746 | 41.7 | 23,386 | 39.4 |
| **AGE AT IMMIGRATION** | | | | |
| <18 years | 11,598 | 35.2 | 9,536 | 16.1 |
| 18–34 years | 9,217 | 28.0 | 19,604 | 33.0 |
| 35–64 years | 10,579 | 32.1 | 24,555 | 41.4 |
| ≥65 years | 1,578 | 4.8 | 5,695 | 9.6 |

| **Characteristics** | **AMIN cohort** | **AMOR cohort** |
|---|---|---|
| | **Mean (median, range)** | **Mean (median, range)** |
| **AGE AT IMMIGRATION** | | |
| Total | 29.1 (27.5, 0–99) | 36.6 (35, 0-98) |
| Men | 27.8 (26, 0-92) | 35.1 (34, 0-95) |
| Women | 30.3 (28, 0-99) | 38.0 (36, 0-98) |

483,371 person-years with a mean follow-up time of 14.7 years. The AMOR cohort accumulated 797,264 person-years with a mean follow-up time of 13.4 years.

In both cohorts there were slightly more women than men (∼52%) and the distribution of immigrating resettlers by immigration period were comparable. Notably, the AMOR cohort contained relatively more resettlers in the immigration period from 1996 and beyond relative to the AMIN cohort. It was also revealed that the study population of the AMIN cohort was younger compared to the mortality cohort.

Between 1994 and 2013, 3.9% ($N = 1{,}291$) of the AMIN cohort individuals were diagnosed with a primary malignant tumor of which 87.6% ($N = 1{,}131$) were histologically confirmed. The five most frequent cancer diagnoses were breast cancer ($N = 183$, 16.2%), colorectal cancer ($N = 155$, 13.7%), lung cancer ($N = 107$, 9.5%), prostate cancer ($N = 106$, 9.4%), and stomach cancer ($N = 69$, 6.1%).

Follow-up was complete for 95.2% of the AMOR cohort and information regarding the cause of death was available for 92.2% of the 5,572 observed deaths. Altogether, 1,533 deaths due to malignant neoplasms were observed, whereof the three most common cancer-sites were lung ($N = 369$), colorectal ($N = 169$), and stomach ($N = 150$).

## SIR and SMR Analyses

**Table 4** shows results of the SIR and SMR analyses for men and women as well as age-standardized mortality rates for the general German population. Cancer incidence for all malignant neoplasms combined was lower among resettlers compared to the Münster population, for both sexes respectively. While cancer mortality for all combined malignant neoplasms was lower among resettler women compared to the general German population, no differences were observed among men.

Stomach cancer incidence and mortality was found to be higher among resettlers compared to the general population, for both sexes respectively. In contrast, resettlers showed lower incidence and mortality of prostate and female breast cancer than that observed within the general populations. Among resettler men, a significantly lower mortality of colorectal cancer was observed, whereas resettler women showed a significant lower incidence of colorectal cancer. There was no difference observed regarding lung cancer incidence among men, however, lung cancer mortality was higher compared to the general population. Resettler women showed both lower lung cancer incidence and mortality than the general populations.

## Time Trend Analyses

**Figure 1** shows modeled SIRs from 1994 to 2013 and modeled SMRs from 1990 to 2009 for men. SIRs combined for two time-periods (1994-2004 and 2005-2013) have been added to the figure, as well as *p*-values of the linear calendar year effect of the Poisson model.

Whereas the incidence risk of all malignant neoplasms combined was lower among resettlers and converged to the incidence risk of the Münster population until the end of observation period, the mortality risk of all malignant neoplasms combined remained unchanged between resettlers and the general German population during the observation period.

Stomach cancer incidence and mortality did not reveal any significant effect over time, whereas lung, colorectal and prostate cancer incidence risks were found to be lower among resettler men than in the German population. Until 2013, the incidence

**TABLE 4 |** Standardized incidence ratios (AMIN cohort, 1994-2013) and standardized mortality ratios (AMOR cohort, 1990-2009) with exact 95% confidence intervals and age-standardized mortality rates for Germany (1990-2009) for all malignant neoplasms combined and the most common cancer-sites, separated by sex.

| | | AMIN cohort (1994-2013) | | AMOR cohort (1990-2009) | | Germany (1990-2009) |
|---|---|---|---|---|---|---|
| **Cause** | **ICD-10 code** | **Observed diagnoses** | **SIR (95%CI)** | **Observed deaths** | **SMR (95%CI)** | **Mortality rates[a]** |
| **MEN** | | | | | | |
| Malignant neoplasms…* | C00-C97 | 556 | **0.87 (0.80–0.95)** | 864 | 1.00 (0.94–1.07) | 237.2 |
| … of stomach | C16 | 43 | **1.62 (1.17–2.19)** | 84 | **1.62 (1.31–2.01)** | 15.3 |
| … of colorectal organs | C18-C21 | 78 | 0.82 (0.66–1.03) | 77 | **0.74 (0.59–0.93)** | 29.2 |
| … of lung, bronchus and trachea | C33-C34 | 94 | 1.02 (0.83–1.24) | 307 | **1.34 (1.20–1.50)** | 61.2 |
| … of prostate | C61 | 106 | **0.72 (0.60–0.88)** | 46 | **0.58 (0.42–0.77)** | 24.8 |
| **WOMEN** | | | | | | |
| Malignant neoplasms…* | C00-C97 | 575 | **0.82 (0.75–0.89)** | 669 | **0.84 (0.78–0.91)** | 145.4 |
| … of stomach | C16 | 26 | 1.32 (0.86–1.94) | 66 | **1.52 (1.19–1.93)** | 8.3 |
| … of colorectal organs | C18-C21 | 77 | **0.79 (0.64–0.99)** | 92 | 0.86 (0.70–1.05) | 19.5 |
| … of lung, bronchus and trachea | C33-C34 | 13 | **0.30 (0.16–0.51)** | 62 | **0.69 (0.54–0.88)** | 15.4 |
| … of breast | C50 | 183 | **0.70 (0.60–0.81)** | 82 | **0.55 (0.44–0.68)** | 28.4 |

*Without non-melanoma skin cancer (ICD-10: C44 diagnoses).
[a]Per 100,000 inhabitants, using European standard population (29).
Significant results are bolded.

risk of colorectal and prostate cancer converged to the incidence risk of the Münster population. Differences in colorectal and prostate cancer mortality did not show any time effects. The incidence risk of lung cancer converged to the incidence risk of the Münster population up until 2005. Afterwards, lung cancer incidence risk among resettler men further increased. For lung cancer mortality, a remaining higher mortality was observed among resettlers compared to Germans.

**Figure 2** shows modeled SIRs from 1994 to 2013 and modeled SMRs from 1990 to 2009 for women. Again, SIRs combined for two time periods (1994-2004 and 2005-2013) have been added to the figure, as well as *p*-values of the linear calendar year effect of the Poisson model.

Among women, the incidence risk of all malignant neoplasms combined also converged to the incidence risk of the Münster population, while differences in mortality of all malignant neoplasms combined did not show any time effects. The mortality risk among resettler women remained lower than in the general German population.

A significant change of cancer incidence risk over time was only found for colorectal cancer. Whereas colorectal cancer incidence was lower among resettler women compared to German women in 1994, the incidence risk converged to that of the Germans until 2013. Breast cancer incidence risk was found to be increasing among resettler women over time, however, the effect was not significant. Stomach and lung cancer incidence risk among resettler women did not show an effect over time. Cancer-site specific mortality time trends did not show any significant effect during the observation time.

## Cancer Stage Analyses

**Table 5** presents the distribution of local, advanced and unknown stages for combined cancer-sites, separated by resettlers and the Münster population (without resettler cohort) and for men and women. The distribution of cancer stage of the most common cancer-sites can be found in the **Supplementary Table 1**. The tables compare cancer stage according to two different applied classification systems. In general, the distribution of stages by the two applied classification systems did not reveal major differences, with the exception of the stage of female breast cancer. The T Classification system showed in general a slightly higher percentage of local cancer stages, whereas the NM Classification system showed a slightly higher percentage of unknown stages. However, no significant difference regarding the stages between resettlers and the Münster population was found in both classification systems, except for women when the T Classification system was applied.

Due to the limited number of observations per specific cancer-site group, adjusted ORs from logistic regression were solely analyzed for combined cancer-sites and are shown in

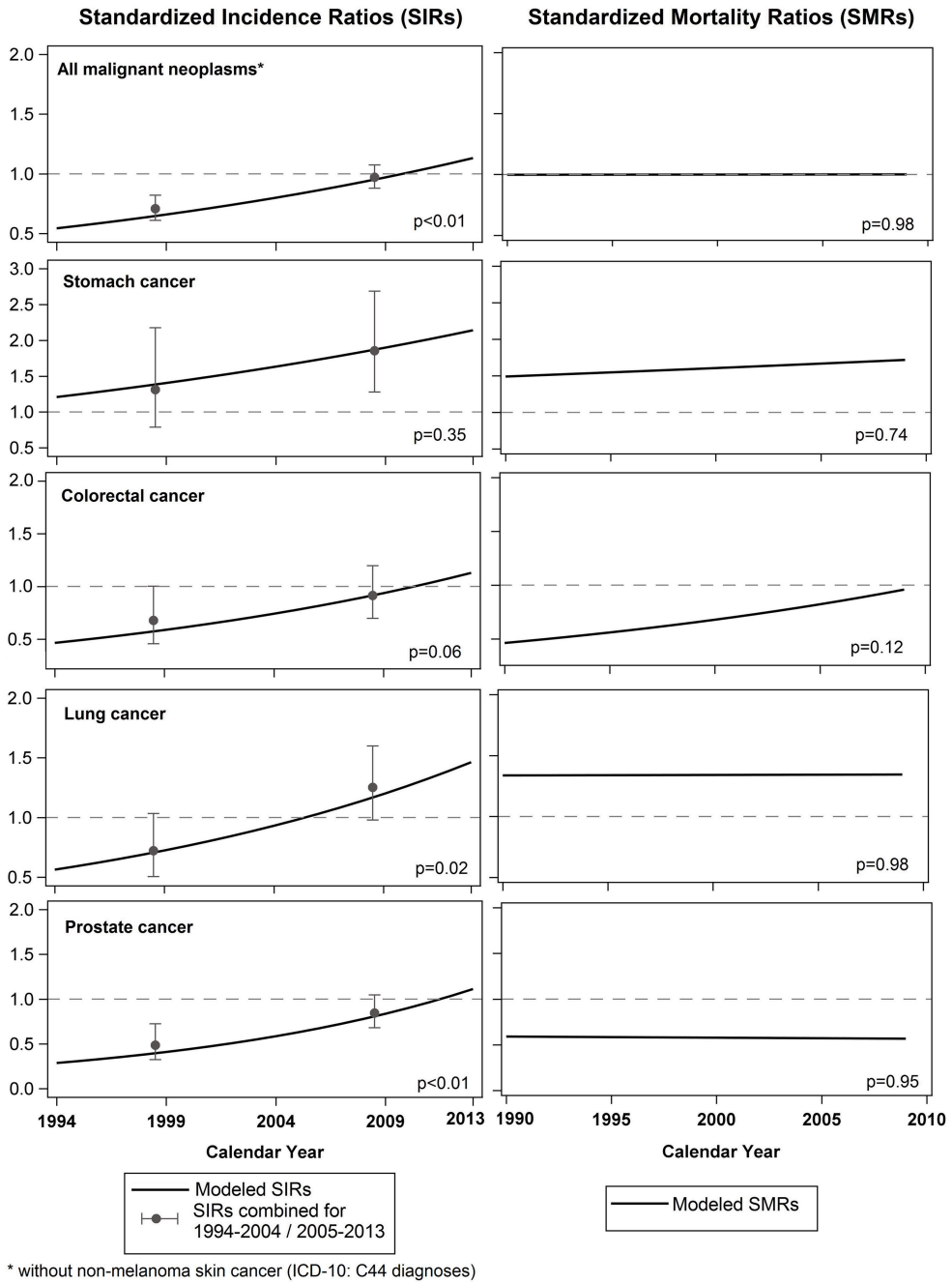


**FIGURE 1 |** Standardized incidence ratios (AMIN Cohort, 1994-2013) & standardized mortality ratios (AMOR Cohort, 1990-2009) for all malignant neoplasms combined and the most common cancer-sites for men with corresponding *p*-values of the linear calendar year effect of the Poisson model.

**Table 6**. In the complete case analysis and the sensitivity analysis II (unknown stage = advanced stage) it was observed that resettler men had higher odds of being diagnosed with an advanced stage than the Münster population, for both classification systems respectively. Among males, the sensitivity analysis I (unknown stage = local stage) showed no differences when the T Classification was applied, while an elevated OR was revealed with the NM Classification system. However, the effect was only significant within the complete case analysis and sensitivity analysis II when the NM Classification was applied. In general, it was observed that the NM Classification showed stronger effects than the T Classification.

For women, results showed no difference regarding the cancer stage at diagnosis when the NM classification was applied. Results for women from the T classification suggest that women

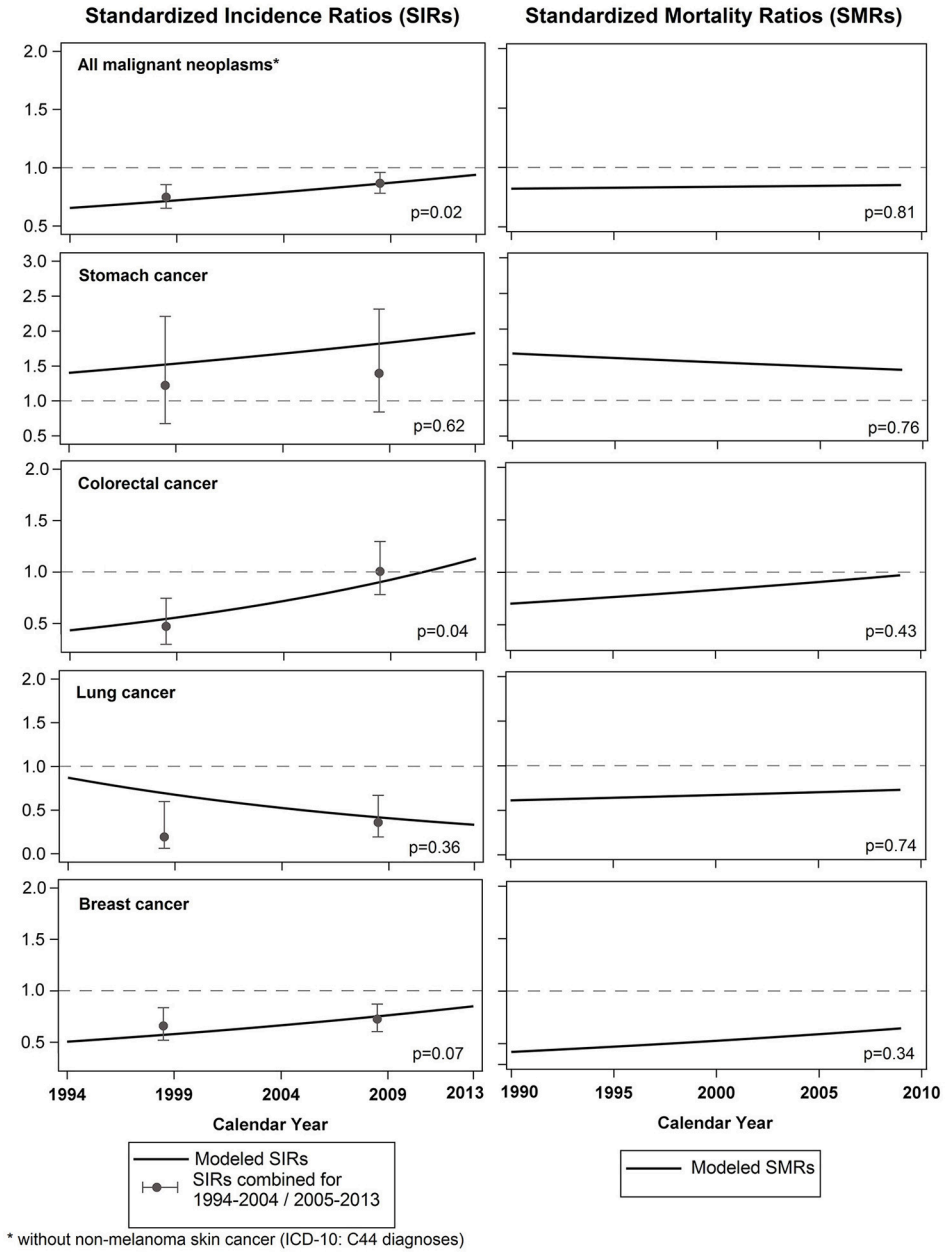


**FIGURE 2 |** Standardized incidence ratios (AMIN Cohort, 1994-2013) & standardized mortality ratios (AMOR Cohort, 1990-2009) for all malignant neoplasms combined and the most common cancer-sites for women with corresponding *p*-values of the linear calendar year effect of the Poisson model.

showed lower odds of being diagnosed with an advanced stage compared to the Münster population. However, the effect was only significant within the sensitivity analysis II.

# DISCUSSION

## Key Findings

We found lower incidence of all malignant neoplasms combined among resettlers (both sexes) compared to the Münster population. While mortality of all malignant neoplasms combined was lower among resettler women as well, no difference was observed among men. However, cancer-site specific analyses showed different results: we observed higher stomach cancer incidence and mortality among both male and female resettlers compared to the general population. Furthermore, lung cancer mortality was observed to be higher among resettler men than among men of the general German population. While stomach cancer incidence (both sexes) did not develop differently compared to the Münster population, lung cancer incidence (men) showed increasing

**TABLE 5 |** Distribution of local, advanced and unknown stages of the most common cancer-sites combined (AMIN cohort, 1994-2013), separated by the two classification systems and sex.

| Cancer stage | T classification | | | | NM classification | | | |
|---|---|---|---|---|---|---|---|---|
| | Resettlers | | Münster population | | Resettlers | | Münster population | |
| | *N* | % | *N* | % | *N* | % | *N* | % |
| **MEN** | | | | | | | | |
| Local | 106 | 33.0 | 21,688 | 33.8 | 91 | 28.4 | 20,301 | 31.7 |
| Advanced | 112 | 34.9 | 22,175 | 34.6 | 107 | 33.3 | 18,146 | 28.3 |
| Unknown | 103 | 32.1 | 20,240 | 31.6 | 123 | 38.3 | 25,656 | 40.0 |
| **WOMEN** | | | | | | | | |
| Local | 198 | 66.2 | 34,152 | 56.9 | 131 | 43.8 | 24,651 | 41.1 |
| Advanced | 60 | 20.1 | 14,535 | 24.2 | 118 | 39.5 | 22,490 | 37.5 |
| Unknown | 41 | 13.7 | 11,370 | 18.9 | 50 | 16.7 | 12,916 | 21.5 |

**TABLE 6 |** Odds ratios for resettlers being diagnosed with an advanced tumor (AMON cohort, 1994–2013), separated by the two classification systems and sex.

| Model | T classification | | NM classification | |
|---|---|---|---|---|
| | OR[1] (95%CI) | *p*-value | OR[1] (95%CI) | *p*-value |
| **MEN** | | | | |
| Complete case analysis (unknown stages excluded) | 1.11 (0.85–1.44) | 0.47 | **1.45 (1.10–1.93)** | **0.01** |
| Sensitivity I (unknown stage = local stage) | 0.96 (0.76–1.21) | 0.74 | 1.20 (0.95–1.52) | 0.13 |
| Sensitivity II (unknown stage = advanced stage) | 1.21 (0.95–1.53) | 0.12 | **1.42 (1.11–1.81)** | **0.01** |
| **WOMEN** | | | | |
| Complete case analysis (unknown stages excluded) | 0.83 (0.62–1.12) | 0.22 | 1.05 (0.82–1.34) | 0.72 |
| Sensitivity I (unknown stage = local stage) | 0.86 (0.65–1.16) | 0.32 | 1.08 (0.86–1.37) | 0.50 |
| Sensitivity II (unknown stage = advanced stage) | **0.78 (0.61–0.99)** | **0.04** | 0.99 (0.79–1.25) | 0.92 |

[1]*Adjusted for age at diagnosis and calendar year.*
*Significant results are bolded.*

disparity over time. Colorectal, lung (female), prostate and female breast cancer incidence was initially found to be lower among resettlers, but the incidence of these cancers converged to the risk of the Münster population over time, with the exception of female lung cancer which remained stable. Mortality time trends showed no significant changes over time for both sexes. Results from logistic regression suggest that resettler men were more often diagnosed with advanced cancer stages compared to the Münster population.

## Shortcomings and Limitations

As the cohorts consist of secondary data, information pertaining to common risk factors such as lifestyle and behavior, health care seeking behavior, infections, education, occupation, and parity were unavailable. Further, the incomplete follow-up of the AMIN cohort and consequently, the estimated person-years of the cohort have to be mentioned. However, the applied estimation procedure was found to be valid and reliable (21). Even though sensitivity analyses on out-migration showed only minor differences in SIRs (data not shown), some uncertainty remains regarding the assumptions on out-migration and mortality.

The incidence follow-up may not have identified all resettler diagnoses due to the possibility of name changes among resettlers. To help correct for this, common Russian-German name translations were considered (as reported in previous cohort studies) (30). Diagnoses among resettlers were more likely to be histologically confirmed than diagnoses among the Münster population, an observation which was particularly pronounced within the early observation period. This discrepancy in diagnoses may be due to reporting differences within the two populations. These differences diminished with time, and in 2005 mandatory reporting was introduced which led to a

further increase in histological confirmation (31). Even though results of all combined malignant diagnoses and histologically confirmed diagnoses were similar, all analyses were restricted to histologically confirmed diagnoses to minimize the possibility of bias.

Another limitation which should be mentioned is the fact that the reported incidence and mortality analyses are based on different cohorts utilizing different standard populations. The standard populations resemble the respective populations, for cancer incidence the population of the administrative district of Münster in the federal state of NRW and for cancer mortality the general German population. A comparison between the standard populations shows slightly higher cancer incidence as well as slightly higher cancer mortality rates in NRW (32). Further, the incidence comparison was done to the Münster population excluding the study population, while mortality was compared to the general German population, which includes the study population. However, it was shown that effects on the SMR are very small (30). Both cohorts result in a 20 year observation period and overlap for 15 years. Although the cohort studies were conducted in different regions, the introduced bias is expected to be neglectable. After arrival, resettlers were quasi-randomly assigned to their first place of residence based on regional population density and economic performance of the federal states (14). Therefore, the resettler cohorts reflect all resettlers from the FSU living in Germany.

## Integration Into the Current Understanding of the Problem

In many migrant studies the healthy migrant effect can at least partly explain a lower mortality among migrants compared to the host population. However, it needs to be emphasized that this is an unlikely explanation for our findings. Resettlers are considered to be a special kind of migrant. Resettlers possessed an invitation to return to Germany irrespective of their qualifications or health status. Upon arrival in Germany, resettlers received German citizenship, access to health care and social system benefits (14). In our study it was observed that resettlers typically did not move to Germany alone; many immigrated to Germany bringing relatives with them. It is assumed that most ethnic Germans moved to Germany (33). Thus, we do not think that a selection of healthy resettlers during the migration process occurred. It is however possible that the "fittest" migrants migrated shortly after 1989.

### Incidence and Mortality

The higher incidence and mortality of stomach cancer among resettlers might be associated with a higher prevalence of a previous helicobacter pylori (h. pylori) infection or with an unhealthy diet (low intake of fruits and vegetables, higher intake of salty, and smoked food) (34). The prevalence of h. pylori infection was found to be higher in individuals belonging to countries of the FSU compared to those in Germany (35). However, a previous study on stomach cancer incidence among resettlers found that higher stomach cancer incidence cannot be explained solely by previous h. pylori infection (36). In addition to dietary composition and obesity, smoking behavior, alcohol consumption and lack of physical activity were found to increase the risk of stomach cancer (34). A previous case-control study on risk factors among resettlers found lower alcohol consumption among resettlers compared to the native German population and no differences regarding fruit and vegetable consumption between resettlers and the German population. Overweight and physical inactivity were found to be more prevalent among resettler women than in German women (37).

Differences in lung cancer mortality may be due to high tobacco smoking prevalence among male and low prevalence among female resettlers. Worldwide, tobacco smoking prevalence in countries of the FSU are among the highest for men but low for women (38). Furthermore, a higher smoking prevalence was found among resettlers compared to the German population (39).

Lower female breast cancer incidence and mortality might mainly be explained by lower age at first pregnancy, higher parity, and lower smoking prevalence as seen in women from FSU countries compared to German women (40). A possible lower participation in the Mammography Screening Program might explain lower incidence, but not lower mortality.

Prevalence of specific lifestyle factors among resettlers may have changed over time. For example, it was observed that smoking behavior decreased among resettler men and increased among women with duration of stay and converged to the smoking rates of the German population (39). This might partly explain the increasing incidence risk of female breast cancer among resettlers, but lung cancer among female resettlers does not yet increase. Additionally, it was observed that the fertility rate among resettlers dropped after arrival in Germany and was found to be even lower than that of German women (41). This might also explain the converging breast cancer incidence. Increasing time trends for colorectal and prostate cancer among men and breast cancer among women further indicate a change of obesity prevalence and dietary composition, which was found previously among resettler women (37). Back in the countries of the FSU, resettlers suffered from food shortages and later on, availability of food was restricted (42). It might be possible that resettlers changed their dietary habits completely once in Germany, due to greater availability and selection of food.

### Cancer Stage at Diagnosis

Analysis of cancer stage at diagnosis did result in higher odds of advanced stages among resettler men, corroborated by a sensitivity analysis using more of the available data. Similar results were seen in another study among resettlers (28). The two classification systems are structurally different. The NM classification system easily defines local stages with a small tumor size as unknown stage, since small tumors are more prone for missing information on N and M. In contrast, the T classification tends to define advanced as local stages, since it ignores the fact that even small tumors might have spread. Therefore, results from both classification systems were reported, representing

a sensitivity analysis with two slightly biased results. Cancer-site specific results did not show significant effects (data not shown), probably due to the small numbers of events overall. Nevertheless, resettler men seem to have a higher chance of getting a cancer diagnosis at an advanced stage than men of the Münster population. Tumor diagnoses at an advanced stage indicate delay in diagnosis, which might be explained by lower uptake of early detection and screening measures. The greater availability of screening measures during the years might explain the significant decreasing odds of having an advanced stage at diagnoses with increasing calendar year. Since our analyses are based on registry data, we do not know whether the possible lower uptake of early detection and screening measures is due to barriers in access to health care, the lack of knowledge of health care services or due to different health beliefs of resettlers. Spallek et al. reported that participation in prevention programs is lower among specific migrant groups in Germany, however, reasons for that need to be investigated in the future (7).

### Future Direction of the Research

Following the results of this study, it is important to investigate risk factor patterns among resettlers, including dietary habits, *H. pylori* infection, physical activity, alcohol consumption, and smoking behavior. In addition, information on education and occupation as well as (epi-) genetic factors should be assessed. The NAKO may become useful for this: it is a large prospective cohort study in Germany, which currently recruits 200,000 representative participants. This study will assess lifestyle and environmental factors, and will investigate (epi-) genetic factors (43). Preliminary data from selected study centers indicate that the NAKO study includes about 2% resettlers which will allow more detailed analyses in that direction.

Additionally, a resettler-specific survey study should be conducted, to investigate key lifestyle, environmental and socioeconomic factors among resettlers. Methods leading to better knowledge regarding early cancer detection practices, access to health care and overall necessity thereof may improve the incidence of early cancer detection in the resettler population and hence should be further investigated.

## DATA AVAILABILITY STATEMENT

Data of the AMIN and AMOR studies are not open access, but we encourage other researchers to contact us and apply for data access based on collaborating projects.

## AUTHOR CONTRIBUTIONS

The cohort studies were initiated by HB and VW and performed by HB, VW, and SK. SK did the statistical analyses and drafted the manuscript. HK provided the incidence data of the AMIN cohort. SK, HK, HB, and VW contributed to writing and editing the manuscript and to the interpretation of the results.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00378/full#supplementary-material

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# Socioeconomic Inequalities in Total and Site-Specific Cancer Incidence in Germany: A Population-Based Registry Study

*Jens Hoebel*[1]*, *Lars E. Kroll*[1], *Julia Fiebig*[2], *Thomas Lampert*[1], *Alexander Katalinic*[3], *Benjamin Barnes*[2] and *Klaus Kraywinkel*[2]

[1] Division of Social Determinants of Health, Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin, Germany, [2] German Centre for Cancer Registry Data, Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin, Germany, [3] Institute for Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany

Most chronic diseases follow a socioeconomic gradient with higher rates in lower socioeconomic groups. A growing body of research, however, reveals cancer to be a disease group with very diverse socioeconomic patterning, even demonstrating reverse socioeconomic gradients for certain cancers. To investigate this matter at the German national level for the first time, this study examined socioeconomic inequalities in cancer incidence in Germany, both for all cancers combined as well as for common site-specific cancers. Population-based data on primary cancers newly diagnosed in 2010–2013 was obtained from the German Centre for Cancer Registry Data. Socioeconomic position was assessed at the district level using the German Index of Socioeconomic Deprivation, which is a composite index of area-based socioeconomic indicators. Absolute and relative socioeconomic inequalities in total and site-specific cancer incidence were analyzed using multilevel Poisson regression models with the logarithm of the number of residents as an offset. Among men, socioeconomic inequalities in cancer incidence with higher rates in more deprived districts were found for all cancers combined and various site-specific cancers, most pronounced for cancers of the lung, oral and upper respiratory tract, stomach, kidney, and bladder. Among women, higher rates in more deprived districts were evident for kidney, bladder, stomach, cervical, and liver cancer as well as for lymphoid/hematopoietic neoplasms, but no inequalities were evident for all cancers combined. Reverse gradients with higher rates in less deprived districts were found for malignant melanoma and thyroid cancer in both sexes, and in women additionally for female breast and ovarian cancer. Whereas in men the vast majority of all incident cancers occurred at cancer sites showing higher incidence rates in more deprived districts and cancers with a reverse socioeconomic gradient were in a clear minority, the situation was more balanced for women. This is the first national study from Germany examining socioeconomic inequalities in total and site-specific cancer incidence. The findings demonstrate that the socioeconomic patterning of cancer is diverse and follows different directions depending on the cancer site. The area-based cancer inequalities found suggest potentials for population-based cancer prevention and can help develop local strategies for cancer prevention and control.

**Keywords: cancer registry data, socioeconomic factors, health inequalities, social class, cancer epidemiology**

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***Correspondence:**
*Jens Hoebel*
*j.hoebel@rki.de*

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## INTRODUCTION

With close to 480,000 incident cases in 2014 and causing approximately 25% of all deaths, cancer is a major health concern in Germany, as in practically all countries with high life expectancies. Although age-specific and standardized mortality rates for total cancer have been steadily declining since the mid-1990s and incidence rates, at least for men, have been showing a modest decrease in recent years, the absolute burden of cancer is increasing due to population aging.

Social epidemiological research consistently shows that socioeconomic position is an important determinant of health and disease (1–5). The term "socioeconomic position" describes the position that an individual or group holds within a vertically structured society by referring to the social and economic factors that influence this position, mainly education, employment, and income (6, 7). Previous research indicates that socioeconomic position exerts its effects on health through various pathways. For instance, people with low socioeconomic position are more likely to be exposed to health risks in the workplace and living environment than those with higher socioeconomic position (8–11). In addition, common lifestyle-related risk factors such as tobacco smoking, physical inactivity, unhealthy diet, and obesity are each more prevalent in lower socioeconomic groups (12–17). As a consequence, people with low socioeconomic position have an increased risk of severe and chronic health conditions, which is ultimately reflected in a higher risk of premature mortality and a lower life expectancy (3, 18–23). The Organization for Economic Co-operation and Development has recently estimated for 23 countries around the globe that, on average, the gap in life expectancy between high and low socioeconomic groups is 8 years for men and 5 years for women at the age of 25 (24). Similar gaps in longevity have also been reported for Germany (25–27).

Over recent decades, socioeconomic determinants have increasingly moved into the focus of cancer epidemiology. As early as 1997, the International Agency for Research on Cancer summarized in a report on the existing evidence that people with lower socioeconomic position tend to have higher cancer incidence than those with high socioeconomic position, although this pattern varies according to cancer site (28). Higher rates in lower socioeconomic groups, typically referred to as the socioeconomic gradient in health, have been found for a variety of cancers, e.g., for cancers of the respiratory tract, oral, and stomach cancer (29–33). A reverse socioeconomic gradient with higher incidence in upper socioeconomic groups has been reported especially for skin cancer and female breast cancer (34–37). In addition, evidence from some high-income countries shows that cancer contributes to a large proportion of the gap in mortality and life expectancy between low and high socioeconomic groups and that the proportion of the mortality gap attributable to cancer has increased overall in recent decades (38–40).

Evidence from Germany on socioeconomic inequalities in cancer incidence is still scarce, but the few studies available are largely consistent with those from other high-income countries in suggesting a strong socioeconomic patterning of cancer incidence for various cancer sites (41–44). However, the few findings from Germany are limited to certain regions, such as single German federal states, or to enrollees in one specific statutory health insurance fund, and therefore do not reflect the population as a whole. The only large-scale study from Germany was restricted to inequalities in cancer survival (45). Moreover, the existing studies from Germany have focused on relative inequalities in cancer between socioeconomic groups, whereas absolute inequalities have largely been neglected. The aims of the present study were therefore to use nationwide data (1) to analyze area-based socioeconomic gradients in the incidence of cancer overall and common site-specific cancers among men and women in Germany, and (2) to examine the magnitude of absolute and relative socioeconomic inequalities in cancer incidence for various cancer sites.

## MATERIALS AND METHODS

### Data Source and Study Population

The analyses were based on population-based registry data from the German Centre for Cancer Registry Data at the Robert Koch Institute. All German federal states maintain population-based cancer registries that provide nationwide assessment of incident primary cancers as well as mortality follow-up. Federal and state laws regulate registry operations and practices. The registries have been operating for various lengths of time, the oldest of which is the Saarland Cancer Registry (since 1970) and the youngest of which is the cancer registry of Baden-Württemberg (since 2009). Each registry transfers an anonymized dataset annually to the Robert Koch Institute, where the data undergo quality checks and are pooled for nationwide and regional analyses. Additionally, registration completeness is estimated by federal state, year and diagnosis group. These estimates are based on comparisons of mortality-to-incidence ratios, with established reference registries providing baseline values. For the present analyses, cancer incidence data for the years 2010 through 2013 were extracted from this pooled dataset. These years were chosen so as to include reliable data from Germany's largest federal state, North Rhine-Westphalia, which established statewide registration in 2005 and achieved good completeness shortly thereafter. For cases identified only through death certificate notification (DCO cases), the date of diagnosis was set to the date of death. Data from four federal states (Baden-Württemberg, Berlin, Hesse and Saxony-Anhalt) were excluded from the present analyses due to low completeness estimates. The included registries cover nearly 59 million residents in 317 German districts (**Table 1**), which is approximately 73 percent of the total resident population of Germany.

### Cancer Sites

The population-based cancer registries in Germany classify cancer diagnoses based on both the tenth edition of the International Classification of Diseases (ICD-10) and the third edition of the International Classification of Diseases for Oncology (ICD-O-3). For the present analyses, the group of all cancers combined included primary malignant cancers without non-melanoma skin cancers (ICD-10 codes C00–C43, C45–C76,

**TABLE 1 |** Description of the study population and dataset, 2010–2013.

| | Men | Women |
|---|---|---|
| Mean population size per year | 28,757,742 | 29,975,640 |
| Mean number of incident cancer cases per year[a] | 191,426 | 171,349 |
| Number of first-level units in the data set[b] | 22,824 | 22,824 |
| Number of districts (second-level units) | 317 | 317 |
| Mean annual number of residents per district | 90,718 | 94,560 |
| –Deprivation quintile 1 (least deprived) | 110,404 | 116,060 |
| –Deprivation quintile 2 | 91,499 | 95,032 |
| –Deprivation quintile 3 | 91,173 | 95,091 |
| –Deprivation quintile 4 | 81,593 | 84,771 |
| –Deprivation quintile 5 (most deprived) | 78,603 | 81,497 |
| Mean deprivation score of included districts (with *SD*) | 0.64 ± 0.16 | 0.64 ± 0.16 |
| Mean deprivation score of excluded districts (with *SD*) | 0.56 ± 0.19 | 0.56 ± 0.19 |

[a] *For all cancer sites (C00–C97 without C44 and C77–C79).*
[b] *Product of the number of age groups (n = 18), districts (n = 317), and observation years (n = 4); SD, standard deviation.*

and C80–C97). Individual cancer sites and cancer site groups were defined according to the given ICD-10 codes. Bladder cancers (C67) were analyzed both including and excluding *in-situ* tumors (D09.0) and tumors of uncertain or unknown behavior (D41.4).

## Socioeconomic Deprivation

Area-based socioeconomic deprivation was measured at the district level using the German Index of Socioeconomic Deprivation (GISD), which has been developed by the Robert Koch Institute for epidemiological research and health reporting in Germany (46). In the present study, we used the second version of the index, which is available for research purposes free of charge at a GitHub repository (47). The index is generally available for regional units at different spatial levels. In this study, it was used at the level of German administrative districts because this was the smallest spatial level that could be analyzed in the nationally pooled cancer registry data used. GISD is a composite index with three classic socioeconomic dimensions: income, education and employment. The income dimension is assessed by area-based mean net household income, tax revenues and debtor quotas. The educational dimension is ascertained using a district's population share of employees with university degree and the share of school dropouts without certificate. In addition, during the revision of the index, the share of school graduates with Abitur (German equivalent of the International Baccalaureate) and the share of employees without any secondary-school degree have been added. Indicators of the employment dimension are the regional unemployment rate, average gross wage of employees and labor force participation rate. Factor analysis is used to weight the single indicators of each dimension. The three dimensions are then given equal weighting in the composite index, thus income, education and employment each contribute one-third to the total index score. A higher index score indicates higher socioeconomic deprivation, i.e., lower socioeconomic position of a district's population. All districts included in our analysis were classified into quintiles of socioeconomic deprivation by year according to their total index scores (**Figure 1**). Further information about the methods and data used in the development of the index have been published elsewhere in detail (46).

## Statistical Analysis

Incidence rates with 95% confidence intervals (CI) were estimated as the number of newly diagnosed cancer cases per 100,000 residents, as predicted by Poisson regression analysis. To account for the clustered and hierarchical structure of the data (age groups nested within districts), multilevel models were used with age groups as first-level and districts as second-level units. The number of incident cancer cases registered within each age group of a district was regressed on the districts' level of socioeconomic deprivation, with age group and calendar year as covariates. Analyses were stratified by sex in order to identify sex-specific patterns of socioeconomic inequalities in cancer risk. In overall models for men and women together, sex was added to the model as an additional covariate. The logarithm of the population size in each age group was included in the models as an offset term to account for the variable number of persons under observation. To obtain age-standardized results, each district's age distribution was weighted to match the 2013 European Standard Population with a collapsed upper age band of 85+ (48). For standard error estimation, the sample size was defined as the total number of first-level units in the dataset ($n = 22{,}824$).

Socioeconomic inequalities in cancer incidence were analyzed by computing simple measures of pairwise group differences by quintiles of socioeconomic deprivation (standardized rate differences, standardized rate ratios) and more sophisticated summary indices of inequality (slope index of inequality [SII], relative index of inequality [RII]). While rate differences and SII quantify the magnitude of absolute inequality, rate ratios and RII represent the magnitude of relative inequality (49, 50). The advantage of the regression-based SII and RII over the simple measures is that they do not simply compare two extreme groups (e.g., the most vs. least deprived quintile), but take into account the association between a socioeconomic variable and a given health outcome across the entire socioeconomic spectrum (50). In other words, these measures make full use of all information available, whereas the simple measures ignore parts of it. To calculate the SII and RII, we used ridit scoring to convert the socioeconomic deprivation index to a fractional rank variable ranging from 0 (least deprived) to 1 (most deprived), which was then entered into the regression model as an independent variable (51, 52). The SII represents the absolute rate difference and the RII the relative rate ratio between people living in the most vs. least deprived districts. Thus, in the present study, they compare the average cancer risk between districts at the very bottom and very top of the regional socioeconomic distribution while taking into account the risk in the intermediate districts through the regression-based estimation method. Treemaps were used to visualize the proportion of all incident cancers diagnosed

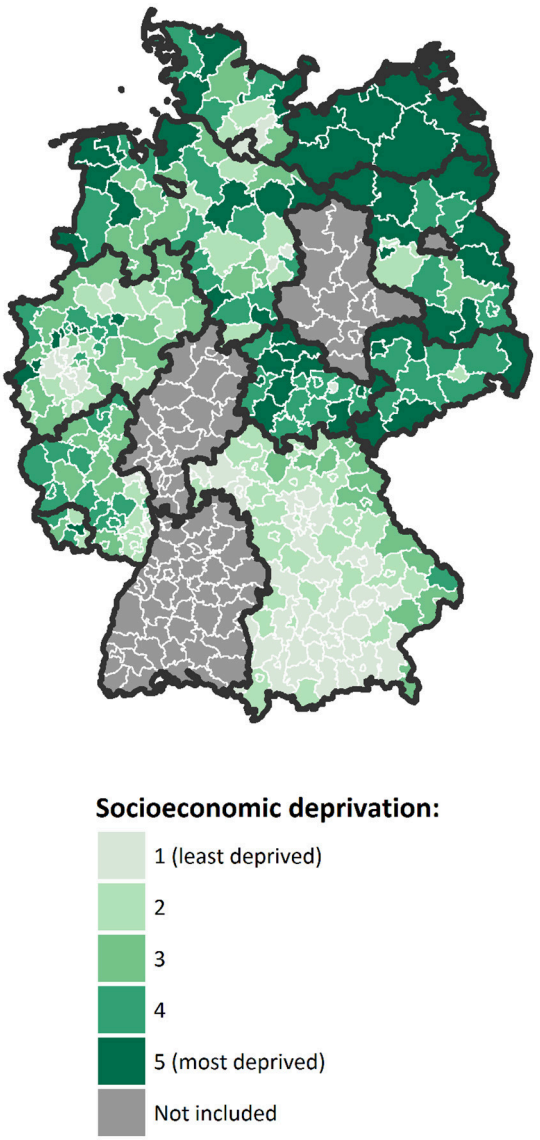


**FIGURE 1 |** Map of Germany with districts included in the analysis, colored according to their mean level of socioeconomic deprivation over the study period, in quintiles (Geodata: © GeoBasis-DE / BKG 2018).

at each specific site in combination with the magnitude of its absolute and relative inequality.

## RESULTS

**Table 2** presents the age-standardized incidence rates for all and site-specific primary cancers, stratified by sex and quintiles of socioeconomic deprivation. Results for the total population (i.e., men and women together) and additional cancer sites can be found in the **Supplementary Tables S1**, **S2**. Among the male population, area-based socioeconomic gradients were evident for all cancers combined and a majority of the site-specific cancers considered, with higher incidence rates in the most deprived districts for cancers of the oral and upper respiratory tract, esophagus, stomach, colorectum, pancreas, lung, kidney, bladder, and lymphoid or hematopoietic neoplasms. Exceptions were malignant melanoma and thyroid cancer incidence, which followed a reverse gradient with higher rates in less deprived districts. Among the female population, socioeconomic gradients with higher rates in more deprived districts were evident for stomach, liver, cervical, kidney, bladder, and lymphoid or hematopoietic cancers. Reverse gradients with higher rates among women in less deprived districts were found for malignant melanoma, thyroid, breast and ovarian cancer. For these cancers (expect for thyroid cancer), the incidence rates among women did not show a consistent gradient, as the rates in the middle deprivation quintile tended to be higher than in the adjacent quintiles, a pattern also evident for male prostate cancer.

**Table 3** shows the measures of absolute inequalities (standardized rate differences and SII) and relative inequalities (standardized rate ratios and RII) in primary cancer incidence by sex. Results for the total population and additional cancer sites can be found in **Supplementary Table S3**. For the overall category of all primary cancers, the age-standardized incidence rate for men living in the most deprived quintile of districts was 47 cases per 100,000 residents higher compared to their counterparts in the least deprived quintile. This rate difference was even larger (71 cases per 100,000 residents) when districts at the very top and very bottom of the regional socioeconomic spectrum were compared and the distribution between them was taken into account, as indicated by the SII. With regard to relative inequalities, the standardized incidence rate was 7% higher among men in the most deprived quintile compared to their counterparts in the least deprived quintile. Again, the increase was larger (11%) when the entire socioeconomic distribution was taken into account, as reflected in the RII. Among men, lung cancer and malignant melanoma showed the highest magnitudes of absolute inequalities, although their socioeconomic inequalities followed different patterns, with higher rates in more deprived districts for lung cancer and a reverse gradient for malignant melanoma. The largest relative inequalities among men were found for thyroid cancer, malignant melanoma, lung cancer, and cancers of the oral and upper respiratory tract.

Among women, neither absolute nor relative inequalities were found for the overall category of all primary cancers. When considering site-specific incidence, however, socioeconomic inequalities of varying degree and direction were evident for many cancer types. The largest absolute inequalities—regardless of the direction—were found for breast cancer and malignant melanoma, both of which showed a lower incidence in the most deprived districts. The largest relative inequalities among women were evident for thyroid cancer, malignant melanoma, and kidney cancer, with the latter showing higher rates in more deprived districts.

The treemaps in **Figure 2** visualize the proportion of incident primary cancers diagnosed at each specific site over the study period in combination with the pattern of its absolute and

**TABLE 2 |** Age-standardized incidence rates among men and women by quintiles of district-level socioeconomic deprivation.

| | Quintiles of socioeconomic deprivation | | | | |
|---|---|---|---|---|---|
| | **1 (least deprived)** | **2** | **3** | **4** | **5 (most deprived)** |
| | **SIR (95% CI)** | **SIR (95% CI)** | **SIR (95% CI)** | **SIR (95% CI)** | **SIR (95% CI)** |
| **ALL CANCERS (C00–C97)[a]** | | | | | |
| Men | 648.7 (635.9–661.6) | 664.9 (653.8–676.1) | 686.8 (675.8–697.8) | 691.8 (680.8–702.8) | 695.9 (683.7–708.0) |
| Women | 491.3 (480.7–501.8) | 488.5 (479.6–497.3) | 497.3 (488.6–505.9) | 489.2 (480.7–497.8) | 486.8 (477.5–496.1) |
| **ORAL AND UPPER RESPIRATORY TRACT (C00–C06, C09–C14, C32)** | | | | | |
| Men | 27.3 (25.9–28.6) | 27.8 (26.5–29.1) | 28.6 (27.3–29.9) | 32.6 (31.2–34.0) | 33.9 (32.3–35.4) |
| Women | 7.8 (7.3–8.4) | 7.8 (7.3–8.4) | 8.0 (7.5–8.5) | 7.6 (7.1–8.2) | 8.3 (7.7–8.9) |
| **ESOPHAGUS (C15)** | | | | | |
| Men | 11.9 (11.3–12.6) | 12.9 (12.2–13.6) | 13.6 (12.9–14.3) | 13.3 (12.6–13.9) | 14.2 (13.5–14.9) |
| Women | 3.1 (2.8–3.4) | 3.0 (2.7–3.2) | 3.3 (3.0–3.5) | 3.0 (2.7–3.3) | 2.8 (2.5–3.0) |
| **STOMACH (C16)** | | | | | |
| Men | 23.7 (22.8–24.7) | 24.5 (23.6–25.5) | 25.9 (24.9–26.9) | 27.4 (26.4–28.4) | 29.0 (27.9–30.0) |
| Women | 12.6 (12.0–13.1) | 13.7 (13.1–14.3) | 13.5 (13.0–14.1) | 14.0 (13.5–14.6) | 14.7 (14.1–15.3) |
| **COLORECTUM (C18–C20)** | | | | | |
| Men | 88.1 (85.5–90.7) | 92.2 (89.6–94.8) | 93.8 (91.3–96.4) | 94.3 (91.8–96.8) | 94.5 (91.9–97.1) |
| Women | 57.1 (55.3–59.0) | 58.7 (56.9–60.5) | 61.8 (60.0–63.6) | 59.4 (57.6–61.1) | 58.9 (57.1–60.7) |
| **LIVER (C22)** | | | | | |
| Men | 16.6 (15.5–17.7) | 15.6 (14.6–16.5) | 14.9 (14.0–15.8) | 16.4 (15.4–17.4) | 16.9 (15.9–17.9) |
| Women | 5.0 (4.7–5.3) | 5.2 (4.9–5.6) | 4.8 (4.5–5.2) | 5.3 (5.0–5.7) | 5.8 (5.4–6.1) |
| **PANCREAS (C25)** | | | | | |
| Men | 22.5 (21.6–23.3) | 21.2 (20.4–22.0) | 21.6 (20.8–22.4) | 22.5 (21.7–23.3) | 24.0 (23.1–24.8) |
| Women | 17.7 (17.2–18.3) | 17.4 (16.8–18.0) | 16.8 (16.3–17.4) | 17.1 (16.5–17.6) | 17.4 (16.8–18.0) |
| **LUNG (C33–C34)** | | | | | |
| Men | 77.4 (74.1–80.8) | 85.1 (81.9–88.2) | 93.1 (89.8–96.4) | 99.9 (96.4–103.3) | 103.1 (99.2–106.9) |
| Women | 35.5 (33.1–37.9) | 35.5 (33.5–37.6) | 38.8 (36.7–41.0) | 38.6 (36.4–40.7) | 37.7 (35.4–40.0) |
| **MALIGNANT MELANOMA OF SKIN (C43)** | | | | | |
| Men | 31.6 (29.8–33.4) | 30.0 (28.4–31.6) | 28.4 (26.9–29.9) | 25.0 (23.6–26.3) | 22.9 (21.6–24.2) |
| Women | 26.8 (25.0–28.7) | 24.7 (23.2–26.2) | 26.1 (24.6–27.6) | 22.4 (21.0–23.7) | 21.1 (19.6–22.5) |
| **BREAST (C50)** | | | | | |
| Women | 159.1 (154.6–163.7) | 156.7 (152.7–160.6) | 158.5 (154.6–162.3) | 152.6 (148.9–156.3) | 151.7 (147.8–155.7) |
| **CERVIX UTERI (C53)** | | | | | |
| Women | 10.9 (10.3–11.5) | 10.7 (10.1–11.3) | 11.3 (10.7–11.9) | 12.5 (11.8–13.1) | 12.1 (11.5–12.8) |
| **OVARY (C56)** | | | | | |
| Women | 17.1 (16.4–17.8) | 17.3 (16.6–18.0) | 17.6 (16.9–18.3) | 16.6 (15.9–17.3) | 15.9 (15.2–16.5) |
| **PROSTATE (C61)** | | | | | |
| Men | 168.8 (163.0–174.7) | 170.8 (165.6–175.9) | 178.8 (173.6–183.9) | 170.6 (165.8–175.5) | 173.1 (167.7–178.5) |
| **KIDNEY (C64)** | | | | | |
| Men | 23.3 (22.2–24.5) | 24.8 (23.6–26.0) | 24.6 (23.5–25.7) | 27.2 (26.0–28.4) | 28.3 (27.1–29.6) |
| Women | 11.1 (10.5–11.7) | 12.1 (11.4–12.7) | 12.1 (11.5–12.8) | 13.2 (12.6–13.9) | 14.3 (13.6–15.0) |
| **BLADDER (C67)** | | | | | |
| Men | 27.7 (26.2–29.2) | 29.4 (27.9–30.9) | 30.9 (29.4–32.4) | 31.9 (30.4–33.5) | 33.2 (31.5–34.8) |
| Women | 7.7 (7.2–8.2) | 8.0 (7.5–8.6) | 8.4 (7.9–8.9) | 8.6 (8.1–9.1) | 9.1 (8.6–9.7) |
| **THYROID GLAND (C73)** | | | | | |
| Men | 6.0 (5.5–6.5) | 5.0 (4.5–5.4) | 5.1 (4.7–5.5) | 4.0 (3.6–4.3) | 3.8 (3.5–4.2) |
| Women | 12.4 (11.4–13.4) | 11.4 (10.6–12.3) | 10.5 (9.7–11.3) | 8.4 (7.8–9.1) | 9.5 (8.7–10.2) |
| **LYMPHOID AND HEMATOPOIETIC NEOPLASMS (C81–C96)** | | | | | |
| Men | 51.3 (49.3–53.3) | 54.4 (52.4–56.4) | 54.3 (52.4–56.2) | 55.3 (53.4–57.3) | 56.3 (54.3–58.4) |
| Women | 33.7 (32.4–35.0) | 35.9 (34.6–37.3) | 36.5 (35.2–37.8) | 37.0 (35.7–38.3) | 37.6 (36.2–38.9) |

[a] *Without C44 and C77–C79; CI, confidence interval; SIR, standardized incidence rate; All rates are predictive margins (predicted cases per 100,000 residents) from multilevel Poisson regression models, weighted according to the 2013 European Standard Population.*

**TABLE 3 |** Absolute and relative inequalities in cancer incidence among men and women by district-level socioeconomic deprivation.

| | Simple measures | | | Summary indices | | |
|---|---|---|---|---|---|---|
| | **SRD (95% CI)** | **SRR (95% CI)** | ***p*-value** | **SII (95% CI)** | **RII (95% CI)** | ***p*-value** |
| **ALL CANCERS (C00–C97)[a]** | | | | | | |
| Men | 47.1 (29.7–64.6) | 1.07 (1.05–1.10) | <0.001 | 71.3 (47.8–94.9) | 1.11 (1.07–1.15) | <0.001 |
| Women | −4.5 (−18.3–9.4) | 0.99 (0.96–1.02) | 0.526 | −7.5 (−26.4–11.5) | 0.98 (0.95–1.02) | 0.440 |
| **ORAL AND UPPER RESPIRATORY TRACT (C00–C06, C09–C14, C32)** | | | | | | |
| Men | 6.6 (4.5–8.6) | 1.24 (1.16–1.33) | <0.001 | 9.8 (7.3–12.2) | 1.38 (1.28–1.50) | <0.001 |
| Women | 0.5 (−0.3–1.3) | 1.06 (0.96–1.17) | 0.246 | 0.4 (−0.5–1.3) | 1.05 (0.94–1.17) | 0.403 |
| **ESOPHAGUS (C15)** | | | | | | |
| Men | 2.3 (1.3–3.2) | 1.19 (1.11–1.28) | <0.001 | 2.5 (1.4–3.6) | 1.21 (1.11–1.31) | <0.001 |
| Women | −0.3 (−0.7–0.1) | 0.90 (0.79–1.02) | 0.106 | −0.3 (−0.8–0.1) | 0.89 (0.77–1.04) | 0.141 |
| **STOMACH (C16)** | | | | | | |
| Men | 5.2 (3.8–6.6) | 1.22 (1.16–1.29) | <0.001 | 6.7 (5.1–8.2) | 1.29 (1.22–1.37) | <0.001 |
| Women | 2.2 (1.3–3.0) | 1.17 (1.10–1.24) | <0.001 | 2.4 (1.5–3.3) | 1.19 (1.12–1.27) | <0.001 |
| **COLORECTUM (C18–C20)** | | | | | | |
| Men | 6.4 (2.8–10.1) | 1.07 (1.03–1.12) | 0.001 | 8.0 (3.6–12.4) | 1.09 (1.04–1.14) | <0.001 |
| Women | 1.7 (−0.9–4.3) | 1.03 (0.99–1.08) | 0.189 | 2.5 (−0.6–5.7) | 1.04 (0.99–1.10) | 0.115 |
| **LIVER (C22)** | | | | | | |
| Men | 0.3 (−1.2–1.7) | 1.02 (0.93–1.11) | 0.714 | 0.4 (−1.3–2.1) | 1.03 (0.92–1.14) | 0.632 |
| Women | 0.8 (0.3–1.3) | 1.16 (1.06–1.27) | 0.001 | 0.8 (0.3–1.4) | 1.17 (1.06–1.29) | 0.003 |
| **PANCREAS (C25)** | | | | | | |
| Men | 1.5 (0.3–2.7) | 1.07 (1.01–1.12) | 0.015 | 1.9 (0.6–3.3) | 1.09 (1.03–1.16) | 0.005 |
| Women | −0.3 (−1.1–0.5) | 0.98 (0.94–1.03) | 0.477 | −0.4 (−1.3–0.5) | 0.98 (0.93–1.03) | 0.379 |
| **LUNG (C33–C34)** | | | | | | |
| Men | 25.6 (20.5–30.7) | 1.33 (1.26–1.41) | <0.001 | 37.1 (30.5–43.7) | 1.50 (1.40–1.61) | <0.001 |
| Women | 2.2 (−1.0–5.5) | 1.06 (0.97–1.16) | 0.183 | 2.7 (−1.7–7.0) | 1.07 (0.96–1.21) | 0.232 |
| **MALIGNANT MELANOMA OF SKIN (C43)** | | | | | | |
| Men | −8.7 (−10.9–−6.5) | 0.72 (0.67–0.79) | <0.001 | −12.3 (−15.0–−9.5) | 0.64 (0.58–0.71) | <0.001 |
| Women | −5.8 (−8.1–−3.5) | 0.78 (0.71–0.86) | <0.001 | −8.3 (−11.3–−5.4) | 0.71 (0.63–0.80) | <0.001 |
| **BREAST (C50)** | | | | | | |
| Women | −7.4 (−13.4–−1.4) | 0.95 (0.92–0.99) | 0.016 | −12.0 (−19.6–−4.4) | 0.93 (0.88–0.97) | 0.002 |
| **CERVIX UTERI (C53)** | | | | | | |
| Women | 1.3 (0.4–2.2) | 1.12 (1.03–1.21) | 0.005 | 2.0 (1.0–3.0) | 1.19 (1.09–1.30) | <0.001 |
| **OVARY (C56)** | | | | | | |
| Women | −1.2 (−2.2–−0.2) | 0.93 (0.87–0.99) | 0.016 | −1.7 (−2.9–−0.6) | 0.90 (0.84–0.97) | 0.003 |
| **PROSTATE (C61)** | | | | | | |
| Men | 4.3 (−3.6–12.2) | 1.03 (0.98–1.07) | 0.286 | 2.6 (−7.7–12.9) | 1.02 (0.96–1.08) | 0.623 |
| **KIDNEY (C64)** | | | | | | |
| Men | 5.0 (3.3–6.6) | 1.21 (1.14–1.29) | <0.001 | 6.3 (4.3–8.3) | 1.28 (1.18–1.38) | <0.001 |
| Women | 3.2 (2.2–4.1) | 1.28 (1.19–1.38) | <0.001 | 4.1 (3.1–5.2) | 1.39 (1.28–1.51) | <0.001 |
| **BLADDER (C67)** | | | | | | |
| Men | 5.5 (3.3–7.7) | 1.20 (1.11–1.29) | <0.001 | 7.4 (4.7–10.0) | 1.27 (1.17–1.39) | <0.001 |
| Women | 1.4 (0.6–2.2) | 1.18 (1.08–1.29) | <0.001 | 1.6 (0.7–2.4) | 1.21 (1.09–1.34) | <0.001 |
| **THYROID GLAND (C73)** | | | | | | |
| Men | −2.2 (−2.8–−1.6) | 0.64 (0.57–0.72) | <0.001 | −2.8 (−3.4–−2.1) | 0.56 (0.49–0.64) | <0.001 |
| Women | −3.0 (−4.2–−1.7) | 0.76 (0.68–0.85) | <0.001 | −5.1 (−6.5–−3.6) | 0.62 (0.54–0.70) | <0.001 |
| **LYMPHOID AND HEMATOPOIETIC NEOPLASMS (C81–C96)** | | | | | | |
| Men | 5.0 (2.2–7.9) | 1.10 (1.04–1.16) | 0.001 | 5.5 (2.1–9.0) | 1.11 (1.04–1.18) | 0.002 |
| Women | 3.8 (2.0–5.7) | 1.11 (1.06–1.17) | <0.001 | 4.2 (2.0–6.5) | 1.12 (1.06–1.20) | <0.001 |

*[a]Without C44 and C77–C79; SRD, standardized rate difference (most vs. least deprived quintile); SRR, standardized rate ratio (most vs. least deprived quintile); SII, Slope index of inequality; RII, relative index of inequality; CI, confidence interval. All measures are age–standardized according to the 2013 European Standard Population.*

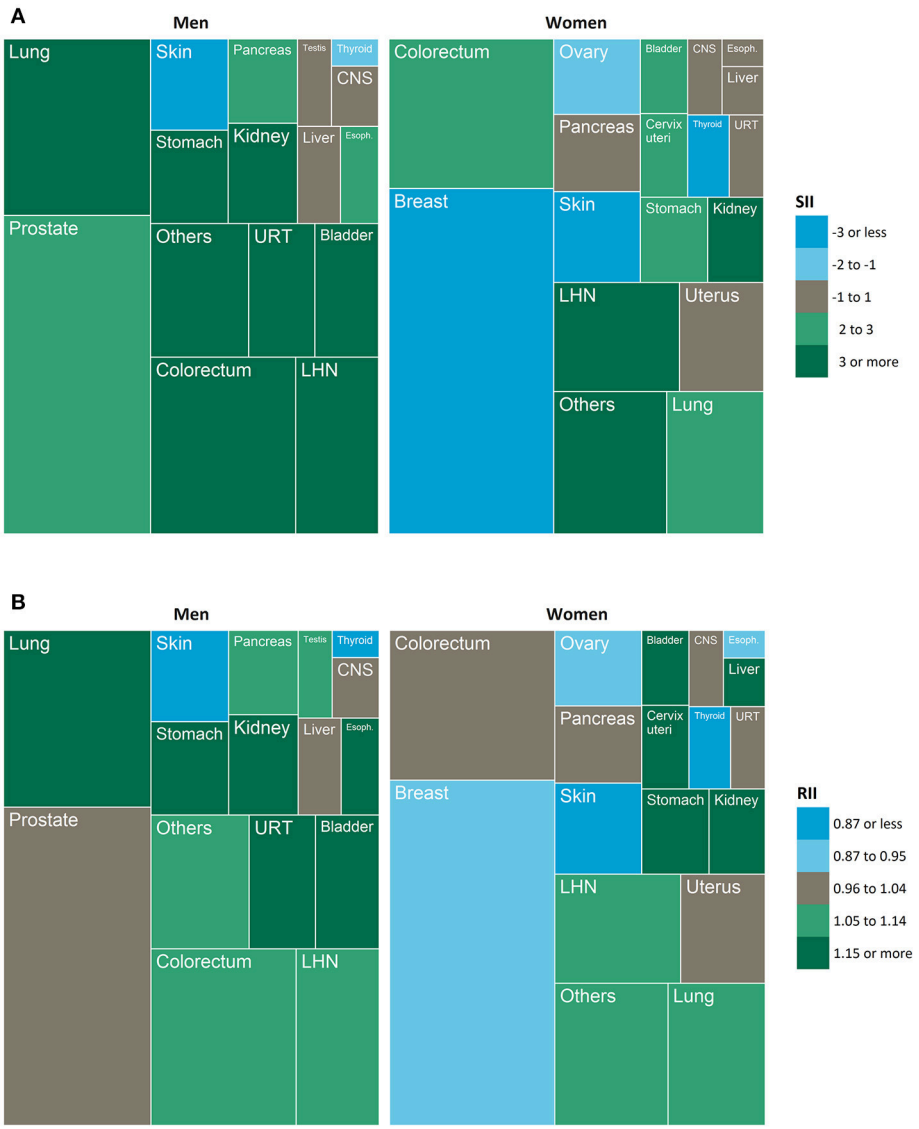


**FIGURE 2 |** Treemaps showing the proportion of all incident cancers diagnosed at each specific site (box size) in combination with the magnitude and direction of a) absolute inequality and b) relative inequality (color). SII, slope index of inequality, RII, relative index of inequality; CNS, central nervous system; URT, upper respiratory tract; LHN, lymphoid and hematopoietic neoplasms; Esoph., esophagus.

relative inequality by socioeconomic deprivation. In men, 90.1% of all incident cancers occurred at cancer sites showing absolute inequalities to the detriment of the most deprived (green); 4.5% at cancer sites with absolute inequalities to the detriment of the least deprived (blue). In women, these proportions were 46.5 and 40.3%. In respect of relative inequalities, 66.5% of all cancers in men arose at sites with relative inequalities to the detriment of the most deprived (green); 4.5% were cancer sites with relative inequalities to the detriment of the least deprived (blue). For women, these proportions were 35.8% and 40.9%, reflecting that breast and ovarian cancer with their reverse gradients made up a large proportion of cancer incidence in women.

# DISCUSSION

## Main Findings

To our knowledge, this is the first study using representative data for the vast majority of Germany's population to examine area-based socioeconomic inequalities in the incidence of cancer overall and for a variety of site-specific cancers. For all cancers combined, we found a socioeconomic gradient with higher incidence rates in more deprived districts for men but not for women. A closer look at site-specific cancers, though, showed that in both men and women, socioeconomic inequalities in cancer incidence do exist for several cancer sites, although their patterns differ between cancer sites, especially in women.

The majority of cancers among men followed a socioeconomic gradient on both the absolute and relative scale with higher rates in more deprived districts, most pronounced for cancers of the lung, oral and upper respiratory tract, stomach, kidney, and bladder. Among women, this pattern was found for cancers of the kidney, bladder, stomach, and cervix uteri. Malignant melanoma of the skin and thyroid cancer were exceptions in both sexes as they showed a reverse socioeconomic gradient with the highest incidence in the least deprived districts. This pattern was also observed for female breast cancer and less clearly for ovarian cancer. Whereas in men, most incident cancers were diagnosed at sites showing a gradient to the detriment of the most deprived, in women the shares of incident cancers showing this gradient and of those with a reverse gradient were more balanced.

## Comparison With Previous Research and Possible Explanations

Our findings support a large and growing body of evidence indicating for various countries that the incidence of cancer is unequally distributed across socioeconomic groups (28, 37, 53, 54). To a large extent, our results are consistent with previous findings from various countries, which have found higher incidence rates in lower socioeconomic groups for a variety of site-specific cancers, e.g., for respiratory tract, oral and stomach cancers (29–33). The reverse socioeconomic gradients in melanoma, female breast cancer and thyroid cancer have been found in other countries before as well (34–37, 55, 56). In addition, our findings largely support those of the few previous studies from Germany. Eberle et al. analyzed socioeconomic inequalities in cancer incidence in Bremen, a major city in northern Germany (42). For all cancers combined, they reported a socioeconomic gradient for men, with higher incidence rates in more deprived town districts, but not for women. Furthermore, they found higher incidence rates for tumors of the oral cavity and pharynx as well as for lung, cervical, and bladder cancers in more deprived town districts and a reverse gradient for female breast cancer, skin and prostate cancer, which is, except for prostate cancer, very much in line with our findings. Kuznetsov et al. examined area-based socioeconomic inequalities in lung and colorectal cancer incidence in Bavaria, a southern German federal state (43, 57). Their results indicate an excess risk in more deprived areas for lung cancer in men and for colorectal cancer in both men and women. Geyer used individual data from one of the German statutory health insurance funds. He found that individuals from the lowest socioeconomic group had increased risks of lung, stomach and intestinal cancer (41). For female breast cancer incidence, however, no socioeconomic gradient was evident in the statutory health insurance data. This may have been related to the fact that high socioeconomic groups are underrepresented in the German statutory health insurance, which is especially the case with the particular insurance fund considered in the study (41, 58).

The literature suggests several explanations for socioeconomic inequalities in cancer risk, including unequal distribution of lifestyle-related risk factors, occupational, and environmental exposures, reproductive and healthcare factors. In many countries around the globe, common lifestyle-related cancer risk factors such as tobacco smoking, unhealthy diets, physical inactivity, and obesity are more prevalent in lower socioeconomic groups (12–17). Accordingly, these factors are often adduced to explain the socioeconomic patterning of cancer. Tobacco smoking, for instance, has been found to explain a major part of socioeconomic inequalities in the incidence of lung cancer (59), but also has explanatory value for socioeconomic inequalities in cancers at other sites (60–62). Regarding overall cancer mortality instead of site-specific cancer incidence, smoking has been found to explain the greatest proportion of the association with area-level socioeconomic deprivation, followed by diet, physical activity, cancer screening behaviors and body-mass-index (63). The fact that we found a socioeconomic gradient in lung cancer incidence for men but not for women is probably due to differences in the evolution of the socioeconomic gradient in smoking habits by sex. Research from Germany suggests that the socioeconomic gradient in smoking among men had already developed early in the 20th century, whereas among women it emerged much later toward the end of the century (64, 65). This difference might lead to a delay of several decades before the socioeconomic gradient in lung cancer also becomes apparent in women. Alcohol consumption has also been found to partially explain socioeconomic inequalities in different cancers (60, 62, 66, 67), but its contribution may generally be smaller than that of smoking. This may partly be due to the fact that fewer cancer cases are attributable to alcohol compared to tobacco (68, 69), but also because alcohol consumption shows only minor variation across socioeconomic groups (70), which has also been found in the German population (71). Conway et al. have found that smoking, alcohol consumption and diets low in fresh fruits and vegetables together explain around two-thirds of the excess risk for upper aerodigestive tract cancer in the lowest socioeconomic group (62). From the unexplained excess risk they conclude that low socioeconomic position seems to be associated with cancer risk for reasons other than only through behavioral risk factors.

In addition to lifestyle factors, the contributions of carcinogen exposure at work and in the living environment to socioeconomic inequalities in cancer risk have also been examined (60). The findings of Menvielle et al. suggest that a substantial proportion of the socioeconomic gap in hypopharyngeal and laryngeal cancer is attributable to occupational exposures to asbestos, coal dust and formaldehyde (60). This finding was supported in a study by Santi et al. who found that exposure to potentially carcinogenic agents at work can explain approximately a quarter of the socioeconomic inequalities in laryngeal cancer (67). Another study showed that occupational exposures to asbestos, heavy metals and polycyclic aromatic hydrocarbons can explain parts of the association between socioeconomic position and lung cancer incidence among men, with asbestos making the largest contribution (72). However, it is not only the workplace where members of lower socioeconomic groups are exposed to carcinogenic agents. Exposures to air pollution in the living environment or tobacco smoke at home can also contribute to socioeconomic inequalities in the risk of respiratory tract cancers (73).

According to a systematic review (36), the reverse gradient in female breast cancer incidence may be primarily explained by reproductive factors. Women with higher socioeconomic position are more likely to be older at first birth and have lower parity, each of which is associated with increased breast cancer risk. Socioeconomic differentials in the use of hormone replacement therapy may also play a role in this context (74), and could also help explain the reverse gradient in ovarian cancer. Concerning the reverse gradient in melanoma of the skin, a systematic review suggests that lifestyle-related risk factors, including recreational sun exposure and tanning, may explain why higher socioeconomic groups show higher melanoma incidence (75).

Mechanisms related to healthcare should not be neglected when it comes to explaining socioeconomic inequalities in cancer incidence, especially when the findings are based on population-based registry data. The reverse gradient in thyroid cancer, for instance, is hypothesized to be attributable to new diagnostic capabilities, which may have led to overdiagnosis and increases in thyroid cancer incidence that have been observed in recent decades (56, 76). As with previous innovations in disease prevention and early disease detection such as the polio vaccine or the pap test (77), innovative diagnostic tools for thyroid cancer detection are likely to be used more often by people from higher socioeconomic groups—at least in the first years after launch—, consequently resulting in higher incidence rates among the better-off. Moreover, the uptake of general health checks and participation in cancer screening has often been found to vary between socioeconomic groups, usually with highest participation rates in middle or upper socioeconomic groups (78–80). This has also been the case for Germany's cancer screening programs during our study period (81). Accordingly, socioeconomic differentials in screening participation may have contributed, at least in part, to the reverse socioeconomic gradients or peak incidence in middle socioeconomic groups we observed for certain cancers. For example, Germany introduced a nationwide skin cancer screening program in 2008, and is thus, to our knowledge, the only country worldwide with such a program on a nationwide scale (82). Melanoma incidence increased in Germany after screening was introduced (83), and screening participation has been higher in the upper socioeconomic groups (84). Therefore, screening may have contributed to our finding of a higher melanoma incidence in less deprived districts. Similarly, Germany has a nationwide mammography screening program for the early detection of female breast cancer, and regular screening participation has been found to be highest in the middle and upper socioeconomic groups (81). Mammography screening may thus also have contributed to our finding that the incidence of breast cancer was highest in the middle and at the top of the socioeconomic spectrum.

## Strengths and Limitations

Our study contributes to the growing interest in analyzing the association between socioeconomic deprivation and cancer. The findings extend those from previous German studies by providing results that are nearly nationally representative, covering 73% of Germany's total population, 12 of the 16 German federal states and 317 of the 402 administrative districts. Previous studies have either been restricted to one federal state or the population of one specific statutory health insurance fund. Including the vast majority of the German population regardless of health insurance status [people with private health insurance have on average a higher socioeconomic position (58)] resulted in greater socioeconomic heterogeneity of the study population.

A strength of the socioeconomic deprivation index used in the present study is that it is based exclusively on the three core dimensions of socioeconomic inequality (education, income, and employment). This facilitates the interpretation of results (46), especially when compared to indices of multiple deprivation that include domains going beyond purely socioeconomic ones, such as social capital, the share of lone-parent households, crime rates, the physical environment or morbidity (85–87). Another advantage of the index used is its public availability, which makes the analysis more easily reproducible. Nevertheless, the composite nature of the index also has some limitations. Analogous to socioeconomic indices at the individual level, composite measures generally have the disadvantage that they can conceal variation in the associations of the single dimensions with the health outcome under study (88). For example, if education were to predict a health outcome such as cancer, income or employment might not. This possibility should be considered when interpreting our results.

It should further be considered that the area-based measure of socioeconomic deprivation is prone to misclassification of subjects when interpreting it at the individual level. The socioeconomic groups in our study were classified by an area-based index, because individual-level information on socioeconomic position was not available in the cancer registry and population data. For example, the area-based approach classifies individuals with high socioeconomic position into the socioeconomically most deprived group when they live in a district with a high share of inhabitants of low socioeconomic position. Therefore, it cannot be inferred directly from our results that individuals of low or high socioeconomic position have higher or lower cancer incidence. Depending on the degree of this misclassification, which cannot be quantified with the data used, the area-based approach may have led to an underestimation of cancer inequalities with regard to individual socioeconomic position in our study. However, the area-based approach helps to identify regions whose populations, from a public health perspective, may have an increased need for cancer prevention measures with respect to specific cancers, although the large size and heterogeneity of some districts may be challenging in this respect.

We compared current cancer incidence with current district-level socioeconomic deprivation. This does not account for changes in a district's deprivation over time, nor does it account for population migration between districts with different deprivation levels. Therefore, although the GISD is fairly stable over time [intra-class correlation ($ICC_{2010-2013}$) = 0.989] and current socioeconomic deprivation may be associated with utilization of certain diagnostic and early detection services, our analyses do not provide a complete picture of the etiologic relevance of socioeconomic deprivation for cancer

incidence. Moreover, considering that a large proportion of highly deprived districts are located in Eastern Germany, it would have been desirable to discriminate the effects of living in a currently deprived district from the effect of being born and raised in the former German Democratic Republic. Since we lacked the necessary background variables in the registry data, we were not able to gain any insights into this matter.

It should be considered that excluding data from four German federal states may have introduced bias into our results. We decided to exclude data from Hesse, Saxony-Anhalt, Baden-Württemberg and Berlin because of insufficient registration completeness (estimated completeness <90%). Therefore, the extent of any associations between socioeconomic deprivation and cancer incidence in these regions remains unknown. The districts excluded from the analysis differed from the included districts in having on average lower deprivation scores and a larger heterogeneity (see **Table 1**), which may have introduced potential selection bias.

Another limitation is related to the heterogeneity of the included districts. In Germany, administrative units at the district level vary considerably in their population size, population density and socioeconomic diversity. Therefore the Modifiable Area Unit Problem (MAUP) (89) has to be taken into account: the MAUP postulates that different regional aggregations of the units of observation may lead to different results and conclusions. However, it has been shown that district-level estimates of the socioeconomic gradient in health for Germany, such as those presented here, tend to find less pronounced associations than estimates at smaller levels of spatial aggregation because differences in deprivation between districts are less pronounced than, for example, differences between individual towns or neighborhoods (46). Therefore, it seems likely that our results, which are in some instances based on districts with more than a million inhabitants (large metropolitan cities forming one independent administrative district), tend to underestimate the association between socioeconomic deprivation and cancer incidence.

## Conclusions

Socioeconomic inequalities in the incidence of common cancers demonstrate potentials for population-based cancer prevention. In view of the major risk factors of common cancers and the explanatory approaches discussed, both behavioral and structural prevention strategies should be identified to reduce socioeconomic differences in morbidity and mortality. In accordance with the health-in-all-policies approach, these should be implemented not only in the health sector, but in all policy areas. The area-based cancer inequalities found in our study can help to identify districts with high rates of certain cancers and to develop local and community-based strategies for cancer prevention and control. In future studies, more in-depth analyses including additional data on tumor stage and cancer mortality could provide additional insights into the social epidemiology of cancer and potential entry points for reducing the health gap between the better- and worse-off.

## DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article can be obtained upon application from the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute. Researchers may submit an application form and a project sketch to access the anonymized dataset. Details for acquiring the data are available at: https://www.krebsdaten.de/Krebs/EN/Content/ScientificUseFile/scientificusefile_node.html

The German Index of Socioeconomic Deprivation (GISD) used in our analysis is available for research purposes free of charge at a GitHub repository: https://lekroll.github.io/GISD.

## ETHICS STATEMENT

Neither approval by the Ethics Committee nor consensus procedures were required as the analyses were based on population-based cancer registry data collected in the German federal states and transferred to the German Centre for Cancer Registry Data in accordance with state and federal laws. Additional interviews, physical examinations, biological sampling or laboratory tests were not performed.

## AUTHOR CONTRIBUTIONS

JH, LK, BB, and KK designed the study. JH performed the statistical analysis. LK and BB contributed to the statistical analysis and preparation of the data for analysis. JF and JH reviewed the literature. JH drafted the manuscript with contributions of all co-authors. TL and KK supervised the study. TL, AK, and KK reviewed the manuscript critically. All authors contributed to interpretation of findings, reviewed, edited, and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00402/full#supplementary-material

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# Inequality in the Incidence of Cervical Cancer: Costa Rica 1980–2010

*Carolina Santamaría-Ulloa*[1]* *and Cindy Valverde-Manzanares*[2]

[1] *Health Research Institute, University of Costa Rica, San José, Costa Rica,* [2] *Health Surveillance Department, Ministry of Health Costa Rica, San José, Costa Rica*

**Introduction:** Cervical cancer is the third most incident and the fourth most lethal cancer among Costa Rican women. The purpose of this study was to quantify incidence inequality along three decades and to explore its determinants.

**Materials and Methods:** This is a population-based study. Main data sources were the National Tumor Registry (1980–2010), CRELES (Costa Rican Longevity and Healthy Aging Study) longitudinal survey (2013), and published indices of economic condition (2007) and access to healthcare (2000). Cartography was made with QGIS software. Inequality was quantified using the Theil-T index. With the purpose of detecting differences by tumor's behavior, inequality was estimated for "*in situ*" and invasive incidence. *In Situ*/Invasive Ratios were estimated as an additional marker of inequality. Poisson and spatial regression analyses were conducted with Stata and ArcMap software, respectively, to assess the association between incidence and social determinants such as economic condition, access to healthcare and sub-utilization of Papanicolaou screening.

**Results:** As measured by Theil-T index, incidence inequality has reached high (83 to 87%) levels during the last three decades. For invasive cervical cancer, inequality has been rising especially in women aged 50–59; increasing from 58% in the 1980's to 66% in 2000's. Poisson regression models showed that sub-utilization of Papanicolaou smear was associated with a significant decrease in the probability of early diagnosis. Costa Rican guidelines establish a Pap smear every 2 years; having a Pap smear every 3 years or longer was associated with a 36% decrease in the probability of early "*in situ*" diagnosis (IRR = 0.64, $p = 0.003$) in the last decade. Spatial regression models allowed for the detection of specific areas where incidence of invasive cervical cancer was higher than expected.

**Conclusion:** Results from this study provide evidence of inequality in the incidence of cervical cancer, which has been high over three decades, and may be explained by sub-utilization of Papanicolaou smear screening in certain regions. The reasons why women do not adequately use screening must be addressed in future research. Interventions should be developed to stimulate the utilization of screening especially among women aged 50 to 59 where inequality has been rising.

**Keywords: developing countries, cervical cancer, social determinants, inequality, Costa Rica**

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*University of São Paulo, Brazil*
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*National Cancer Institute (NIH), United States*
*Anna Louise Beavis,*
*Johns Hopkins University, United States*

***Correspondence:**
*Carolina Santamaría-Ulloa*
*carolina.santamaria@ucr.ac.cr*

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## INTRODUCTION

In 2005, the World Health Organization (WHO) created the Commission on Social Determinants of Health with the purpose of helping nations to face the social causes of health and reduce inequity (1). An explanatory model of the way by which health status is produced or affected within a population points to four categories of determinants: biological, environmental, health-service related and socio-economic as well as cultural (2).

The nature and the magnitude of inequality on health outcomes need to be investigated. On one hand, the nature refers to the origin of each situation; it allows to better understand the ways in which differences developed. On the other hand, assessing the magnitude may be associated with the impact this situation has on a population. Quantifications of inequality are used in the current study and further discussed under the framework of the social determinants of health to examine the incidence of cervical cancer as a health outcome.

Cervical cancer is the third most incident malignant tumor among Costa Rican females, with a rate of 30 cases per 100,000 women in 2015. This incidence is only surpassed by skin and breast cancer with rates of 61 and 60 cases per 100,000 women, respectively (3). It is the fourth most important cause of malignant cancer mortality among the female population with a rate of 6 deaths per 100,000 women in 2016. Cervical cancer mortality is only surpassed by breast, stomach, and colon cancer (4).

In Costa Rica, like in other countries, an association between cervical cancer incidence and geographic location has been previously described. Using data from the National Tumor Registry for the period 1980 to 1983, [Sierra and Barrantes (5)] found a higher incidence of cervical cancer in the coastal vs. non-coastal areas. Further, the Ministry Health (3) documented higher prevalences of cervical cancer in coastal regions. The geographical distribution of incidence shows that Costa Rican women are not affected in a homogeneous manner within the country.

The human papilloma virus (HPV) is the most important risk factor for the development of cervical cancer (6). The 2015 Costa Rican National Survey on Reproductive and Sexual Health indicates that in the country only 45% of women and 44% of men recognize the HPV as a sexually transmitted infection (7). Sexual behavior is an important risk factor for cervical cancer and socioeconomic status has been associated with sexual behaviors that favor the acquisition of HPV. [De Sanjosé and collaborators (8)], in two case-control studies carried out in Colombia and Spain, determined that human papilloma virus was more frequent in women of low vs. high socio-economic status. Moreover, another study confirmed the association between socioeconomic status and HPV for different cancer sites, including cervical cancer (9). However, higher prevalence of HPV in middle and high socio-economic status in Latin America and in developed countries, may evidence that socioeconomic differences in incidence result from access to screening inequality rather than HPV prevalence inequality. Sancho-Garnier et al. (10), make a case of how high income countries with established preventive programs have persistent inequalities in detection because of inequality in access to screening programs.

Starting in the 1960s and up to the 1980s, cervical cancer cases were primarily detected via population-based screening programs such as Papanicolaou smear, a conventional cytology that tests for the presence of precancerous or cancerous cells on the cervix. More recently, screening by human papillomavirus (HPV) testing has been established as more accurate and effective. Although HPV testing is expected to become the preferred screening test in the medium and long term (11), Pap smear is still the recommended screening procedure in healthcare protocols in Costa Rica. Timely access to screening services allows early detection of malignant tumors. In general, low-income women show higher rates of cancer detection at advanced stages (12). It is therefore frequently assumed that inequality in cervical cancer incidence in diverse populations may be the result of unequal access to screening services. If this were indeed the case, it would be expected that a public policy to improve access to screening would lead to a reduction of inequality (13).

In an exploratory analysis using geographic information systems and data from the National Tumor Registry between 1990 and 1997, [Santamaría (14)] reported a significantly higher incidence of cervical cancer in southern and Caribbean regions of the country, primarily in the provinces of Puntarenas and Limon, where the relative risk of invasive cervical cancer reached values that were 2.1 times higher than in the rest of the country. These regions have the lowest indices of human and social development in Costa Rica.

There is evidence that cervical cancer affects Costa Rican women in a heterogeneous manner; and it is also evident that this phenomenon has persisted for several decades in the country. Nevertheless, neither the magnitude of this existing inequality has been quantified, nor has the research on inequality been approached from the perspective of the social determinants of health. The aim of this study is to determine the magnitude of the disparities in cervical cancer incidence within Costa Rica and to identify factors associated with incidence, in order to inform policies to reduce disparities.

## METHODS

This study was conducted after obtaining approval from the Scientific Ethics Committee at the University of Costa Rica (VI-3621-2012). This is a population-based study, geographic units rather than individuals are its units of analysis. Costa Rica has an area of 51,100 km$^2$, administratively divided into 7 provinces. In 2018, a total of 82 counties and 484 districts were contained within those provinces. Cervical cancer incidence was analyzed both at the county and the district level for a 31-year time period: 1980 to 2010.

Analyses were conducted for total, *in situ*, and invasive cervical cancer incidence. Most of analyses were broken down into 3 periods: 1980–1989, 1990–1999, and 2000–2010. Regression models were estimated for the last period: 2000–2010.

## Data Description

Five sources of information were used: (1) Cancer cases from National Tumor Registry, (2) Population exposed from Official Population Estimations, (3) Population economic condition from the Social Development Index, (4) Population access to healthcare from a geographical access to healthcare index, and (5) Papanicolaou sub-utilization from the survey CRELES: Costa Rican Longevity and Healthy Aging Study.

Cancer cases come from the National Tumor Registry (NTR) database from 1980 to 2010. Access to the NTR was provided by the Costa Rican Ministry of Health. The standard NTR record contains age, calendar year, and place of residence at diagnosis. A count of cases for each geographical unit was made for each of the time periods of interest. This nationwide population-based registry has been maintained by the Ministry of Health since 1977. Since 1980 all hospitals and private pathologists have agreed to report any hospitalizations or outpatient biopsies associated with a cancer diagnosis (15). This registry has high indices of data quality (16) and since the 1980s this NTR's coverage has been estimated to be around 98% (17).

Population exposed from 1980 to 2010 within each geographical unit was estimated based on the official updated estimation figures for female population. These estimations are jointly elaborated by the National Institute for Population Statistics and Census and the Central American Population Center of the University of Costa Rica (18).

Using data from the NTR on newly diagnosed cases of cervical cancer as well as the official population estimations, we estimated cervical cancer incidence rates. Data from the NTR constitutes the numerator of the cervical cancer incidence rate for each geographic unit. The denominator of the rate is the female population at mid-period, multiplied by the number of years included in the numerator, in order to estimate annualized rates. Because age distribution in this population was not significantly different from Segi's world standard population (chi = 128, $p = 0.292$), crude incidence rates per 100,000 women were estimated for this study. QGIS software (19) was used to represent incidence rates in maps.

The following three data sources were used in regression models to explain incidence for the 2000–2010 period. Because of availability of data, they belong to different years, which are the closest possible to the 2000–2010 period.

Data on economic condition in 2007 is the official estimation of the Social Development Index' economic component, which is estimated by the Costa Rican Ministry of Planning. The economic dimension of the index is a compound measure of residential electricity consumption and residential access to Internet. It captures population capability of acquiring goods and services, and population's technology access (20).

Access to healthcare in 2000 is measured as a comprehensive index of geographic accessibility to healthcare facilities in Costa Rica. All healthcare facilities are included in this index: primary healthcare facilities, clinics and hospitals. It was created using Geographic Information System (GIS) technologies and aggregating characteristics of both population and healthcare facilities (21).

Sub-utilization of Papanicolaou screening in 2013 is estimated from the survey CRELES: Costa Rican Longevity and Healthy Aging Study. Data from this longitudinal survey is publicly available (22).

## Statistical Analyses

The Theil T index (23) was used to quantify inequality at a district level. Incidence rates were the basis for the quantitative estimation of inequality in the distribution of this pathology. This index has been widely used to measure inequality in different health and social outcomes. It has for example been used to measure income inequality in Latin America (24) or inequality in access to improved water in different world regions (25).

This indicator was selected because it can estimate inequality even when geographical units have a null incidence rate. Having a number of geographical units with no cases is an expected scenario given the small size of the unit of analysis (district) and the fact that the event is considered to be infrequent. Theil-T is a population weighted index that is sensitive to health differences further from the average rate (26).

The Theil-T index is defined as follows:

$$T = \sum_{u=1}^{N} y_u \log \frac{y_u}{\frac{1}{N}} \quad (1)$$

Where:

For each $u = 1,2,\ldots,$ geographical units (districts)

$y_u$ = number of cases of cervical cancer diagnosed in district u

$N$ = female population size.

Carcinoma *in situ*/Invasive Cervical Cancer Ratios (CIS/ICC) were estimated as an additional marker of inequality. A CIS/ICC = 1 means that for each carcinoma *in situ*, there is another invasive cervical cancer detected. Ideally the incidence of carcinoma *in situ* should exceed that of invasive cancer (CIS/ICC > 1), indicating a majority of cases being detected at an early stage (27). CIS/ICC were represented in maps using QGIS software (19).

Multivariate regression analyses were also carried out at the district level in the 2000–2010 period. Poisson and geographically weighted spatial regression models were estimated with Stata (28) and ArcMap (29) software respectively, to assess the association between incidence and social determinants such as economic condition, access to healthcare and sub-utilization of Papanicolaou smear. Cervical cancer counts and incidence rates were the dependent variable of Poisson and spatial regression models, respectively. The social determinants of this health outcome (economic condition, access to healthcare, and sub-utilization of Papanicolaou smear) were controlled for as independent variables in both types of models.

Because cervical cancer is an infrequent event, cases are assumed to be generated from a Poisson distribution. Poisson is adequate to model cases of infrequent illnesses with a small number of cases (30). When the dependent variable is a counting (number of new cervical cancer cases on each district), that takes the form of entire non-negative values, a Poisson specification is

an improvement over Ordinary Least Squares (31). The Poisson distribution provides the probability of the number of events; and the parameters correspond to the expected number of occurrences as a function of the independent variables (32). This model was estimated using Stata software (28).

Using the count of cases as the dependent variable in Poisson regression models, suggests the need to control for female population exposed to cervical cancer in each district, because each count of cases refers to areas of different underlying populations. The observed number of cases $b_i$ was the dependent variable, and the expected number of cases $b_i^E$ was the offset variable introduced in the right hand side of the model. The Poisson regression model is defined as follows:

$$b_i = P(b_i, x) \tag{2}$$

$$b_i^E = \sum (M_i x^* W_i^S x) \tag{3}$$

Where:

$b_i$ is the observed number of cases at location *i*;

*P* indicates a Poisson function;

*x* is the age group;

$b_i^E$ is the expected number of cases at location *i*;

$M_i$ *x* is the observed population size in location *i* at age *x*; and

$W_i^S$ *x* is the incidence rate in the standard population at age x.

A geographically weighted regression was also carried out. This spatial regression tool is based on mathematical models that take into account spatial auto-correlation and it has been previously used in cancer research conducted in Costa Rica (33). Counties close to each other have a greater probability of sharing characteristics among themselves due to their geographic proximity than those that are located more distantly from one another, which makes this methodology relevant for the current study. This model was estimated using the GWR (Geographically Weighted Regression) tool in ArcMap software (29) and maps were made using QGIS software (19).

Parameters in a global regression model are very likely not constant across space, and geographically weighted regressions allow determining how each parameter varies across a geographical area. This statistical tool helps understand spatial heterogeneity in data (33), which justifies its use in this study.

Social determinants were used as independent variables in both the Poisson and the spatial regression model. The Costa Rican Ministry of Health (34), following Lalonde (2), classifies social determinants into four categories: (1) biological determinants; (2) environmental determinants; (3) socioeconomic as well as cultural determinants; and (4) determinants related to the healthcare services. Controlling for all four categories of determinants in regression models would be optimal. Nevertheless, at the population level there is no information regarding the first category of biological factors such as the population prevalence of human papilloma virus (HPV). There is also no data available on the second category of environmental factors that may be associated with the incidence of cervical cancer such as tobacco smoking (35).

Although for the purpose of this study it is not possible to explore the association between cervical cancer and biological and environmental factors, the third and fourth categories of determinants—socioeconomic and healthcare—have been included in the analyses.

Regarding the third category of socioeconomic determinants, it is desirable to consider several dimensions of socioeconomic status (36). The economics dimension of the social development index (SDI) was used in this study as a measure of economic condition at the district level (20). This approach of quantifying socioeconomic determinants is similar to the one used in a previous research (37).

Regarding the fourth category of determinants related to the healthcare services, density index of access to healthcare services and sub-utilization of Papanicolaou smear were included.

Although access to healthcare is a concept with at least two dimensions: geographic and social (38), geographic access is what this index measures. Geographical access to healthcare facilities in 2,000 is measured using a comprehensive index of accessibility that results from the aggregation of all facilities weighted by their size, proximity, and characteristics of both the population and the facility. The density index of access to healthcare services uses physician hours per capita yearly as the metric. The greater the value a district has for this index, the better access to health services has its population. Greater details on the construction of this index can be found in Rosero-Bixby (21).

Sub-utilization of Papanicolaou screening in 2013 was obtained from CRELES: Costa Rica Study of Longevity and Healthy Aging. Rates are based on a question about when was the last time women had a Papanicolaou screening. According to national attention guidelines, Papanicolaou screening should be conducted at least every 2 years (39). A measure of the proportion of female population who had their last screening 3 years ago or longer is used as an indicator of sub-utilization of Pap smear in this study. Because of sampling issues, it was not possible to obtain district level estimations; therefore the indicator was estimated for counties, which are larger geographic units.

## RESULTS

A total of 22,279 incident cases of cervical cancer occurred in Costa Rica during the 1980–2010 time period. Because this study is based on geographical units, 5.4% of cases were not included on the grounds of not containing any information about patient's place of living at diagnosis.

A total of 21,075 cases were included in the analyses. In absence of information, district or county imputation was conducted in 7.0% of cases (5.3% of cases with no district information and 1.7% of cases with no county information). Imputation was made under of the assumption that missing information followed the distribution of non-missing cases within its corresponding county or province.

Cases were distributed along the period of study as follows: 26% during 1980–1989, 31% in 1990–1999, and 42% in 2000–2010. The number of cases had a 79% increase from the 1980s to the 2000s, which is mainly attributed to an increase in the detection of carcinoma *in situ*. Details on numerators,

**TABLE 1 |** Descriptive data on cervical cancer incidence, by time period. Costa Rica: 1980–2010.

| Indicator | 1980–1989 | 1990–1999 | 2000–2010 | Total |
|---|---|---|---|---|
| **CERVICAL CANCER CASES** | | | | |
| Excluded from analyses | | | | |
| No geographical location available | 595 | 47 | 562 | 1.204 |
| Included in analyses | | | | |
| *In situ* | 2,998 | 3,421 | 6,202 | 12,621 |
| Invasive | 2,239 | 2,559 | 3,656 | 8,454 |
| Total cases included in analyses | 5,237 | 5,980 | 9,858 | 21,075 |
| Total cases reported in NTR | 5,832 | 6,027 | 10,420 | 22,279 |
| **POPULATION EXPOSED** | | | | |
| Female population at mid-period | 1,281,313 | 1,671,216 | 2,065,853 | 1,671,216 |
| **CERVICAL CANCER ANNUALIZED INCIDENCE RATE PER 100,000 WOMEN** | | | | |
| *In situ* | 23.40 | 20.47 | 27.29 | 24.36 |
| Invasive | 17.47 | 15.31 | 16.09 | 16.32 |
| Total | 40.87 | 35.78 | 43.38 | 40.68 |
| *In situ*/Invasive Incidence Rate Ratio | 1.34 | 1.34 | 1.70 | 1.46 |

denominators, incidence rates, and ratios by period are included in **Table 1**.

Inequality was analyzed by first describing geographical differences in the incidence of cervical cancer and then measuring the association between such health outcome and its social determinants as an approach to hypothesize on explanations to disparities. The estimation of the degree of inequality was carried out for each of the three decades and it was also analyzed by tumor behavior (*in situ* or invasive) with the purpose of determining the existence of differences. Analyzing results by tumor behavior is meaningful for understanding health disparities because behavior is itself an indication of how timely the cancer was diagnosed.

In the first phase of the analysis, a description of inequality was made by using cartographic representations and by estimating the Theil-T index for incidence of cervical cancer in Costa Rica. Across three decades, the incidence of carcinoma *in situ* has been heterogeneously distributed along the territory, although in terms of territory extension the 1990s had the greatest area of high *in situ* cases incidence rates (**Figure 1**).

A distribution pattern is more evident when examining the incidence of invasive cervical cancer, which has more clearly concentrated in the country's coastal and border areas along the last 31 years (**Figure 2**).

Theil-T index values are estimated on a scale that ranges from zero to 100%, where zero is perfect equality and 100% is perfect inequality. As measured by the Theil-T index, inequality has moved from 87 to 83% and from 85 to 83% for *in situ* and invasive cervical cancer, respectively, along three decades (**Figure 3**). All of these values over 80% are evidence of high inequality levels. But in spite of this rather high level of inequality, two important phenomena have taken place. On one hand, inequality of *in situ* cervical cancer has decreased in the population younger than 40 (left hand side of **Figure 3**).

On the other hand, inequality in invasive cervical cancer has increased in the older population aged 40 to 59, but especially in the 50–59 age group (right hand side of **Figure 3**), where the inequality increased 11% from the 1980s to the 1990s and reached a total 14% increase during the 31 year period from 1980 to 2010 (**Table 2**). The increase in inequality observed for invasive cancer in women aged 50–59 was greater than any decrease in inequality observed in other age groups (**Table 2**).

Carcinoma *in situ*/Invasive Cervical Cancer Ratios (CIS/ICC) are also presented as indicators of inequality. They have the advantage of allowing a cartographic representation of geographical areas where inequalities occur. In Costa Rica, the CIS/ICC ratio averaged 1.46 from 1980 to 2010 (**Table 1**). Results from this indicator were presented in maps with ratios divided into three categories: $< 1$ in red color (mostly late detection), 1–1.49 in white color (around national average ratio), and $> 1.50$ in blue color (mostly early detection).

CIS/ICC shows a concentration of red geographical units in border areas, these are areas of late detection for cervical cancer, meaning that a majority of new cases are diagnosed in late stages rather than *in situ*. This inequality concentrates to the North where border is shared with Nicaragua, to the South where Costa Rica shares a limit with Panama, and in some coast areas (**Figure 4**).

In the second phase of the analysis, Poisson and spatial regression models were estimated to measure the association between incidence and its social determinants. This was done as an exercise to generate hypotheses about the factors that may explain the inequality found in the first phase of analysis.

Poisson regressions were modeled at the geographical district level. Incidence for the 2000–2010 period was modeled as a function of economic condition, geographical access to healthcare facilities and sub-utilization of papanicolaou screening, which were in turn proxy measures of the social determinants of incidence.

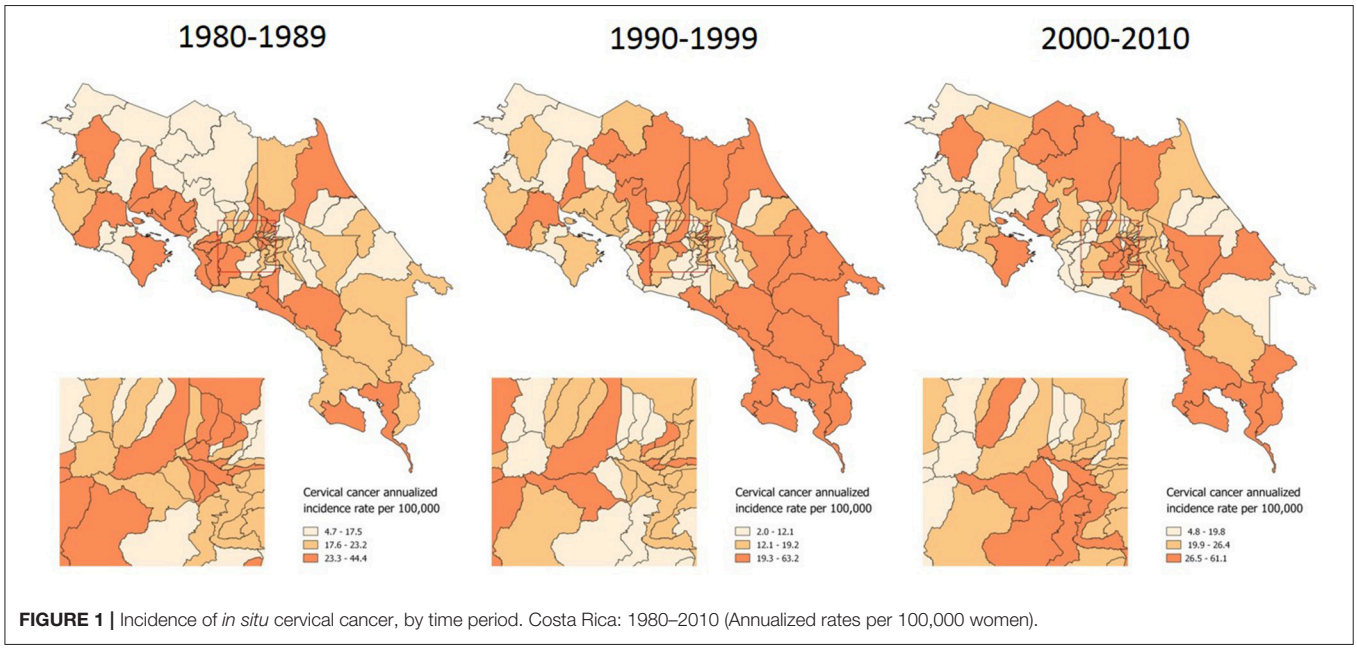


**FIGURE 1 |** Incidence of *in situ* cervical cancer, by time period. Costa Rica: 1980–2010 (Annualized rates per 100,000 women).

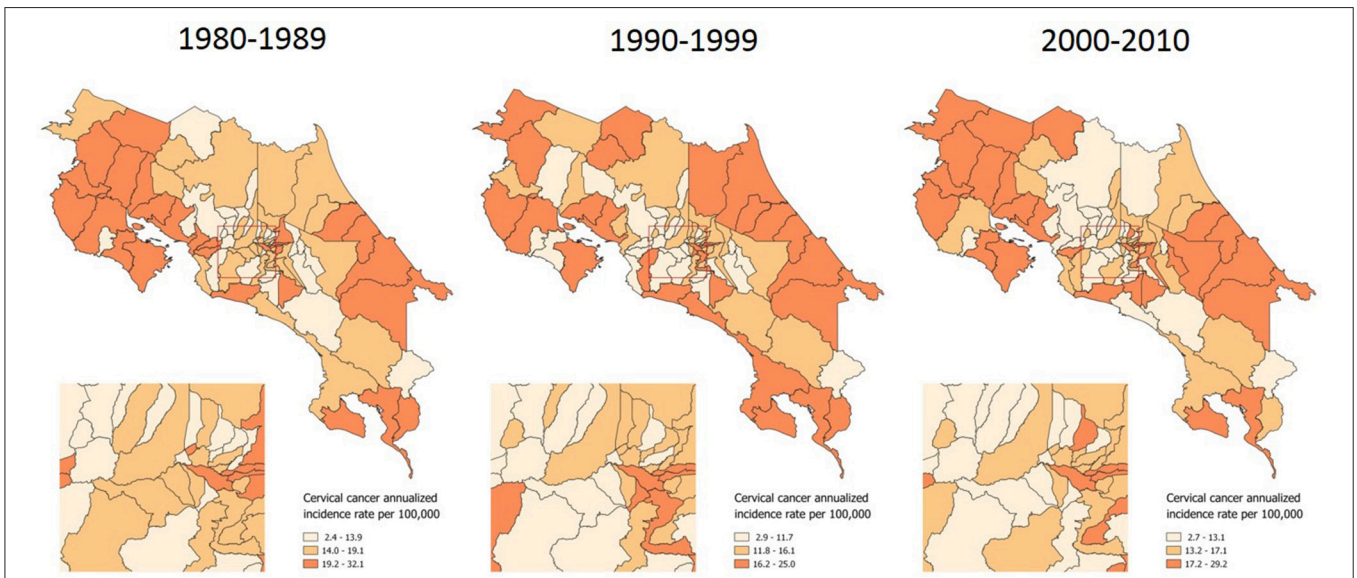


**FIGURE 2 |** Incidence of invasive cervical cancer, by time period. Costa Rica: 1980–2010 (Annualized rates per 100,000 women).

These Poisson regression analyses were conducted for total incidence and they were also stratified by tumor behavior; that is, for *in situ* and for invasive diagnosis. Incidence Rate Ratios (IRR) were estimated. Sub-utilization of Papanicolaou was significantly associated with a 36% decrease in the probability of early "*in situ*" diagnosis (IRR = 0.637, $p = 0.003$) (**Table 3**).

Finally, geographic regression analyses were conducted for invasive cervical cancer incidence. Same as with Poisson models, this regression was estimated for the 2000–2010 period. The same set of independent variables that were used in the previous models, was used for this spatial regression model: economic condition, geographical access to healthcare services and sub-utilization of Pap smear. Standardized residuals resulting from this modeling are shown in **Figure 5**. These residuals represent the difference between the observed incidence of invasive cervical cancer and the incidence that was predicted by the spatial regression equation. Areas where the incidence was lower than expected are represented in blue; areas where the incidence is approximately the same as expected are represented in white and those where the incidence is greater than expected are represented in red.

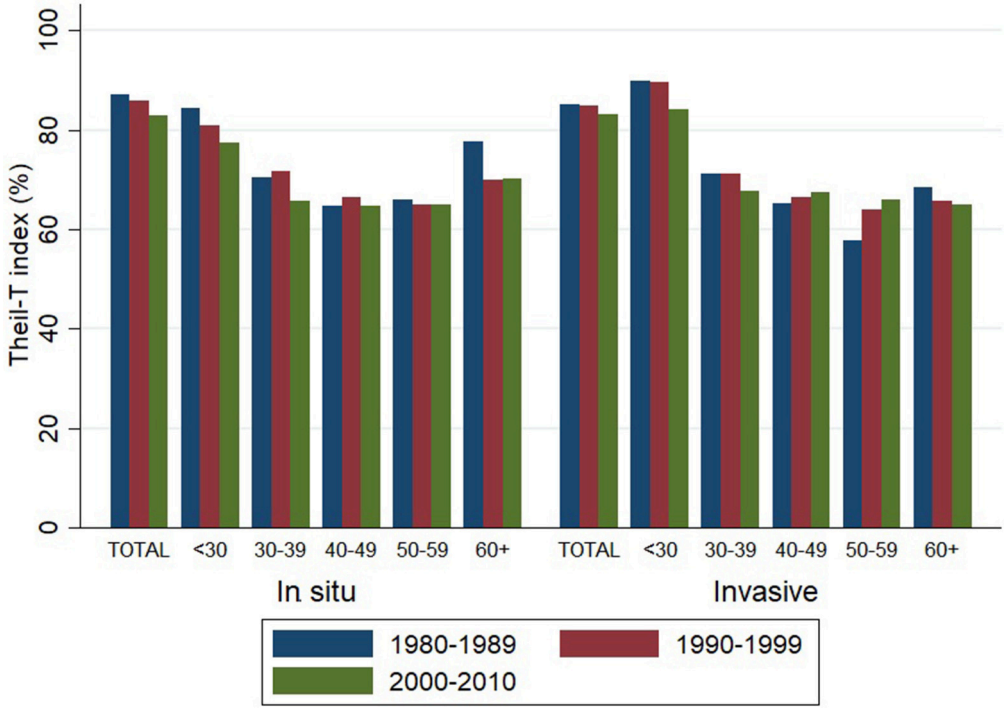


**FIGURE 3 |** Inequality in the incidence of cervical cancer, by tumor behavior and time period. Costa Rica: 1980–2010 (Theil-T Index, %).

**TABLE 2 |** Relative (%) change in inequality as measured by Theil-T index in the incidence of cervical cancer, by tumor behavior and period of change. Costa Rica: 1980–2010.

| Age | *In situ* | | | Invasive | | |
|---|---|---|---|---|---|---|
| | 1980s−1990s | 1990s−2000s | 1980s−2000s | 1980s−1990s | 1990s−2000s | 1980s−2000s |
| <30 | −4.0 | −4.2 | −8.0 | −0.5 | −6.2 | −6.6 |
| 30–39 | 1.7 | −8.1 | −6.6 | 0.2 | −5.1 | −4.9 |
| 40–49 | 2.6 | −2.7 | −0.2 | 1.6 | 1.8 | 3.4 |
| 50–59 | −1.6 | 0.1 | −1.5 | 10.7 | 2.9 | 13.9 |
| 60+ | −10.0 | 0.5 | −9.6 | −4.0 | −1.1 | −5.0 |
| Total | −1.2 | −3.7 | −4.8 | −0.2 | −2.2 | −2.4 |

## DISCUSSION

In Costa Rica the Cervical Cancer Prevention Program was created in 1960. Beginning the 1970s Papanicolaou screening was increasingly taking part of sexual and reproductive programs targeted to women 15 to 49 years of age. As a result, Pap smear coverage had an important upsurge. In the early 1980s, the national coverage of at least one Pap smear during lifetime was 51% for women aged 15–49, but it reached 70% in 1986 and 74% in 1993 (40–42). The geographical pattern observed in the incidence of *in situ* cervical cancer from the 1980s to the 1990s decade, when the greatest territory extension of *in situ* high rates occurred, illustrates the expansion of the screening program that has just been described.

Nonetheless, as Theil-T index results showed, the most relevant decrease in inequality occurred from the 1990s to the 2000s rather than from the 1980s to the 1990s. In 1995, a health sector reform was initiated in lower socioeconomic regions of the country, and it was progressively expanded to the entire country. This reform implied a better allocation of resources given the fact that instead of having two government institutions providing services, the Social Security System was assigned to offer healthcare services and the Ministry of Health was assigned a directing role. Rosero-Bixby (43) showed that this reform had an impact on reducing inequality in access to primary healthcare services. Our study findings support Rosero-Bixby's conclusion of a decrease of inequality in cervical cancer incidence from the 1990s to the 2000s that is probably a result of the combination of a well-established Cervical Cancer Prevention Program in

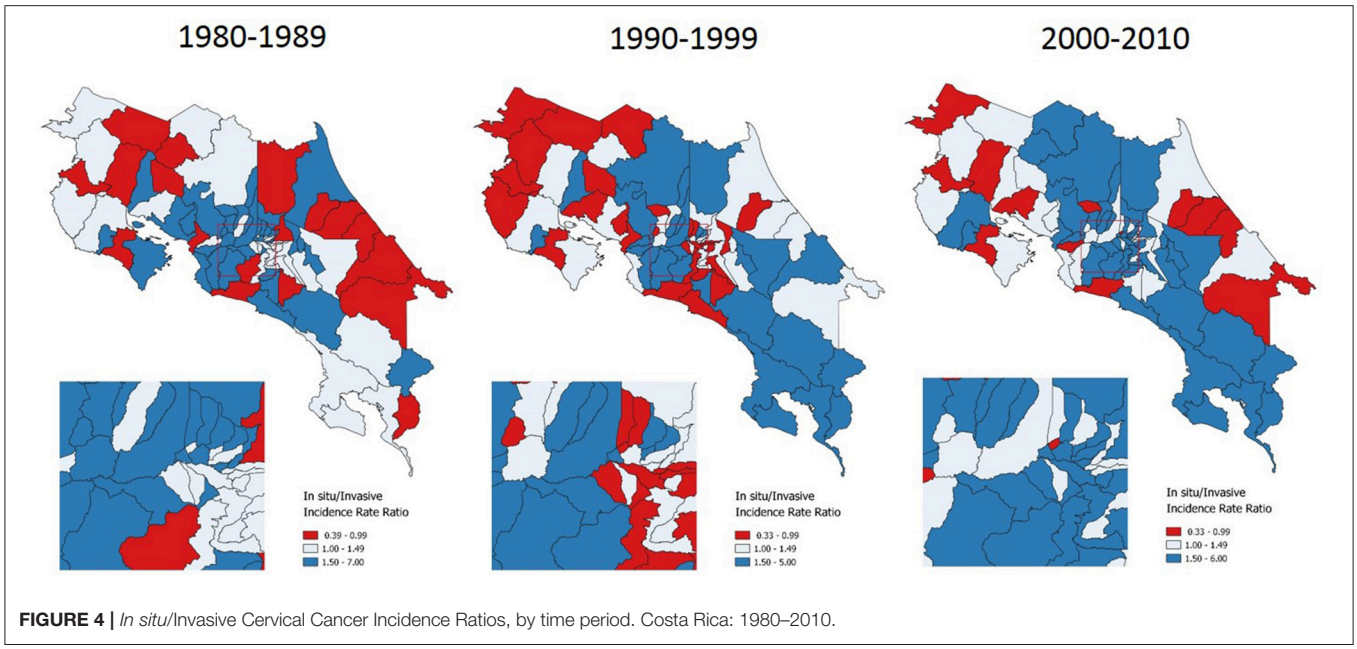


**FIGURE 4 |** *In situ*/Invasive Cervical Cancer Incidence Ratios, by time period. Costa Rica: 1980–2010.

**TABLE 3 |** Incidence rate ratios from a Poisson regression model to explain the incidence of cervical cancer, by tumor behavior. Costa Rica: 2000–2010.

| Independent variables | *In situ* | | Invasive | | Total | |
|---|---|---|---|---|---|---|
| | IRR | p | IRR | p | IRR | p |
| Economic condition | 1.002 | 0.175 | 1.008 | <0.001 | 1.004 | <0.001 |
| Geographic access to healthcare | 1.001 | <0.001 | 1.001 | <0.001 | 1.001 | <0.001 |
| Pap sub-utilization | 0.637 | 0.003 | 1.020 | 0.921 | 0.755 | 0.022 |

the context of a health sector reform. This inequality decrease however, did not occur for all age groups and geographic areas of the country.

Female population younger than 40 years experienced the benefits of a national prevention program that was probably more successful in screening women at reproductive age, than it was in following-up and treating, especially after childbearing. Inequality in cervical cancer showed a modest decrease in 31 years, a decrease that could have been more important had older age groups received equal benefits that were received by younger women. In this context, although it is known that after the age of 40 the risk of cervical cancer decreases, that is the age that signals inequality rises in Costa Rica. Women aged 50 to 59 is the worst off group. The increase in inequality in this group is greater than any gain in terms of equality occurred in the rest of age groups along three decades. These disadvantaged women belong to cohorts that, in terms of age, either were part or soon became part of the prevention program target population. In the 1960s the prevention program started. Women aged 50 to 59 in the 1980s were around 30 back then. Those aged 50 to 59 in the 1990s were about 20 when the prevention program started. And those aged 50 to 59 in the 2000s were around 10 years of age. These cohorts probably experienced the advantages of the prevention program in terms of screening, but also experienced the disadvantages of lack of follow-up. Not only these cohorts have not had a decrease in the *in situ* incidence inequality, but also have had the most important inequality increase in invasive cervical cancer, representing lost opportunities in cancer prevention.

In terms of geographic inequality, coast areas have long been described as the highest incidence regions the country. Between 1980 and 1983 Guanacaste and Puntarenas, both of them coast provinces, were shown to have the highest incidence; and Limón, another coast province, had the highest mortality. Unequal access to screening in Limón, as well as sexual behavior patterns in the coast were hypothesized as possible causes of geographic inequality (42). Between 1986 and 1987, (44) conducted a case-control study and concluded that the higher incidence of cervical cancer in coastal vs. metropolitan areas could not be attributed to differential access to Papanicolaou screening but to differences in reproductive behavior among populations. They observed these differences in age at first intercourse, number of sexual partners, number of children, and history of sexually transmitted infections, among others. (45) showed how Limón is a province of high inequality in terms of cervical cancer,

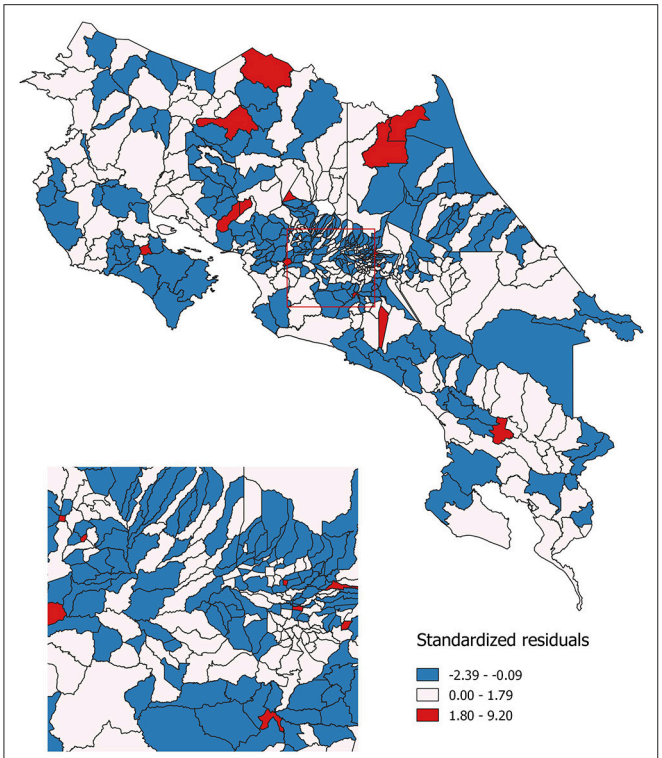


**FIGURE 5 |** Observed as compared to expected probability of invasive cervical cancer incidence. Costa Rica: 2000–2010.

with the highest share of invasive as compared to *in situ* incidence.

Our study findings regarding the geographical pattern of invasive cervical cancer show again how coast areas continue having the highest rates, as well as the lowest *In situ*/Invasive Cervical Cancer Ratios along three decades. Given the lack of population based data, testing an association between sexual behavior differences (42, 44) and incidence rates was not feasible in this study. However, an association between screening sub-utilization and incidence was found. The fact that after controlling for the effect of both economic condition and geographical access to healthcare services, screening sub-utilization is significantly associated with a lower probability of early detection is an important finding.

Previous studies have also found an association between cervical cancer incidence and low utilization rates of screening (46, 47). It has been described that cultural and social values are factors that influence access to cervical cancer screening (48). Future research should address the reasons why in a universal healthcare system such as the Costa Rican one, women still do not adequately access Papanicolaou screening. Geographical access according to our study can be ruled out, but cultural aspects may be mediating decisions to access screening services. This study results highlight finer tuned places where more research should be conducted to explain an incidence of invasive cervical cancer that exceeds what could be predicted.

## CONCLUSION

An unequal distribution of cervical cancer incidence has been described around the world. Disparities resulting from unnecessary, avoidable and unjust inequality occur globally (49). Although cervical cancer mortality rates have decreased over time, inequality has persisted in different contexts all over the globe. Taken altogether this study results provide evidence of inequality and highlight age groups and geographical areas that merit special attention. Inequality in the incidence of cervical cancer must be avoided regardless of women's age or place of residence. Age groups where inequality has been increasing and areas with a significantly higher than expected incidence of invasive cervical cancer represent opportunities to target early detection initiatives.

Most of cervical cancer cases may be detected with screening. Timely access to preventive services facilitates the detection of this neoplasm in early stages. Nevertheless, in general, low-income women have higher detection rates in late stages (12). In the United States, similar to what happens in Costa Rica and other countries; incidence has significantly decreased since the introduction of Papanicolaou screening. Nonetheless, even with the existence of screening, disparities in the incidence of cervical cancer persist in the US (50) as well as in other populations such as Costa Rica where a universal healthcare system is in place.

Cancer control and prevention are key to decrease inequality (51, 52). Response to cervical cancer can be divided into primary and secondary care. Focused on prevention, vaccination constitutes an advisable primary care strategy. Over the years, the use of the HPV vaccine has demonstrated to be an effective way to prevent cervical cancer. Including the HPV vaccine in the vaccination scheme has been previously suggested as a mean to improve the effectiveness of the Cervical Cancer Prevention Program in Costa Rica (45). Although the HPV vaccine is not yet available for the entire population in Costa Rica, it has recently been approved to be included in the social security system's vaccination scheme starting in 2019 in 10-year-old girls.

Secondary care is based on two elements, early diagnosis, and screening. Improving detection and offering opportune treatment of diagnosed cases are necessary conditions to alleviate the cervical cancer burden. Differences in Pap screening procedures among regions within the country and long waiting times between sampling and availability of laboratory results have been previously described as critical points in the Cervical Cancer Prevention Program in Costa Rica (53). Since the 1990s, human papillomavirus HPV-DNA testing has been proposed for the detection of cervical cancer precursors, either as a complement or as an alternative method to Pap smear. Epidemiological studies in Costa Rica and other developing countries have evidenced the effectiveness of HPV-DNA testing (54–56). [Quirós (45)] has suggested the inclusion of HPV-DNA testing in the Cervical Cancer Prevention Program in Costa Rica, which may be of special interest in the context described in this study.

Once inequality exists, it can only decrease if actions are taken toward such purpose. Policy aimed at specifically diminishing inequality in cervical cancer incidence is warranted. Results from this study identify regions of the country where actions may be focused in order to reduce gaps in women's health. Populations in the coast and border regions of the country should be prioritized. Integrated and inter-institutional approaches to education and health promotion are recommended. Strategies to promote an adequate use of screening with priority among women aged 50 to 59 years should be established in Costa Rica.

## AUTHOR CONTRIBUTIONS

CS-U: Study design, data analysis, manuscript writing; CV-M: Manuscript writing.

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# Global Cancer Inequalities

*Miranda M. Fidler* and Freddie Bray*

*Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France*

Social inequalities in cancer are increasingly relevant to research, implementation science, and policy. In this brief perspective we provide an overview of global cancer inequalities by assessing different outcomes according to the Human Development Index (HDI); the HDI is a United Nations Development Programme composite indicator including the following measures: (i) access to education (based on mean and expected years of schooling), (ii) a long and healthy life (based on life expectancy), and (iii) a decent standard of living (based on gross national income per capita). We additionally touch upon the importance of prevention, access to oncological services, and the need to monitor progress in reducing and avoiding inequalities at subnational, national, world region, and global levels.

**Keywords: social inequalities, cancer, global, incidence, mortality, DALYs**

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*Friederike Erdmann,*
*Danish Cancer Society, Denmark*

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*Bárbara Peleteiro,*
*Universidade do Porto, Portugal*
*Alireza Sadjadi,*
*Tehran University of Medical Sciences, Iran*
*Kjetil Søreide,*
*University of Bergen, Norway*

****Correspondence:***
*Miranda M. Fidler*
*fidlerm@fellows.iarc.fr*

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Although social inequalities are well documented in cancer at macro and micro levels (1), their strong and persistent presence across the cancer continuum is increasingly relevant to research, implementation science, and policy. Cancer disparities research has moved beyond macroeconomic analyses involving comparative assessments of socioeconomic status or national income to investigate the multiple determinants of social inequality, exemplified through the assessment of demographic factors, including gender, age, race and ethnicity, and indigenous status. The enquiry as to how the global cancer burden (incidence, mortality, survival, disability-adjusted life years) is impacted by inequalities in socioeconomic development has moved on too. The exploration of the scale and profile of cancer, once set against the time-honored dichotomy of populations being "developing" or "developed," has been superseded by the four-tier Human Development Index (HDI) (2), a broad marker of inequality and cancer transition between countries (3, 4).

The HDI asserts that an assessment of development is not just about economic growth but rather how national policies impact on human choices. The indicator is a composite measure incorporating (i) access to education (based on mean and expected years of schooling), (ii) a long and healthy life (based on life expectancy), and (iii) a decent standard of living (based on gross national income per capita) (2). It is commonly presented, as it is here, according to United Nations Development Programme's pre-defined cut-points representing four tiers of the HDI (from low HDI, e.g., nations with lowest human development values, through to medium, high, and very high, e.g., those with highest human development values).

Using this criterion, a strong correlation between the magnitude of the overall cancer incidence and the corresponding HDI level can be observed, with the overall cancer rates broadly increasing with level of human development (4). When assessed by specific cancers, positive relationships between the HDI level and incidence rate in 2012 were observed in both sexes for the following cancers: brain/nervous system, colorectum, gallbladder, kidney, leukemia, lung, multiple myeloma, pancreas, and thyroid; a positive relationship was also observed for bladder, lip/oral cavity, other pharyngeal, and testicular cancers, Hodgkin lymphoma, and melanoma in males, and breast, corpus uteri, and ovarian cancers and non-Hodgkin lymphoma in females (4). A negative association

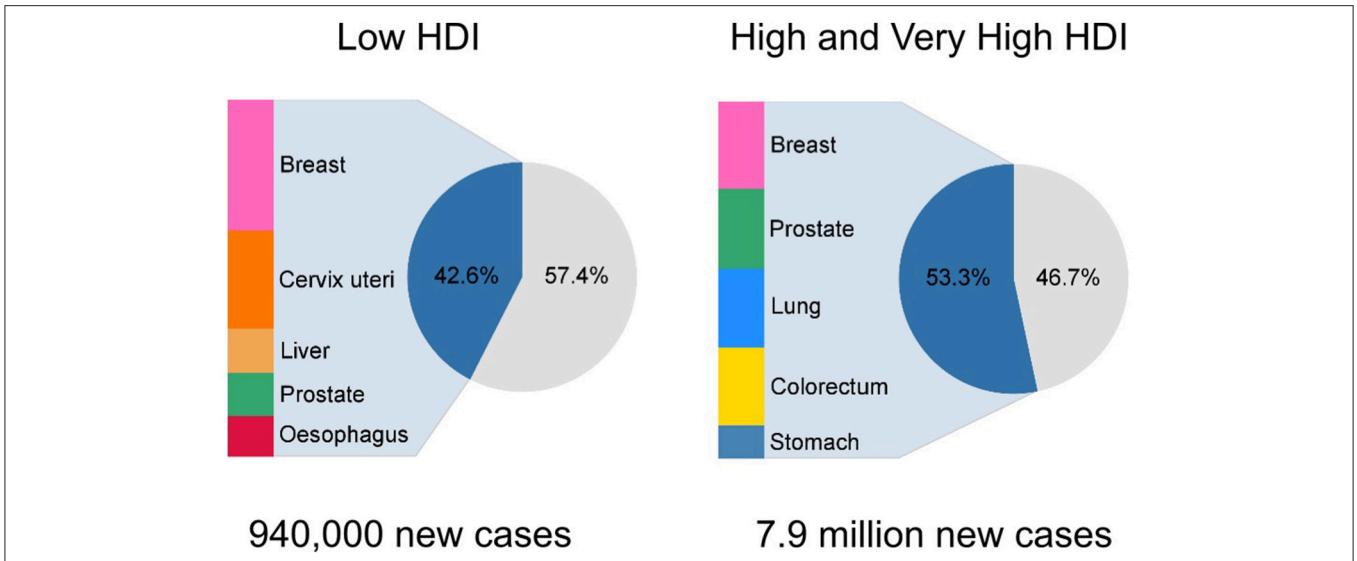


**FIGURE 1 |** Number of new incidence cases and proportion of top five cancers in for the low Human Development Index (HDI) and high/very high HDI level as estimated in GLOBOCAN 2012.

between the HDI level and incidence rate was observed for cervical and other pharyngeal cancers and Kaposi sarcoma in females (4).

In terms of cancer profiles, the distribution of common cancers is quite different by HDI level, with infection- and poverty-related cancers (e.g., cervical and liver cancer) still dominating in low HDI nations, in contrast to high and very high HDI countries, where prostate, breast, colorectal, and lung are the major cancers (**Figure 1**). An increased burden of infection-related cancers with lower HDI is highlighted when one examines the population fractions of cancers attributable to infectious agents, which were estimated to be 25, 22, 13, and 8% in low, medium, high, and very high HDI countries, respectively, in 2012 (5).

Other inequalities in the global cancer burden have also been noted when assessed by the HDI, including mortality (6), disability-adjusted life years (7), and relative gains in life expectancy (8). An important additional marker of cancer inequality pertains to HDI stratifications of the future cancer incidence burden, which reveals that the number of new cancer cases in future years will be proportionally greatest in lower HDI settings (**Figure 2**), with low and medium HDI countries projected to see a 112 and 86% respective increase in their incidence burden from 2012 to 2035. Hence the nations currently least equipped to deal with a pending increase in the number of cancer patients year-on-year will be most impacted.

Such inequalities can only be expected to widen unless resource-dependant, effective, and cost-effective interventions are urgently implemented (9, 10). In particular, vaccination will be a key preventive strategy in low HDI settings given the high burden of infection-related cancers (5). Among the most important infections associated with cancer are hepatitis B virus and human papillomavirus, both of which have highly effective vaccines to prevent liver cancer and cervical, anal, vulvar, vaginal, and penial cancers, respectively (11). Tobacco control is another main priority for cancer control in transitioning countries given the number of smokers is projected to increase in these countries (12, 13). Finally, as social and economic transition increases the prevalence of sedentary jobs, urban living, and high caloric intake, an opportunity for prevention exists for less developed countries to avoid known adverse lifestyle risk factors like obesity, low physical activity, and higher alcohol intake, which cause many of the cancers commonly seen in the most developed countries.

With a growing cancer burden, access to appropriate, affordable, and equitable treatment will also be crucial in lower HDI settings, especially as the current availability of essential cancer medicines (14), cancer surgery (15), and radiotherapy facilities (16) is sparse. Preventing exposures to risk factors, early detection, effective treatment, and palliative care requires support and resources, however. More broadly, governments from around the world adopted a Cancer Resolution at the World Health Assembly in 2017, building on the United Nations Sustainable Development Goals 2030 (SDG), and the SDG 3.4 target of a reduction of the premature mortality from non-communicable diseases by one-third by 2030. Prevention and early detection are given prominence in the Resolution, with an emphasis on tobacco control policies within the World Health Organization Framework Convention on Tobacco Control, as well as affordable and feasible vaccine and screening programs. Furthermore, measuring the cancer burden to inform planning, through the development of population-based cancer registries, is also given central importance.

In summary, the HDI provides a useful framework to map out the continuing transitions in cancer globally, and highlights the clear reality of increasing inequalities in countries

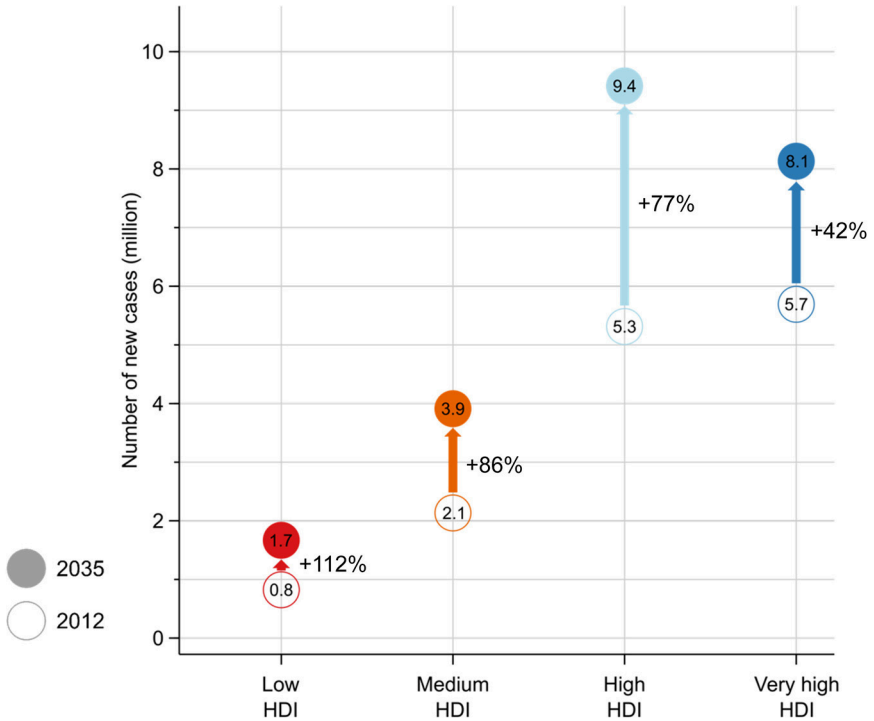


**FIGURE 2 |** Number of estimated new cancer cases in 2012 and 2035 by the four-tier Human Development Index (HDI), with the proportional increase (%) in the number of cases indicated.

presently indexed at lower levels of the HDI. That said, there remains a need for an integration of social indicators in cancer research across the continuum, as well as the use of innovative methodologies, in order to monitor progress in reducing and avoiding inequalities at subnational, national, world region, and global levels. This is exemplified by the fact that governments have acknowledged the presence of social inequalities in cancer in the Cancer Resolution, which notes that "…certain population groups experience inequalities in risk factor exposure and in access to screening, early diagnosis and timely and appropriate treatment, and that they also experience poorer outcomes for cancer," and recommends including measurements of inequalities in the collection of high-quality population-based incidence and mortality data on cancer.

As cancer is emerging as the leading cause of premature death, given ongoing displacements of deaths from infection and parasitic diseases in the lower HDI spectrum and cardiovascular diseases in decline at the higher end (8), the development and implementation of operational cancer control plans that include feasible, affordable, and sustainable interventions is now imperative worldwide, and most markedly in countries undergoing major social and economic transition. Such efforts can therefore be seen not only as an effort to reduce the widening gaps in cancer inequality, but also as a means to decrease inequalities across the spectrum of causes.

## DATA SOURCE AVAILABILITY

GLOBOCAN 2012 data is freely available for download at http://globocan.iarc.fr/Default.aspx. Human Development Index data is freely available for download at http://hdr.undp.org/en/data.

## AUTHOR CONTRIBUTIONS

MF drafted the article, FB revised the article, MF and FB agreed to submission.

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# Disadvantageous Socioeconomic Position at Specific Life Periods May Contribute to Prostate Cancer Risk and Aggressiveness

*Sreenath Madathil*[1,2†], *Christine Blaser*[1,2†], *Belinda Nicolau*[2], *Hugues Richard*[1] and *Marie-Élise Parent*[1,3*]

[1] Epidemiology and Biostatistics Unit, INRS-Institut Armand-Frappier, Université du Québec, Laval, QC, Canada, [2] Division of Oral Health and Society, Faculty of Dentistry, McGill University, Montreal, QC, Canada, [3] School of Public Health, Université de Montréal, Montreal, QC, Canada

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**Edited by:**
*Dana Hashim,*
*Cancer Registry of Norway, Norway*

**Reviewed by:**
*Jianguang Ji,*
*Lund University, Sweden*
*Alessandro Giuliani,*
*Istituto Superiore di Sanità (ISS), Italy*
*Jerry Polesel,*
*Centro di Riferimento Oncologico di Aviano (IRCCS), Italy*

***Correspondence:**
*Marie-Élise Parent*
*marie-elise.parent@iaf.inrs.ca*

[†] *These authors have contributed equally to this work*

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**Background:** Previous studies on socioeconomic position (SEP) and risk of prostate cancer (PCa) have produced contradictory results. Most measured SEP only once during the individuals' life span. The aim of the study was to identify life course models that describe best the relationship between SEP measured during childhood/adolescence, early- and late-adulthood, and risk of PCa overall as well as according to tumor aggressiveness at diagnosis.

**Methods:** We used data from a population-based case-control study of PCa conducted in the predominantly French-speaking population in Montreal, Canada. Cases ($n = 1{,}930$) with new, histologically-confirmed PCa were ascertained across hospitals deserving the French-speaking population in 2005–2009. Controls ($n = 1{,}991$), selected from Quebec's list of French-speaking electors, were frequency-matched to cases (±5 years). In-person interviews collected information on socio-demographic and lifestyle characteristics, and a complete occupational history. Measures of SEP during childhood/adolescence included parents' ownership of a car and father's longest occupation, while the subject's first and longest occupations were used to indicate early- and late-adulthood SEP, respectively. We used the Bayesian relevant life course exposure model to investigate the relationship between lifelong SEP and PCa risk.

**Results:** Cumulative exposure to disadvantageous SEP was associated with about a 50% increase in odds of developing PCa. Late-adulthood SEP was identified as a sensitive period for aggressive PCa. Childhood/adolescence SEP based on parents' ownership of a car was associated with non-aggressive PCa. Associations were independent from PCa screening.

**Conclusion:** Disadvantageous SEP over the life course was associated with higher PCa incidence, with consistent evidence of sensitive time periods for cancer aggressiveness. The mechanisms through which disadvantageous SEP relates to PCa risk need to be further elucidated.

**Keywords: life course, prostate cancer, socioeconomic position, childhood, adolescence, occupation, Bayesian relevant life course exposure model**

## INTRODUCTION

In Canada, one out of five newly detected cancers in 2017 were prostate cancers (PCa), making these the most common solid-tumor cancer among men (1). It was also the third cause of male cancer-related deaths. A few non-modifiable risk factors such as age, family history of PCa, and ancestry have been established (2). Regarding the latter, data from the United-States indicate striking racial/ethnic differences in PCa incidence and mortality rates (3) with American Asian/Pacific Islanders having the lowest incidence of PCa, followed by whites and African-Americans who experience the highest burden of the disease (4). These racial/ethnic disparities are not well-understood, but it is believed that they result from the interplay between biological, environmental, and social risk factors in cancer initiation (5, 6).

Socioeconomic position (SEP) (7) represents an umbrella of factors that may collectively influence the burden of PCa, including behavioral and environmental risk factors as well as access to health care (e.g., cancer screening). There is mounting evidence that a favorable SEP is associated with better PCa survival (8–10). However, the relationship between SEP and PCa incidence is much less clear, with studies documenting positive, negative, or no associations (11–24), even when the timing of introduction of the prostate specific antigen (PSA) test is taken onto account. These inconsistencies might be explained by the fact that most of the work investigating this association assessed SEP only once during the individual's life span usually in adult life, potentially overlooking other relevant exposure periods.

Studies of the developmental origins of adult health and disease have produced evidence highlighting the importance of prenatal and infant life (25). They led to the understanding that exposure to insults during rapid organ system development is critical to adult health. The prostate gland is essentially dormant until puberty, when a complex interaction between sex and other growth hormones induces rapid development (26, 27). Studies examining pre-adult exposures and risk of PCa remain rare (28).

Life course epidemiology (29) offers a framework to further our understanding of the long term effects of SEP on PCa risk. The theory can be operationalized under three main models: (i) accumulation, in which exposures throughout life are equally important and their effects accumulate over time; (ii) critical period, in which exposures during a specific period in life lead to irreversible effects regardless of exposures in other periods; and (iii) sensitive period, in which exposure during one or more periods have a higher effect compared to the others.

Important insights into PCa etiology may be gained by identifying which life course model describes best the role of SEP in cancer risk. For example, adolescence is a time of rapid and profound change in hormone levels and in body composition, entailing the development of secondary sexual characteristics and achievement of fertility (30). It is possible that early-life SEP shapes the environment during this important developmental window of vulnerability, increasing the risk of PCa.

Moreover, exposures in specific periods may be hypothesized to affect tumor aggressiveness. Aggressive and non-aggressive PCa appear to have different sets of anthropometric (31), lifestyle (32) and occupational (33) risk factors, supporting the notion that their etiology might be under distinct influences. Recent observations also indicate that grade is established early in prostate tumor pathogenesis (34). This raises the possibility that aggressive cancers represent a specific etiological entity, possibly developing under exogenous influences that operate at a specific time over the life course.

In this paper, we identify the life course models that describe best the relationship between life course SEP measured during childhood/adolescence, early- and late-adulthood and the risk of incident PCa overall as well as according to tumor aggressiveness at diagnosis.

## MATERIALS AND METHODS

### Study Population and Data Collection

#### Study Population

The Prostate Cancer & Environment Study (PROtEuS), set in Montreal, Canada, has been described previously (32, 35). In order to ensure comprehensive population coverage at recruitment and comply with institutional regulations, the study base was restricted to men who referred or would be expected to refer to a French hospital for a PCa diagnosis. This represents the vast majority of Montreal residents, as more than 75% of them speak French at home (36). Cases ($n$ = 1,930), aged $\leq$75 years, newly diagnosed with histologically-confirmed PCa (ICD-10, code C61), were identified from pathology departments across seven French hospitals between September 1, 2005 and December 31, 2009. Comparison with the provincial tumor registry indicates that these represented over 80% of all incident PCa cases in the area. Control subjects ($n$ = 1,991) were recruited concurrently from Quebec's continually updated electoral list of French-speaking individuals. The electoral list is considered to include nearly all Canadian citizens living in Quebec. Controls were randomly selected from an area comprising 39 electoral districts, corresponding to those of the cases, and frequency-matched by 5-year age groups. Participation rates among cases and controls were 79 and 56%, respectively. Reasons for non-participation, among cases and controls, were refusal (94 and 86%, respectively), unable to trace (3 and 11%), death with no proxy available (2 and 1%), language barrier (1 and 1%) or too sick to participate (1% of controls). Ethics committees of all participating hospitals approved the study. All participants provided written informed consent.

#### Data Collection

As part of in-person interviews, specially trained interviewers collected data on a wide range of exposures including socio-demographic characteristics, lifestyle (physical activity level, smoking, alcohol consumption, body mass index, etc.) and a detailed occupational history for all jobs held throughout the lifetime. Gleason scores were extracted from pathology reports.

#### Measurement of Life Course SEP

Three periods in life were considered to compile the SEP variables from collected data: childhood/adolescence, early-adulthood (first entry into job market) and late-adulthood.

Childhood/adolescence SEP was assessed using two different indices. The first consisted of participants' report of parents' ownership of a car (yes/no) when they were younger than 16 years old. Those who did not have car access were assigned a disadvantageous SEP (coded 1), while others were classified in the advantageous SEP category (coded 0). The second index used was the longest occupation held by the participant's father, which was coded according to the 1988 International Standard Classification of Occupations (37), then assigned a binary SEP level (described below).

SEP during early- and late-adulthood periods were assessed using the first and longest occupation held by the participant, respectively. Careful evaluation of job descriptions and additional information about employment was conducted to assign a job title to each occupation lasting 1 year or more. Occupations were coded according to the four-digit 1988 International Standard Classification of Occupations (37). These codes were collapsed into 10 categories of increasingly disadvantageous SEP according to the European Socioeconomic Classification (ESeC) (38). We used the dichotomized version of advantageous /disadvantageous SEP in our analyses where "lower services" (category 8), "lower technical"( category 9) and "routine" (category 10) were grouped as disadvantageous SEP (coded 1) while categories 1–7 fell into the advantageous SEP (coded 0) group.

## Statistical Analyses

### Study Sample

There were 3,921 subjects (1,930 cases and 1,991 controls) available for analyses. However, some of these were excluded owing to missing values for some of the SEP indicators, i.e., 20 (0.5%) for parent's car ownership and 133 (3%) for the fathers' longest occupation. Missing values for covariates (ranging from 0 to 2.9%) were assigned to a missing indicator category.

### Bayesian Model for Life Course Investigation

We recently proposed a Bayesian relevant life course exposure model (BRLM) to identify periods of life in which exposure have the highest impact on the outcome (39). Although we used continuous exposures to demonstrate the technique, it can be used for binary exposures. Briefly, the model assumes weights for exposures occurring at different periods of life and an overall effect for the lifetime exposure. Thus, it allows exposures to contribute differently to the disease process depending on the life period when it happened and also allows the accumulation of these effects temporally. The values estimated for the weights jointly provide information on the life course hypothesis supported by the data. For three life periods, as in our study, the joint distribution of estimates can be visualized using a ternary plot (**Figure 1A**). The vertices represent critical period hypotheses and the central point represents the accumulation hypothesis. Distributions with higher densities at areas not close to these points represent the sensitive period hypothesis. Each side in the ternary plot represents the weights corresponding to one life period.

The joint posterior distribution of weights needs to be interpreted together with the overall effect. The weights represent the relative importance of being in a disadvantageous SEP during different life periods and provide information on the life course hypothesis supported by the data. The overall effect represents the effect of being in a disadvantageous compared to advantageous SEP during all life periods. This effect is equivalent to the maximum accumulated effect of SEP over the life course. An alternative way of inference is to compute period specific effects. These estimates represent the time dependent association between the exposure and outcome. The period specific estimates are combination of overall effect and relative weights estimated from the BRLM.

We used the BRLM, with unconditional logistic regression likelihood, to identify the period (childhood/adolescence, early-adulthood, and late-adulthood) during participants' lives that is most sensitive to disadvantageous SEP exposure in relation to the risk PCa later in life.

The BRLM provides the opportunity to transparently include prior beliefs about life course hypotheses in the analysis. However, in case of little or no prior evidence in the field, a non-informative prior can be used to allow the data to drive the results; such a prior will give equal weak support to all life course hypotheses. We used a non-informative Dirichlet (1, 1, 1) prior for the weights (**Figure 1B**) and a weakly informative student_t (3,0,2.5) prior for other regression parameters. Mean and 95% credible intervals (95%Crl) for weights and odds ratios (OR) for the overall effect were computed from their corresponding posterior distributions.

PCa screening is a strong determinant of cancer diagnosis. Inclusion of latent, undetected PCa in the control series would lead to an attenuation of risk estimates. Moreover, screening can be related to SEP, thereby confounding associations. In order to rule out the role of screening practices, we restricted the analyses to participants who were screened at least once for PCa in the previous 2 years.

Further, to investigate the association between disadvantageous SEP and PCa aggressiveness, we conducted analyses stratifying the cases according to cancer grade. Tumors with Gleason scores $<7$ were defined as non-aggressive, while scores $\geq 7$ designated aggressive tumors (40).

Main analyses were adjusted for age (continuous), ancestry (categorical) and family history of PCa (yes, no), cigarette smoking (ever, never), alcohol consumption (drink-years), physical activity (not very active, moderately active, very active), and body mass index (BMI) 2 years prior to the diagnosis or interview (continuous).

### Sensitivity Analyses

We conducted a series of sensitivity analyses to explore different dimensions of our findings. We refit all our models replacing the variable on parental car ownership by the longest occupation held by the father of the participant. In addition to being a common measure of SEP during childhood and adolescence, the use of this occupational variable standardizes the indicator of SEP across the life course.

To assess the impact of restricting participants to men who were recently screened, we conducted a sensitivity analysis including all participants regardless of their screening status. Further, to assess the influence of lifestyle factors on the

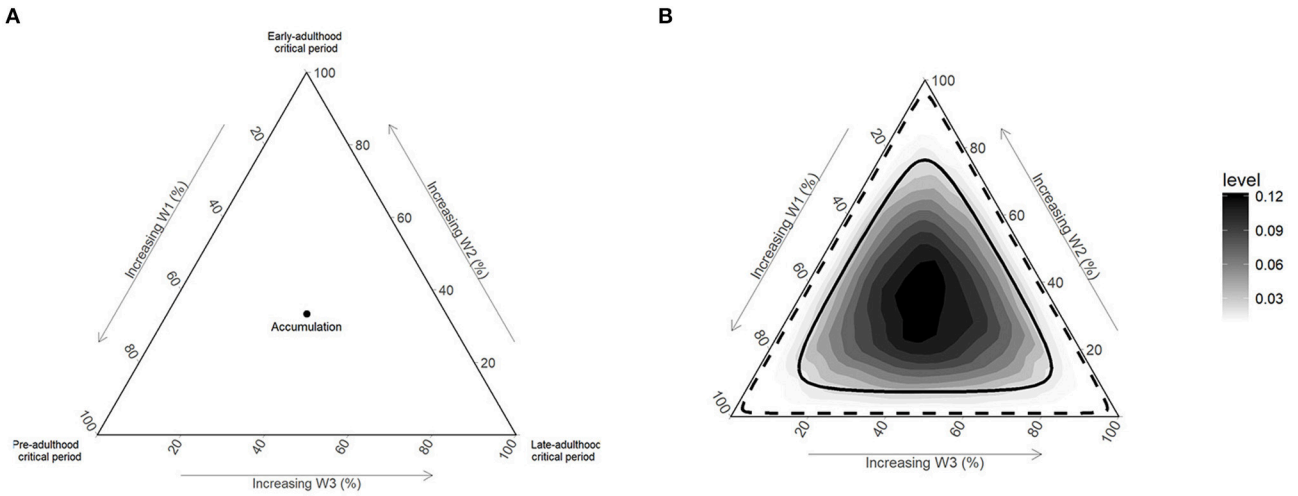


**FIGURE 1 |** Illustration of life course hypotheses and non-informative prior distribution on ternary plots. **(A)** Vertices of ternary plot represents critical period hypotheses, center points represent the accumulation hypothesis and other point in the plot represent sensitive period hypothesis; **(B)** Dirichlet (1, 1, 1) prior with 50% (solid line) and 95% (dashed line) credible intervals.

association between SEP and PCa, we compared the results from the full model used in the main analyses with those from a reduced model in which only age, ancestry, and family history of PCa were considered as potential confounders.

All analyses were performed using the R package to fit Bayesian models using Stan (41, 42).

## RESULTS

Selected characteristics of the 1,930 cases and 1,991 controls are presented in **Table 1**. Controls were about 1 year older, on average, than cases, reflecting the slightly longer time needed to recruit controls. As expected, cases presented a significantly higher proportion of first-degree family members with PCa, had a higher proportion of participants of African ancestry, and a lower proportion of Asians than controls. No major differences between the groups were observed in relation to cumulative use of alcohol and smoking status as well as physical activity levels. Nearly all cases and 76% of controls had been screened in the 2 years prior to diagnosis/interview. The Gleason score was missing for three participants. The proportion of participants with at least one first-degree relative with PCa was higher among non-aggressive cases compared to aggressive ones.

Being in a disadvantageous compared to an advantageous SEP during all three periods (childhood/adolescence, early adulthood, and late adulthood) increased the odds for overall PCa by 49% (OR = 1.49; 95%CrI = 1.20–1.83) (**Table 2** and **Figure 2A**). There was evidence for a sensitive period of exposure to disadvantageous SEP in early life (childhood/adolescence period) for the risk of PCa (posterior probability 83.7%). Disadvantageous SEP in childhood/adolescence increased the odds of PCa by 26% (OR = 1.26; 95%CrI = 1.06–1.48) (**Supplementary Table 1**).

When we conducted analyses stratifying by PCa aggressiveness, we observed a similar pattern of association for non-aggressive PCa. Being in a disadvantageous compared to an advantageous SEP during all three periods increased the odds for PCa by 48% (OR = 1.48; 95%CrI = 1.17–1.84) (**Table 2** and **Figure 2B**). Also, there was evidence for a sensitive period early in life in the relationship between disadvantageous SEP and non-aggressive PCa (posterior probability 95.9%). Being in a disadvantageous SEP during childhood/adolescence increased the odds of PCa by 32% (OR = 1.32; 95%CrI = 1.08–1.58) (**Supplementary Table 1**).

Although disadvantageous SEP during all three life periods increased the odds of aggressive PCa by 52% (OR = 1.52; 95%CrI = 1.11–2.04), results support a sensitive period in late adulthood (posterior probability 79.6%) (**Table 2** and **Figure 2C**). Being in a disadvantageous SEP during late adulthood increased the odds of aggressive PCa by 28% (OR = 1.28 95%CrI = 1.02–1.63) (**Supplementary Table 1**).

Results from our sensitivity analysis replacing the childhood/adolescence SEP indicator parental car ownership by the father's longest occupation are presented in the **Supplementary Tables 2**, **3** and **Supplementary Figures 1A–C**. Although the overall direction of associations was similar, point estimates were attenuated when using the father's occupation, especially for non-aggressive PCa (**Supplementary Table 2**). Furthermore, the joint posterior distribution of weights for non-aggressive PCa showed no considerable difference from the non-informative prior distribution (**Figure 1B**, **Supplementary Figure 1B**), indicating a lack of information in the data to disentangle the life course hypotheses when using the father's occupation.

Including lifestyle covariates in our models tended to attenuate associations, but only marginally.

The results of sensitivity analyses including all participants regardless of screening for PCa showed agreement with main results for the direction of association, with weaker risk estimates.

**TABLE 1 |** Selected characteristics of study participants.

| | Controls | Cases[a] | | |
|---|---|---|---|---|
| | (*n* = 1,991) | All cancers (*n* = 1,930) | Non-aggressive cancers (*n* = 1,376) | Aggressive cancers (*n* = 532) |
| **Age (Mean ± SD)** | 64.84 ± 6.88 | 63.56 ± 6.80 | 63.17 ± 6.83 | 64.61 ± 6.61 |
| **Ancestry, *n* (%)** | | | | |
| African | 87 (4.4) | 126 (6.5) | 95 (6.8) | 31 (5.8) |
| Asian | 67 (3.4) | 22 (1.1) | 14 (1.0) | 8 (1.5) |
| European | 1,649 (82.8) | 1,654 (85.7) | 1,196 (85.9) | 455 (85.0) |
| Other | 174 (8.7) | 116 (6.0) | 80 (5.7) | 36 (6.7) |
| Do not know | 14 (0.7) | 12 (0.6) | 7 (0.5) | 5 (0.9) |
| **Timing of last prostate cancer screening, *n* (%)** | | | | |
| Never | 191 (9.6) | 3 (0.2) | 2 (0.1) | 1 (0.2) |
| Within last 2 years | 1,509 (75.8) | 1,910 (99.0) | 1,375 (98.8) | 532 (99.4) |
| More than 2 years ago | 234 (11.8) | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| Do not know | 57 (2.9) | 16 (0.8) | 14 (1.0) | 2 (0.4) |
| **Cigarette smoking, *n* (%)** | | | | |
| Never | 514 (25.8) | 515 (26.7) | 386 (27.7) | 129 (24.1) |
| Ever | 1,476 (74.1) | 1,414 (73.3) | 1,006 (72.3) | 405 (75.7) |
| Do not know | 1 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.2) |
| **Alcohol use, *n* (%)** | | | | |
| Never | 231 (11.6) | 210 (10.9) | 154 (11.1) | 56 (10.5) |
| Ever | 1759 (88.3) | 1718 (89.0) | 1237 (88.9) | 478 (89.3) |
| Do not know | 1 (0.1) | 2 (0.1) | 1 (0.1) | 1 (0.2) |
| **Physical activity, *n* (%)** | | | | |
| Not very active | 486 (24.4) | 435 (22.5) | 327 (23.5) | 107 (20.0) |
| Moderately active | 558 (28.0) | 524 (27.2) | 383 (27.5) | 140 (26.2) |
| Very active | 946 (47.5) | 971 (50.3) | 682 (49.0) | 288 (53.8) |
| Do not know | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| BMI (Mean ± SD) | 27.18± 4.43 | 26.75 ± 4.01 | 26.72 ± 3.92 | 26.83 ± 4.24 |
| **First-degree family history of prostate cancer, *n* (%)** | | | | |
| No | 1,737 (87.2) | 1,414 (73.3) | 1,002 (72.0) | 411 (76.8) |
| Yes | 198 (9.9) | 450 (23.3) | 344 (24.7) | 105 (19.6) |
| Do not know | 56 (2.8) | 66 (3.4) | 46 (3.3) | 19 (3.6) |

[a] *Low-grade (Gleason <7) defined as non-aggressive cancer; high-grade (Gleason ≥7) defined as aggressive cancer.*

However, given the wide credible intervals, the results are inconclusive (**Supplementary Tables 2**, **3**).

All other sensitivity analyses showed no considerable differences in direction or point estimate for the association compared to the main analyses.

## DISCUSSION

To the best of our knowledge, this is the first large case-control study applying the life course epidemiology framework to investigate the association between life course SEP and risk of PCa.

We observed a positive association between disadvantageous SEP when considering together childhood/adolescence, early- and -late adulthood, and PCa. The overall effect of disadvantageous SEP showed a ≈50% increase in odds of the disease. The estimates demonstrated the cumulative nature of the effects; the trajectory with disadvantageous SEP during all three periods showed the strongest association with risk of PCa. In addition, we consistently identified the late-adulthood period as sensitive for aggressive PCa, independently from screening. Childhood/adolescence SEP was related to risk of non-aggressive PCa when using parental car ownership as indicator.

Previous studies have shown contradictory results on the association between adult SEP and incident PCa. Positive associations (10–14, 18, 19, 21), inverse associations (15, 20, 22, 24) or no association (23) have indeed been observed. Inconsistent results have also been reported across studies that considered the period of introduction of PSA testing (7, 43–46). Potential reasons behind these inconsistencies may relate to the assessment of SEP only once during the life course or to the use of different indicator variables for SEP.

There is no single best indicator of SEP suitable for all study aims and applicable at all-time points in all settings (7,

**TABLE 2 |** Association between a disadvantageous socioeconomic position and prostate cancer risk.

| | Controls *n* (%) | Cases *n* (%) | OR (95% CrI)[a] | Mean weight (95% CrI) |
|---|---|---|---|---|
| **Any type of PCa** | **(*n* = 1,438)** | **(*n* = 1,773)** | | |
| **Overall effects** | | | 1.49 (1.20 - 1.83) | |
| **Weights[b]** | | | | |
| Childhood & adolescence (w1) | 677 (47.1) | 845 (47.7) | | 0.59 (0.25–0.87) |
| Early Adulthood (w2) | 839 (58.3) | 1064 (60.0) | | 0.12 (0.00–0.37) |
| Late Adulthood (w3) | 657 (45.7) | 876 (49.4) | | 0.29 (0.03–0.63) |
| Posterior probability for an early-life sensitive period hypothesis (w1 > w2 & w3) = 83.7% | | | | |
| **Non-aggressive PCa** | **(*n* = 1,438)** | **(*n* = 1,282)** | | |
| **Overall effects** | | | 1.48 (1.17 - 1.84) | |
| **Weights** | | | | |
| Childhood & adolescence (w1) | 677 (47.1) | 612 (47.7) | | 0.71 (0.38–0.94) |
| Early Adulthood (w2) | 839 (58.3) | 750 (58.5) | | 0.12 (0.01–0.36) |
| Late Adulthood (w3) | 657 (45.7) | 604 (47.1) | | 0.17 (0.01–0.47) |
| Posterior probability for an early-life sensitive period hypothesis (w1 > w2 & w3) = 95.9% | | | | |
| **Aggressive PCa** | **(*n* = 1,438)** | **(*n* = 489)** | | |
| **Overall effects** | | | 1.52 (1.11 - 2.04) | |
| **Weights** | | | | |
| Childhood & adolescence (w1) | 677 (47.1) | 232 (47.4) | | 0.22 (0.01–0.59) |
| Early Adulthood (w2) | 839 (58.3) | 312 (63.8) | | 0.20 (0.01–0.60) |
| Late Adulthood (w3) | 657 (45.7) | 271 (55.4) | | 0.58 (0.12–0.92) |
| Posterior probability for a late-life sensitive period hypothesis (w3 > w1 & w2) = 79.6% | | | | |

[a] *OR, Odds ratio; CrI, Credible interval. Model adjusted for age, ancestry, family history of PCa, body mass index, physical activity, cigarette smoking and alcohol drinking.*
[b] *w1, weight 1; w2, weight 2; w3, weight 3. Weight 1 (childhood & adolescence) based on parents' ownership of a car, weight 2 (early adulthood) based on first occupation, weight 3 (late adulthood) based on longest occupation.*
*n, Number of study subjects.*

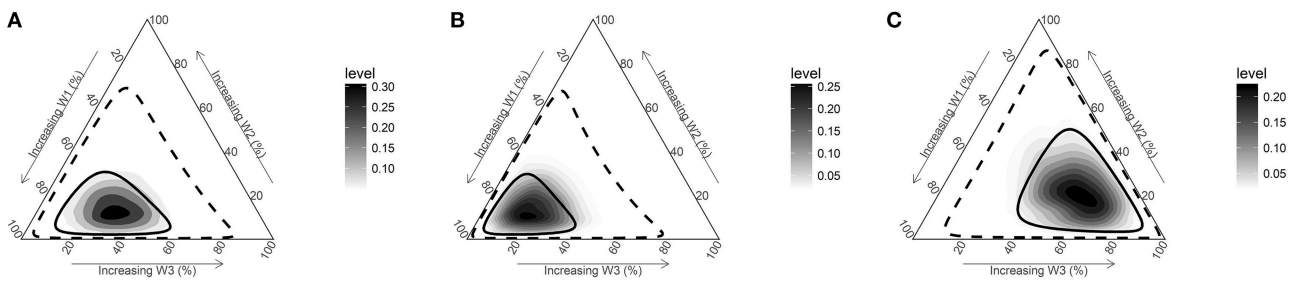


**FIGURE 2 |** Posterior joint distribution of weights (w) estimated for three periods (childhood & adolescence based on parents' ownership of a car [w1], early adulthood [w2], late adulthood [w3]). **(A)** All PCa cases vs. control. **(B)** Non-aggressive PCa cases (Gleason <7) vs. controls. **(C)** Aggressive PCa cases (Gleason≥7) vs. controls. Solid and dashed line represents 50% and 95% credible intervals and darker areas represent higher posterior densities.

47). Each indicator measures different, often related aspects of socioeconomic stratification. For childhood/adolescence SEP, we performed a sensitivity analysis using two indicators, namely parents' ownership of a car and the father's longest occupation. While the latter is one of the most widely used SEP indicator for early life (43), car ownership, a marker of material living standards (7, 37), has been shown to be a useful indicator of childhood SEP in older adults in contemporary developed country populations (7, 44, 45). The indices we used were weakly correlated with one another, further suggesting that these may measure different constructs of SEP (**Supplementary Table 4**). One reason that might also explain the difference in our findings when using different SEP indicators during childhood/adolescence is measurement error. More subjects could not report their father's occupation, as compared to parental car ownership, potentially reflecting greater recall issues and thus measurement error.

In our study, when we replaced the indicator variable parents' ownership of a car for the father's longest occupation, results became largely inconclusive. Interestingly, a life course investigation on SEP and nine cancer types using data from a study conducted in Montreal also supports early life as sensitive period for PCa (any type), this time using the father's main occupation (48). However, the multi-site study was conducted

approximately 25 years before PROtEuS, which may indicate that car ownership is a more sensitive measure of SEP in the more recent era, when the current study was conducted.

We elected to use the subjects' occupations from the lifetime work histories as indicators of early and late-adulthood SEP (7). A major focus of our main study is to evaluate the role of occupational exposures in PCa. To this end, we collected a detailed description of all jobs held over the lifetime, which is something other studies rarely have. This is important in the context of evaluating SEP at specific time periods such as here. With increasing interest in the role of SEP across the life course, other studies have used individuals' occupations at different stages in adult life (46). We used the first occupation to represent SEP in early adulthood, and the longest occupation to represent late-adulthood SEP. This choice was motivated by the mean age at the beginning and end of these jobs. In our data, the mean age of participants at beginning of their first job was 20 $\pm$ 4 years and at end of first job it was 27 $\pm$ 11 years (mean duration = 8 $\pm$ 10 years). Corresponding values for the longest job were 33 $\pm$ 10 years and 55 $\pm$ 10 years (mean duration = 22 $\pm$ 9 years), respectively. The correlation between the two occupations used was moderate, at 0.55, indicating that only about 30% of the variance in SEP based on one occupation explained the variation in the other. This provided us with the ability to assign SEP at the two time points of interest.

Studies observing increased risk among advantageous SEP groups attributed such finding to greater medical attention, lifestyle (13, 49) and access to PSA screening (12, 21). Our study was set in Montreal, where the population has free, universal access to health care and where, at the time the study was conducted, PCa screening was often part of the yearly routine exam. Screening uptake was high in our analytical sample with 76% of controls having been screened for PCa in the 2 years preceding the interview. This reduces the likelihood that PCa detection would be an important factor underlying our findings. Of note, associations went in the same direction, albeit stronger, when restricting analyses to men recently screened.

In addition, our analysis took into consideration PCa aggressiveness, defined by tumor grade. Gleason's grade describes tumor cell differentiation patterns, with higher-grade tumors being more aggressive and having a poorer prognosis (34); it does not reflect disease progression (50). Few previous studies have distinguished localized and aggressive PCa or cancer stage (11, 13, 20, 22). Our findings suggest that the effects of SEP were different for low- and high-grade cancers. This observation could be interpreted as indicative of the existence of two types of cancer with different etiologies, which has also been proposed by others (13). Recent findings indeed suggest that PCa grade may be established early in tumor pathogenesis and that Gleason grade progression is uncommon (34). Low-grade PCa has been shown to diverge early from high-grade PCa and there appears to be no direct progression from low-grade to metastatic disease (51).

The effect of disadvantageous SEP in childhood/adolescence suggested by our findings could be attributable to several factors. For example, a poor diet can disturb the pre-adulthood hormonal milieu (52) at the time when the prostate develops most quickly. This is reflected in lower height (53) and childhood obesity (54). Similarly, disadvantageous SEP in early years could lead to more stress, which is also known to negatively affect growth and development (55). Although previous studies have examined the effect of adiposity (27) and energy restriction during adolescence as well as height and weight (27, 56, 57) on PCa risk, results are conflicting.

Adult SEP may also act through common risk factors such as health behaviors (e.g., tobacco smoking and excessive alcohol consumption) or obesity, which are more prevalent among individuals with disadvantageous SEP (58). However, adjustment for these factors had a modest impact on results. There are as yet very few confirmed risk factors for PCa, leaving uncertainty about the covariates to be adjusted for when studying PCa risk. While our analysis took into account a number of health behaviors, residual confounding or lack of adjustment for factors not yet recognized in PCa development cannot be ruled out. Disadvantageous SEP during adulthood may be linked to occupational features associated with PCa such as shift work (59) and exposure to chemical agents (33, 60). Further adjustment for these factors did not alter findings (data not shown). SEP is a complex construct that represents an array of combined exposures and it may not accurately represent specific risk factors. Conversely, it may be that these factors act differently in puberty and adulthood.

The role of life course SEP in PCa risk has not been studied extensively. The mechanisms underlying the associations observed are not known. Yearly PCa screenings were common in this study population and associations with SEP were even stronger in analyses restricted to men recently screened, suggesting that screening does not explain the SEP-PCa relationship in our study base. It also appears that the lifestyle factors we considered were not major explanatory factors. Hypothetically, some factors unaccounted for and influencing cancer promotion, possibly diet, could underlie the late-adulthood SEP-aggressive PCa association.

There are several limitations that need to be considered when evaluating this work. The first relates to the misclassification of exposure to SEP. Although we used several SEP indicators, these might not capture the full spectrum of this construct. Variables were based on self-reports, which likely entailed errors, possibly more so among older subjects. Our age limit of 75 years for study participation may have helped alleviate age-related reporting errors to a certain extent. However, it is likely that reporting errors affected cases and controls in a similar fashion, thus keeping the risk estimates closer to unity. We conducted a sensitivity analysis excluding proxy respondents, who might be less cognizant of subjects' exposures, and observed no difference in results. Nevertheless, occupational circumstances are a specific focus of the PROtEuS study and our team has considerable experience in eliciting detailed work histories and in assigning occupational titles (33, 61). Moreover, reports of work histories have been shown to be valid (62). The commonly used ISCO 1988 and ESec were applied to classify occupations and assign SEP. Car ownership

by parents may have different meanings, although in the era when subjects were growing up, it probably was a reasonable indicator of affluence. SEP was dichotomized in a crude fashion into advantageous and disadvantageous, which may have masked differentials in exposure. While there was overlap in the coverage of SEP assessments in adulthood for some subjects, these were generally discriminatory in terms of time periods.

Another issue may arise from participation rates in the study. Although rates were similar or better than those in similar population-based studies, they were imperfect, with a lower response among controls. This might have influenced the socioeconomic profile of participants. To evaluate the potential for selection bias into the study, we conducted analyses comparing study participants and non-participants using four ecological variables derived from census tract data for 2006. The percentages of subjects living in areas with a greater proportion of recent immigrants within the previous 5 years were 5 and 6%, for participants and non-participants, respectively. Corresponding values were 7 and 7% for higher unemployment rate, 20 and 21% of adults without a high school diploma, and 23 and 25% in the lowest quintile of household income, suggesting a slight trend toward more advantageous SEP among participants. This held true in analyses by case/control status. Based on these observations, it appears that there was no major selection bias in our study. Characteristics on non-participants are rarely collected in epidemiologic studies, leaving uncertainties on potentially inherent selection biases that might have occurred in previous investigations.

Advantages of the study include its relatively large sample, the quality of job history information, the inclusion of different indicators of SEP at three points in time and the detailed data collection enabling the consideration of several co-factors, including PCa screening, as well as the ability to take into account cancer aggressiveness. Finally, we used a novel Bayesian approach for investigating life course models, which allowed us to estimate the probability that the data supports the models.

## CONCLUSION

Our study examined the association between life course SEP and the risk of PCa. Overall, our findings provide evidence for periods in life which are more sensitive to exposure to disadvantageous SEP in relation to PCa risk. Late adulthood was consistently found to be a sensitive period to disadvantageous SEP exposure in relation to risk of aggressive PCa. An association between SEP during childhood/adolescence and non-aggressive PCa was also observed, but based on only one of the SEP indicators used. Our findings require replication and warrant for more detailed exploration into the mechanisms through which disadvantageous SEP affects PCa risk during different exposure periods. From a prevention perspective, these results provide a valuable starting point for future research and suggest periods when intervention may be more beneficial.

| **What is already known on this subject?** |
| --- |
| The role of socioeconomic position in prostate cancer development remains debated. Most previous studies have relied on one or two indicators of socioeconomic position assessed during adulthood, which may not have captured the whole exposure period or changes over the lifetime. |
| **What this study adds?** |
| The present study builds on a more comprehensive assessment of socioeconomic position using the life course approach measuring socioeconomic position from childhood to adulthood. The study provides evidence for a differential role of socioeconomic position in prostate cancer aggressiveness depending on the period of exposure. |

## ETHICS STATEMENT

Ethics committees of Maisonneuve-Rosemont Hospital, Jean-Talon Hospital, Charles-Lemoyne Hospital, Centre hospitalier Fleury, Institut National de la Recherche Scientifique (INRS), and the Ethics Committee for Health Research of the Université de Montréal approved the study. All participants provided written informed consent.

## AUTHOR CONTRIBUTIONS

SM and CB (equal contribution) conceived the conceptual framework and co-wrote the draft manuscript. SM performed the data analysis. BN contributed to the design and analysis strategy of the study. HR prepared the databases and contributed to the analyses. M-ÉP conceived and conducted the main PROtEuS study. All authors read, commented and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00515/full#supplementary-material

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# The Ethnic-Specific Spectrum of Germline Nucleotide Variants in DNA Damage Response and Repair Genes in Hereditary Breast and Ovarian Cancer Patients of Tatar Descent

*Olga I. Brovkina[1†], Leila Shigapova[2†], Daria A. Chudakova[3†], Marat G. Gordiev[4], Rafael F. Enikeev[4], Maxim O. Druzhkov[4], Dmitriy S. Khodyrev[1], Elena I. Shagimardanova[2], Alexey G. Nikitin[1,5] and Oleg A. Gusev[2,6*]*

[1] Federal Research and Clinical Center, Federal Medical-Biological Agency of Russia, Moscow, Russia, [2] Kazan (Volga Region) Federal University, Kazan, Russia, [3] Institute of Natural and Mathematical Sciences, Massey University, Auckland, New Zealand, [4] Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan, Kazan, Russia, [5] Pulmonology Research Institute, Federal Medical-Biological Agency of Russia, Moscow, Russia, [6] RIKEN, Yokohama, Japan

The Russian population consists of more than 100 ethnic groups, presenting a unique opportunity for the identification of hereditary pathogenic mutations. To gain insight into the landscape of heredity pathogenic variants, we employed targeted next-generation sequencing to analyze the germline mutation load in the DNA damage response and repair genes of hereditary breast and ovary cancer syndrome (HBOCS) patients of Tatar ethnicity, which represents ∼4% of the total Russian population. Several pathogenic mutations were identified in DNA double-strand break repair genes, and the spectrum of these markers in Tatar patients varied from that previously reported for patients of Slavic ancestry. The CDK12 gene encodes cyclin-dependent kinase 12, the key transcriptional regulator of the genes involved in DNA damage response and repair. *CDK12* analysis in a cohort of HBOCS patients of Tatar decent identified a c.1047-2A>G nucleotide variant in the *CDK12* gene in 8 of the 106 cases (7.6%). The c.1047-2A>G nucleotide variant was identified in 1 of the 93 (1.1%) HBOCS patients with mixed or unknown ethnicity and in 1 of the 238 (0.42%) healthy control patients of mixed ethnicity (Tatars and non-Tatars) ($p = 0.0066$, OR = 11.18, CI 95% = 1.53–492.95, Tatar and non-Tatar patients vs. healthy controls). In a group of mixed ethnicity patients from Tatarstan, with sporadic breast and/or ovarian cancer, this nucleotide variant was detected in 2 out of 93 (2.2%) cases. In a cohort of participants of Slavic descent from Moscow, comprising of 95 HBOCS patients, 80 patients with sporadic breast and/or ovarian cancer, and 372 healthy controls, this nucleotide variant was absent. Our study demonstrates a strong predisposition for the *CDK12* c.1047-2A>G nucleotide variant in HBOCS in patients of Tatar ethnicity and identifies *CDK12* as a novel gene involved in HBOCS susceptibility.

**Keywords: breast cancer, *BRCA1*, *BRCA2*, *CDK12*, homologous recombination repair, next-generation sequencing, ovarian cancer**

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*Jian Gu,*
*University of Texas MD Anderson Cancer Center, United States*

***Correspondence:**
*Oleg A. Gusev*
*oleg.gusev@riken.jp*

*† These authors contributed equally to this work as a co-first authors*

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## INTRODUCTION

Ovarian (OC) and breast (BC) cancers are the leading causes of oncological mortality in women worldwide (1). Both cancers are highly heterogeneous with a strong hereditary component, as ∼10–15% of OC and 5–7% of BC cases are hereditary (2). The hereditary predisposition for these cancers (hereditary breast and ovarian cancer syndrome, HBOCS) is caused by germline mutations in several genes, primarily those linked to DNA damage recognition and repair. Early diagnosis reduces the disease-associated mortality rate. Therefore, genetic testing for HBOCS predisposition would be a beneficial addition to routine clinical practices.

Currently, genetic risk assessment for HBOCS profiles pathogenic DNA nucleotide variants for a panel of candidate genes. This approach allows for a stratification of patients into different subgroups with tailored therapies and for the identification of individuals at risk of HBOCS before there is a clinical manifestation of the disease (3). Importantly, the distribution pattern of the pathogenic DNA nucleotide variants may differ significantly across different ethnic populations due to the "founder effect" (4), and genetic tests developed for European populations may be clinically uninformative for patients of non-European ancestry. Therefore, genetic testing of patients with diverse ethnic backgrounds should be performed using a panel of markers established specifically for their ethnic group. In Russia, most genetic risk assessment tests for HBOCS include a panel of pathogenic nucleotide variants that are common among patients of European descent such as 5382insC, C61G, 185delAG, 4154delA, and 2080delA variants in the *BRCA1* gene. While those nucleotide variants have been comprehensively characterized in Russian Slavic populations (2, 5–7), recent data indicates that many of them are absent in patients from the Tatar ethnic origin (8). Therefore, there is a clear clinical demand for identification of novel HBOCS predisposing nucleotide variants specific for the Tatar population.

Genomic instability is a hallmark of cancer (9). Defects in DNA damage recognition and repair are associated with a plethora of malignancies including prostate cancer, ovarian cancer, leukemia, and breast cancer (10–13). In hereditary cancers, a major cause of genomic instability is the inability of the cell to repair DNA damage properly due to germline mutations in genes encoding DNA-repair proteins.

In mammals, the major pathways for DNA repair are base-excision repair (BER), nucleotide-excision repair (NER), non-homologous end joining (NHEJ), and homologous recombination repair (HRR) (14). DNA double-strand breaks (DSBs) are repaired by NHEJ and HRR. The NHEJ pathway orchestrates re-ligation of DSB ends, after removal of damaged nucleotides (15). The HRR pathway repairs DSBs using undamaged homologous DNA as a template sequence. NHEJ is less accurate than HRR, while HRR is characterized by high fidelity and is, therefore, essential for the maintenance of genomic integrity. For many of the genes involved in the HRR pathway, an association with tumorigenesis was clearly demonstrated in both sporadic and hereditary cancers.

The role of DSB repair pathway genes in susceptibility to breast and ovarian cancer has been heavily investigated. The panel of the genes contributing to HBOCS includes several DSB repair genes such as *BRCA1, BRCA2,* and others (16–19). Mutations in *BRCA1* and *BRCA2* genes, which inactivate the corresponding proteins and compromise the function of HRR pathways, contribute to ∼20–25% of HBOCS cases (20, 21). However, the remaining cases are comprised of patients with functional BRCA1 and BRCA2 proteins (BRCA1/2 negative HBOCS). For many of these cases, none of the currently used diagnostic markers are present and the predisposition genes remain obscure.

A number of publications indicate that Cyclin-dependent kinase 12 (CDK12), also known as KIAA0904, CRK7, CRKR, or CRKRS, is involved in human tumorigenesis (22). There are recurrent somatic mutations in the *CDK12* gene identified in OC (23). Moreover, somatic mutations resulting in *CDK12* inactivation are associated with genomic instability in OC (24). *CDK12* is also an emerging candidate BC tumor suppressor gene (25).

CDK12 is a serine/threonine protein kinase, a member of the cyclin-dependent kinase family. It is a multifunctional protein involved in many cellular processes such as alternative last exon mRNA splicing (21), embryonic stem cells renewal (26), cellular stress-response (27), and regulation of global transcription by targeting of RNA polymerase II, the polymerase that transcribes mRNA for protein-coding genes (28). Importantly, CDK12 is a key regulator of expression of DNA damage response genes. While depletion of CDK12 does not significantly affect global transcription, it dramatically diminishes transcription of the genes involved in DNA damage response and repair pathways including *BRCA1,* a gene established to convey HBOCS predisposition. Furthermore, cells with CDK12 depletion are more sensitive to DNA damaging agents and exhibit a higher rate of spontaneous DNA damage (29). Thus, CDK12 plays a pivotal role in the maintenance of genomic stability (30). However, currently there is little data on the role of *CDK12* germline mutations in HBOCS pathogenesis. We propose that *CDK12* is a candidate gene for HBOCS predisposition.

The aim of this study was to identify a panel of DNA nucleotide variant markers for HBOCS syndrome genetic screening in patients of Tatar ethnic origin. Using Targeted Next Generation Sequencing, we tested a panel of markers in the ATM, BARD1, BRCA1, BRCA2, CDH1, CDK4, CDK12, CDKN2A, CFTR, CHEK1, CHEK2, CTNNA1, EPCAM, FANCI, FANCJ/BRIP1, FANCL, MLH1, MSH2, MSH6, MUTYH, PALB2, PARP1, PDGFRA, PMS2, PPP2R2A, PRSS1, RAD51B, RAD51C, RAD51D, RAD54L, SPINK1, STK11, TP53, and XRCC3 genes of 199 HBOCS patients (Tatars and non-Tatars from the Volga District, Tatarstan Republic). Several pathogenic nucleotide variant markers were identified in the BRCA1, BRCA2, CDH1, CDK12, CHEK2, FANCI, MUTYH, MSH2, and RAD51C genes. The marker distribution profile in Tatars was found to be different than those in the Slavic group, though there is a relatively low prevalence of BRCA1 and BRCA2 founder mutations in Slavic populations. This suggests that HBOCS genetic predisposition tests for Tatar patients should be different

than those used for Slavic populations. We found a novel c.1047-2A>G nucleotide variant of the CDK12 gene that was strongly associated with HBOCS and present only in HBOCS patients of Tatar ethnic origin. To the best of our knowledge, our study is the first demonstrating that CDK12 c.1047-2A>G nucleotide variation results in HBOCS predisposition, indicating CDK12 involvement in HBOCS.

## MATERIALS AND METHODS

The study cohort comprised of female patients with a familial history of OC and/or BC (HBOCS) as well as healthy donors without a familial history of OC and/or BC obtained from the Republican Clinical Oncology Dispensary of the Ministry of Healthcare of Tatarstan Republic (RCOD MHTR), Volga District of Tatarstan Republic, or the Federal Scientific Clinical Centre of Federal Medical-Biological Agency Russian Federation (FSCC FMBA RF), Moscow, Russia. The clinical and demographic characteristics for the study participants are summarized in **Tables 1**, **2**. The study participants in the Tatar group self-identified as Tatars. The non-Tatar group included participants of unknown or mixed ancestry from Volga District of Tatarstan Republic. The study participants in the Slavic group self-identified with some or several Slavic ethnicities from Moscow, Russian Federation. All participants provided informed consent.

### DNA Isolation

Whole blood samples were collected from all study participants. Genomic DNA was isolated from the blood using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen) and quantified using the NanoVue Plus Spectrophotometer (GE Healthcare).

### Targeted Next-Generation Sequencing (NGS)

Targeted NGS was performed in a cohort of 199 HBOCS patients from the Volga District of the Tatarstan Republic. DNA (100 ng) was used to generate sequencing libraries. The NimbleGen SeqCap EZ Choice kit ("Roche") was used for target enrichment and sequencing was performed using the Illumina MiSeq ("Illumina") following the manufacturer's protocol. Raw-data reads were aligned to the human reference genome (hg19) using the aligner BWA (MEM algorithm) with BamQC, FastQC, and NGSrich quality control checks. GATK Haplotype v3.6 was applied for variant calling. Variant Call Format files were annotated using SnpSift & SnpEff, ANNOVAR, and Alamut Batch. MaxEnt, NNSPLICE, and HSF were used as *in silico* splice-prediction tools. The HGMD Professional 2017.1 and BIC databases were used to identify pathogenic nucleotide variants. Prediction of pathogenicity was determined by *in silico* tools SIFT, PolyPhen2, MutationTaster, FATHMM, CADD13, DANN, REVEL. The gene panel included *ATM, BARD1, BRCA1, BRCA2, CDH1, CDK4, CDK12, CDKN2A, CFTR, CHEK1, CHEK2, CTNNA1, EPCAM, FANCI, FANCJ/BRIP1, FANCL, MLH1, MSH2, MSH6, MUTYH, PALB2, PARP1, PDGFRA, PMS2, PPP2R2A, PRSS1, RAD51B, RAD51C, RAD51D, RAD54L, SPINK1, STK11, TP53,* and *XRCC3.*

### RT-PCR Assay

RT-PCR analysis was used to assess the presence or absence of a *CDK12* c.1047-2A>G nucleotide variant in 93 patients with sporadic OC and/or BC, 238 healthy participants of Tatar ethnic origin, 95 HBOCS patients, 80 patients with sporadic OC and/or BC, and 372 healthy participants of Slavic ethnic origin. RT-PCR was performed using TaqMan probes (FAM-atttcCtAcTgGaAaa-BHQ-1 for wild-type, VIC-atttcCtAcCgGaAaa-BHQ-2 for c.1047-2A>G mutation) and the following primers: forward 5′-TGGCACTTAATCTATTTTACA-3′, reverse 5′-GGATCTCTTCTTTTTACTATGA-3′. RT-PCR was carried out on a thermal cycler "StepOnePlus" (Applied Biosystems, USA) with a 10 μL final volume containing TurboBuffer (Evrogen, Russia), 400 nM forward and reverse primers, 150 nM probes, 1.5 unit Taq DNA polymerase, and 20–50 ng of genomic DNA. Thermocycling conditions: a first cycle at 95°C for 2 min; 40 cycles at 94°C for 10 s, and 40 cycles at 56°C for 90 s. PCR product size was 200 bp. Analysis of the amplification product was performed with the "end point" detection method using built-in thermocycler software tools accompanying SDS version 1.4. Positive control DNA was used to validate assay sensitivity of and analyzed in parallel with all samples. Presence of *CDK12* c.1047-2A>G nucleotide variation was determined by targeted NGS and confirmed by RT-PCR assay.

### Statistical Analysis

Standard statistical tests were used to analyze the data, including a two-tailed Fisher exact test performed with the R software (v.3.3). Statistical significance was defined as a p value less than 0.05. Values was obtained from *fisher.test* function.

## RESULTS

In a group of 199 HBOCS patients from the Volga district, Republic of Tatarstan (106 of Tatar ancestry and 93 of mixed or unknown ancestry) we employed Targeted NGS to detect a total of 38 germline nucleotide variant markers in 8 genes from a panel of 33 genes. The frequencies of the markers are shown in **Table 3.**

We also performed Targeted NGS for the *CDK12* gene and identified a c.1047-2A>G nucleotide variant in 8 of the 106 patients of Tatar descent. The presence of c.1047-2A>G in the *CDK12* gene, identified by Targeted NGS, was confirmed by RT-PCR (data not shown). In a cohort of Slavic participants from Moscow, this nucleotide variant was absent in 95 patients with HBOCS, 80 patients with sporadic BC and/or OC, and 372 healthy controls as determined by RT-PCR. In a cohort of participants from the Volga District, Republic of Tatarstan, the frequency of c.1047-2A>G mutation was significantly higher in HBOCS patients compared to healthy controls (9/199 vs. 1/238, $p = 0.0066$, OR = 11.18, CI 95% = 1.53–492.95, **Table 4**). The cohort of HBOCS patients from the Republic of Tatarstan included 106 patients of Tatar ethnicity, and 93 patients of non-Tatar, mixed, or unknown ethnicity. Given that the Tatars ethnic group is one of the most common in the Republic of Tatarstan, constituting almost 50% of the total population, we assume that

**TABLE 1 |** The demographic characteristics of the participant cohorts.

| Geographic region | Healthy donors | | Sporadic BC and/or OC | | HBOCS patients | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Mean age, years (range) | No. | Mean age, years (range) | All | BC | | OC | |
| | | | | | No. (%) | No. (%) | Mean age, years (range) | No. (%) | Mean age, years (range) |
| Volga District of Tatarstan Republic | 238 | 54 (32–74) | 93 | 56 (32–86) | 199 (100) | 88 (44) | 49 (23–88) | 111 (56) | 55 (22–86) |
| Moscow | 372 | 55 (34–78) | 80 | 55 (34–75) | 95 (100) | 40 (42) | 48 (32–72) | 45 (58) | 52 (30–74) |

**TABLE 2 |** The clinical characteristics of the HBOCS patients from Tatarstan Republic.

| Geographic region | All patients, No. (%) | *BRCA1* mutation, No. (%) | *BRCA2* mutation, No. (%) | Mutations in non-*BRCA1/2* genes, No. (%) | No mutations or variants of uncertain significance, No. (%) |
|---|---|---|---|---|---|
| Volga District of Tatarstan Republic | 199 (100) | 54 (27) | 24 (12) | 22 (11) | 99 (50) |
| | | | Age at disease manifestation Mean age, years (range) | | |
| | 51 (22–88) | 48 (28–82) | 51 (32–70) | 52 (31–79) | 54 (22–88) |

about half of the healthy donors randomly recruited to this study in the Tatarstan Republic were also of Tatar ancestry.

All HBOCS patients with *in silico* pathogenic mutations of the *CDK12* gene had negative HER2 status.

We also found several other nucleotide variants in the CDK12 gene in the group of HBOCS patients (**Table 5**), with a deleterious prediction of pathogenicity determined by *in silico* tools (SIFT, PolyPhen2, MutationTaster, CADD, DANN, REVEL). Among the patients with HBOCS harboring CDK12 nucleotide variants determined as pathogenic, 21% also had pathogenic nucleotide variants in BRCA1 gene.

Forty three percent of the patients in HBOCS cohort were HER2 positive, but all patients carrying CDK12 c.1047-2A>G nucleotide variant were HER2 negative (**Table 5**).

We hypothesized that the c.1047-2A>G nucleotide variant in the *CDK12* gene could potentially affect splicing. *In-silico* splice site prediction analysis of the *CDK12* c.1047-2A>G variant by MaxEnt, NNSPLICE, and HSF tools suggests that the variant is a splice site substitution in the acceptor splice site of intron 1, likely resulting in a skip of exon 2. Therefore, the *CDK12* c.1047-2A>G mutation may lead to production of a shorter alternative splice transcript. Interestingly, we also found several other nucleotide variants in the CDK12 gene in the group of HBOCS patients (**Table 5**), with a greater than 90% deleterious prediction of pathogenicity determined by *in silico* tools. Among the patients with HBOCS harboring CDK12 nucleotide variants determined as pathogenic, 21% also had pathogenic nucleotide variants in BRCA1 gene.

## DISCUSSION

The Russian population includes many ethnicities, and is characterized by huge genetic diversity. Slavic and non-Slavic ethnicities in Russia may have different profiles of nucleotide variants resulting in HBOCS predisposition. Therefore, it is possible that identification of novel ethno-specific markers will decrease false-negative results of genetic risk assessment. There is a degree of variability in the frequency of HBOCS-associated nucleotide variants in the BRCA1 and BRCA2 genes of non-Caucasian populations (31, 32). Indeed, one of the most common markers in European populations, BRCA1 5382insC, was not found in hereditary BC patients from several non-Slavic indigenous populations (Altaians, Buryats, and Tuvinians) in Russia (31). Our previously published data on germline BRCA1 and BRCA2 nucleotide variants in a small group of Tatar patients with BC indicated the same trend (8). To the best of our knowledge, no data exists on the spectrum of disease-associated nucleotide variants in HBOCS patients of Tatar descent.

We tested multiple-gene panels for the presence of HBOCS predisposition markers in Tatar patients and detected several germline nucleotide variants in the BRCA1, BRCA2, CDK12, CDH1, CHEK2, FANCI, MUTYH, MSH2, and RAD51C genes, including some pathogenic variants previously reported in other populations. Strikingly, their prevalence and spectrum in Tatar HBOCS patients was found to be different to that reported in European populations, particularly in Russia (2, 6, 32).

Currently, nucleotide variants in the *CDK12* gene are not included in panels of HBOCS predisposition markers, despite the fact that several lines of evidence strongly suggest CDK12 involvement in OC and BC pathogenesis. *CDK12* has been found to be one of the most frequently mutated genes in high grade serous OC, harboring mutations in 3% of cases (23). In OC, *CDK12* mutations deregulate expression of HRR pathway genes (33). In BC, *CDK12* is found to be frequently co-amplified with the oncogene ERBB2. Such amplification may contribute to BC pathogenesis (34). Recent

**TABLE 3 |** Germline nucleotide variants in HBOCS patients from Volga District, Republic of Tatarstan and in healthy subjects from Non-Finish European population (NFE).

| Gene | Hg19 coordinate | Transcript:cDNA | Protein | N | Frequency in HBOCS patients from Tatarstan, % | Frequency in NFE |
|---|---|---|---|---|---|---|
| BRCA1 | chr17:41209079 | NM_007300.3:c.5329dup (also known as 5382insC) | p.Gln1777Profs*74 | 9 | 4.5 | $1.6*10^{-4}$ |
| BRCA1 | chr17:41215382 | NM_007300.3:c.5224C>T | p.Gln1742* | 4 | 2.0 | $8.9*10^{-6}$ |
| BRCA1 | chr17:41258504 | NM_007300.3:c.181T>G (also known as T300G) | p.Cys61Gly | 2 | 1.0 | $6.3*10^{-5}$ |
| BRCA1 | chr17:41209095 | NM_007300.3:c.5314C>T | p.Arg1772* | 2 | 1.0 | $7.9*10^{-6}$ |
| BRCA2 | chr13:32906576 | NM_000059.3:c.965_966dup | p.Val323Lysfs*2 | 2 | 1.0 | N/A |
| CDH1 | chr16:68844220 | NM_004360.4:c.808T>G | p.Ser270Ala | 2 | 1.0 | $4.7*10^{-4}$ |
| CHEK2 | chr22:29130389 | NM_001005735.1:c.319+2T>A | - (splice site) | 2 | 1.0 | $1.1*10^{-4}$ |
| MUTYH | chr1:45797228 | NM_001128425.1:c.1187G>A | p.Gly396Asp | 2 | 1.0 | $4.8*10^{-3}$ |
| BRCA1 | chr17:41246513 | NM_007300.3:c.1034_1035insC | p.Pro346Serfs*4 | 1 | 0.5 | 0.0 |
| BRCA1 | chr17:41245587 | NM_007300.3:c.1961del (also known as 2080delA) | p.Lys654Serfs*47 | 1 | 0.5 | $6.7*10^{-5}$ |
| BRCA1 | chr17:41243924 | NM_007300.3:c.3624del | p.Lys1208Asnfs*2 | 1 | 0.5 | N/A |
| BRCA1 | chr17:41245587 | NM_007300.3:c.1961del (founder mutation 2080delA) | p.Lys654Serfs*47 | 1 | 0.5 | $6.7*10^{-5}$ |
| BRCA1 | chr17:41244614 | NM_007300.3:c.2934del | p.Arg979Valfs*21 | 1 | 0.5 | N/A |
| BRCA1 | chr17:41244282 | NM_007300.3:c.3266del | p.Leu1089Cysfs*20 | 1 | 0.5 | N/A |
| BRCA1 | chr17:41215890 | NM_007300.3:c.5215+1G>T | - (splice site) | 1 | 0.5 | N/A |
| BRCA1 | chr17:41244761 | NM_007300.3:c.2787del | p.Pro930Leufs*70 | 1 | 0.5 | N/A |
| BRCA1 | chr17:41246083 | NM_007300.3:c.1465G>T | p.Glu489* | 1 | 0.5 | N/A |
| BRCA1 | chr17:41245918 | NM_007300.3:c.1630del | p.Gln544Lysfs*2 | 1 | 0.5 | N/A |
| BRCA1 | chr17:41246633 | NM_007294.3:c.915T>A | p.Cys305* | 1 | 0.5 | $1.8*10^{-5}$ |
| BRCA2 | chr13:32900279 | NM_000059.3:c.468dup | p.Lys157* | 1 | 0.5 | $6.7*10^{-5}$ |
| BRCA2 | chr13:32906625 | NM_000059.3:c.1010_1011insTG | p.Asp339Leufs*11 | 1 | 0.5 | N/A |
| BRCA2 | chr13:32907409 | NM_000059.3:c.1796_1800del | p.Ser599* | 1 | 0.5 | $9.2*10^{-6}$ |
| BRCA2 | chr13:32968950 | NM_000059.3:c.9381G>A | p.Trp3127* | 1 | 0.5 | N/A |
| BRCA2 | chr13:32968836 | NM_000059.3:c.9269del | p.Phe3090Serfs*14 | 1 | 0.5 | $4.8*10^{-5}$ |
| BRCA2 | chr13:32906843 | NM_000059.3:c.1231del | p.Ile411Tyrfs*19 | 1 | 0.5 | N/A |
| BRCA2 | chr13:32915113 | NM_000059.3:c.6622_6623del | p.Asn2208Tyrfs*16 | 1 | 0.5 | 0.0 |
| BRCA2 | chr13:32915062 | NM_000059.3:c.6574del | p.Met2192Trpfs*14 | 1 | 0.5 | N/A |
| BRCA2 | chr13:32914265 | NM_000059.3:c.5773del | p.Gln1925Argfs*38 | 1 | 0.5 | $9.0*10^{-6}$ |
| CHEK2 | chr22:29091857 | NM_001005735.1:c.1229del | p.Thr410Metfs*15 | 1 | 0.5 | $2.5*10^{-6}$ |
| CHEK2 | chr22:29099504 | NM_001005735.1:c.1022_1026del | p.Tyr341Cysfs*12 | 1 | 0.5 | N/A |
| CHEK2 | chr22:29090060 | NM_001005735.1:c.1550G>A | p.Arg517His | 1 | 0.5 | $1.1*10^{-4}$ |
| FANCI | chr15:89838324 | NM_001113378.1:c.2635C>T | p.Arg879* | 1 | 0.5 | $1.7*10^{-5}$ |
| MSH2 | chr2:47630353 | NM_000251.2:c.23C>T | p.Thr8Met | 1 | 0.5 | $1.6*10^{-4}$ |
| MUTYH | chr1:45800146 | NM_001128425.1:c.74G>A | p.Gly25Asp | 1 | 0.5 | N/A |
| MUTYH | chr1:45800167 | NM_001128425.1:c.53C>T | p.Pro18Leu | 1 | 0.5 | $3.1*10^{-5}$ |
| MUTYH | chr1:45798269 | NM_001128425.1:c.667A>G | p.Ile223Val | 1 | 0.5 | $3.4*10^{-4}$ |
| RAD51C | chr17:56801399 | NM_058216.2:c.905-2_905-1del | - (splice site) | 1 | 0.5 | 0.0 |

*N/A, not available.*

breakthroughs in molecular diagnostic techniques have allowed the incorporation of NGS into clinical practice, allowing identification of small deletions/insertions, single nucleotide variants, and other variations in the sequence of candidate genes predisposing patients to various diseases such as HBOCS (34). We proposed that CDK12 is involved in HBOCS and performed a Targeted NGS-based approach to identify disease-associated nucleotide variants of the *CDK12* gene in the Tatar population.

In this study, we detected a novel germline nucleotide variant c.1047-2A>G in the *CDK12* gene in a group of Tatar patients with HBOCS. The percentage of *CDK12* c.1047-2A>G variants in Tatar and non-Tatar patients (106 and 93 patients assessed, respectively) was 4.5%, that is significantly higher than the

**TABLE 4 |** *CDK12* gene c.1047-2A>G nucleotide variant frequency distribution.

| Geographic region | Ethnicity | HBOCS | | Sporadic BC and/or OC | Healthy controls | HBOCS vs. controls (9/199 vs. 1/238) | Sporadic BC/OC vs. controls (2/93 vs. 1/238) |
|---|---|---|---|---|---|---|---|
| Volga District, Republic of Tatarstan | Tatars | 8/106 (7.6%) | 9/199 (4.5%) | 2/93 (2.2%) | 1/238 (0.42%) | $p = 0.0066$ OR = 11.18 CI 95% = 1.53–492.95 | $p = 0.20$ OR = 5.07 CI 95% = 0.26–301.34 |
| | Non-Tatars, Mixed or Unknown | 1/93 (1.1%) | | | | | |
| Moscow | Slavic | | 0/95 (0%) | 0/80 (0%) | 0/372 (0%) | – | – |

**TABLE 5 |** All *in silico* pathogenic *CDK12* nucleotide variants in HBOCS patients from Volga District, Tatarstan Republic.

| Patient | Hg19 coordinate transcript:cDNA protein | Frequency in gnomAD NFE(%) | Number in our study | Frequency in our study(%) | Other mutations | Immunohistochemistry(%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ER | PR | HER2 | KI-67 |
| Pat.1 | | 0.052 | 9 | 4.5 | BRCA2:NM_000059.3:c.3689C>T:p.Ser1230Phe RAD54L:NM_001142548.1:c.2213G>A:p.Arg738His | 8 | 6 | 0 | 20 |
| Pat.2 | | | | | **BRCA1:NM_007300.3:c.181T>G:p.Cys61Gly*** | 0 | 0 | 0 | 0 |
| Pat.3 | | | | | FANCI:NM_001113378.1:c.286G>A:p.Glu96Lys ATM:NM_000051.3:c.5975A>C:p.Lys1992Thr | 7 | 7 | 0 | 60 |
| Pat.4 | chr17:37627130 NM_016507.3: c.1047-2A>G p.? | | | | BRCA2:NM_000059.3:c.9976A>T:p.Lys3326* | - | - | - | - |
| Pat.5 | | | | | Absent | - | - | - | - |
| Pat.6 | | | | | Absent | 3 | 4 | 0 | 10 |
| Pat.7 | | | | | **BRCA1:NM_007300.3:c.5224C>T:p.Gln1742*** | 5 | 5 | 0 | 10 |
| Pat.8 | | | | | Absent | - | - | - | - |
| Pat.9 | | | | | CDKN2A:NM_001195132:c.C496T:p.H166Y MSH6:NM_000179.2:c.2633T>C:p.Val878Ala | ? | ? | ? | ? |
| Pat.10 | chr17:37687333 NM_016507.3:c.4237C>T p.His1413Tyr | 0.0019 | 1 | 0.5 | BRCA1:NM_007300.3:c.4946T>C:p.Met1649Thr | 8 | 8 | 0 | 0 |
| Pat.11 | chr17:37627556 NM_016507.3:c.1471C>T p.Leu491Phe | 0.0045 | 1 | 0.5 | BARD1:NM_000465.3:c.104C>G:p.Ala35Gly | 0 | 0 | 0 | 97 |
| Pat.12 | chr17:37627187 NM_016507.3:c.1102T>A p.Ser368Thr | 0.02 | 1 | 0.5 | MLH3:NM_001040108.1:c.1870G>C:p.Glu624Gln | 7 | 8 | 0 | 30 |
| Pat.13 | chr17:37673748 NM_016507.3:c.2902T>C p.Tyr968His | 0.0045 | 1 | 0.5 | BRIP1:NM_032043.2:c.728T>C:p.Ile243Thr | 0 | 0 | 0 | 0 |
| Pat.14 | chr17:37676286 NM_016507.3:c.3041C>T p.Thr1014Ile | 0.0012 | 1 | 0.5 | **BRCA1:NM_007300.3:c.4327C>T:p.Arg1443*** RAD54L:NM_001142548.1:c.1317G>C:p.Glu439Asp | 0 | 0 | 0 | 0 |

**"-"- patients with ovarian cancer, receptor status is usually not determined in clinical practice; "?" – patients with breast cancer with unknown receptor status.*

0.42% observed in a group of 238 healthy donors of mixed or unknown ancestry (Tatar and non-Tatar) from the same geographical region. One potential weakness of this study is the possibility that the healthy control group consists of primarily non-Tatar participants, which would result in a difference in the c.1047-2A>G nucleotide variant frequency between the HBOCS and control groups solely because the c.1047-2A>G variant occurs more frequently in the Tatar population. However, given that Tatar is one of the major ethnic groups in the Republic of Tatarstan, comprising almost 50% of the total population, we assume that about half of the healthy donors are of Tatar ethnicity. We also recruited a relatively large number of participants in a healthy control group (238 participants), to ensure a cohort that better represents the entire population. The frequency of the *CDK12* c.1047-2A>G nucleotide variant in Tatar patients is relatively high and similar to the frequency

of the *BRCA1* 5382insC, a founder-mutation present in many Russian populations. The c.1047-2A>G variant was detected in patients from apparently non-related families. Therefore, it is possible that *CDK12* c.1047-2A>G is a founder mutation in the Tatar population, at least for the Tatar sub-population in the Kazan region. Importantly, carriers of the *CDK12* c.1047-2A>G variant in the group of non-Tatar HBOCS patients from the Volga District were of Chuvash ethnicity, which is closely related to Tatars and belongs to the Turkic ethnic group under which Tatars are classified.

Overall, we conclude that *CKD12* is a candidate gene for HBOCS syndrome. Currently, there is only one other report describing cancer patient carrying the *CDK12* c.1047-2A>G nucleotide variant. Remarkably, it is also a patient with OC found in a cohort of OC patients in USA (35). We propose that *CDK12* is involved in pathogenesis of other malignancies characterized by impaired HRR (10, 12), and that c.1047-2A>G may be associated with such diseases. This indicates that *CDK12* c.1047-2A>G could be used as a diagnostic marker.

Frequencies of this mutation in samples from the Exome Aggregation Consortium database [http://gnomad.broadinstitute.org/](36) are extremely low (**Table 6**). Nevertheless, it is present in several populations, with highest frequency of 0.1% occurring in South Asian populations. We determined the frequency of *CDK12* c.1047-2A>G mutation in healthy participants from the Volga District of the Republic of Tatarstan to be 0.42%. This raises the question whether c.1047-2A>G should be classified as a mutation or a nucleotide polymorphism (37). Therefore, we define c.1047-2A>G as a nucleotide variant and classify it as pathogenic in accordance with recommendations of the American College of Medical Genetics and Genomics (ACMG) (38).

The Tatar population in the Volga region has low interpopulation differentiation (39), which indicates that the results of the current study may be extrapolated to the whole Tatar population in the Volga region of the Republic of Tatarstan. Importantly, Tatars who live in the eastern regions of Tatarstan have genetic similarity to the Bashkirs ethnic group (39). Thus, we expect that the c.1047-2A>G nucleotide variant in the *CDK12* gene might be involved in HBOCS in individual of Bashkirs ethnicity as well, which should be addressed in further studies. The relatively high percentage of c.1047-2A>G among healthy participants in our study may have several explanations. There is a possibility that even if asymptomatic carriers of c.1047-2A>G have not developed the disease yet, they eventually will. Alternatively, c.1047-2A>G may result in a "disease predisposing" phenotype, but the second mutation, present among patients but is absent in healthy controls, is necessary to trigger the disease as delineated by the "two hit" hypothesis (40). Finally, carriers of the c.1047-2A>G nucleotide variant in healthy group may also harbor "protective" nucleotide variant(s) (yet unknown), which neutralize the pathogenic effect of c.1047-2A>G (41). Identifying such protective nucleotide variants would open an avenue for new therapeutic strategies.

The *CDK12* gene is located on chromosome 17q12 and is comprised of 14 exons. Currently, there are two identified isoforms of the *CDK12* gene, a shorter and longer isoform, differing in one exon. The shorter splice isoform results in an 1481 amino acid protein and the longer splice isoform encodes an 1,490 amino acid protein, with both harboring the same functional domains (22). It should be noted that mutations introducing a new splice-site sequence may result in loss of functional domains or altered folding of the CDK12 protein. The c.1047-2A>G mutation in the *CDK12* gene may alter splicing. We speculate that the c.1047-2A>G variant results in a truncated CDK12 protein and loss of function, leading to impaired HRR. It has previously been shown that CDK12 protein inactivation results in cells more sensitive to genotoxic insult and that tumors with an HRR pathway deficiency are highly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors. In particular, inactivation of CDK12 in OC cells sensitizes them to the DNA cross-linking agent cisplatin and to PARP inhibitors such as veliparib and olaparib (42, 43). In BC, pharmacological inhibition of CDK12 reverses PARP inhibitor resistance in both BRCA wild-type and BRCA-mutant cells (44). If carriers of the c.1047-2A>G nucleotide variant have non-functional CDK12 protein, they may exhibit increased sensitivity to PARP inhibitors.

*CDK12* gene is located in close proximity to the oncogene *ERBB2*, also known as *HER2*. In BC, *CDK12* is frequently co-amplified with the *HER2* (34). Previously, a correlation of HER2 status and CDK12 level was found in a cohort of BC patients. In most of the HER2 amplified tumors level of CDK12, both mRNA and protein, was high, while absence of CDK12 was rarely observed (45). While 43% of patients in the cohort were HER2 positive, all patients harboring pathogenic nucleotide variants in *CDK12* were HER2 negative. Whether HER2 negative status is a functional consequence of the presence of pathogenic nucleotide variants in *CDK12* is beyond the scope of current research, but should be addressed in future studies.

Overall, our study demonstrates that prevalence of disease-associated mutations in the *BRCA1* and *BRCA2* genes in the Russian population is significantly different in patients of Tatar and Slavic ethnic origins. We identified the c.1047-2A>G germline nucleotide variant in the *CDK12* gene, which may result in an alternative *CDK12* splice variant and is strongly associated with HBOCS. We recommend that this variant become part of the standard testing panel for HBOCS susceptibility markers in Tatar patients with a family history

**TABLE 6 |** *CDK12* gene c.1047-2A>G nucleotide variant frequencies in populations (Genome Aggregation Database).

| Population | Allele number | Allele frequency |
|---|---|---|
| South Asian | 26564 | 0.1% |
| European (Non-Finnish) | 120204 | 0.05% |
| European (Finnish) | 25106 | 0.02% |
| African | 23590 | 0.004% |
| Latino | 28642 | 0.003% |
| Ashkenazi Jewish | 8670 | 0% |
| East Asian | 17724 | 0% |

of OC and BC. Incorporation of the c.1047-2A>G marker in this genetic diagnostic panel may also lead to improved therapeutic strategies, such as stratification of the patients according to potential sensitivity to PARP inhibitors. This finding also confirms the role of *CKD12* as a candidate gene for HBOCS predisposition.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of International code of medical ethics, ethical committee of Federal Research and Clinical Center of Federal Meadical and Biological Agency of Russia. The protocol was approved by the ethical committee of Federal Research and Clinical Center of Federal Meadical and Biological Agency of Russia. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

AN, DK, ES, LS, OB, OG, MD, MG, and RE data collection, analysis and interpretation. AN, DC, ES, OB, and OG study conception and design. AN and DC drafting and critical revision of the manuscript.

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# Responsiveness of Physical Rehabilitation Centers in Capital of Iran: Disparities and Related Determinants in Public and Private Sectors

*Manijeh Alavi[1,2], Mohammad Reza Khodaie Ardakani[1], Maziar Moradi-Lakeh[3], Homeira Sajjadi[4], Mohsen Shati[5], Mehdi Noroozi[1] and Ameneh Setareh Forouzan[1]**

[1] Social Determinants of Health Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran, [2] Research and Technology Department, Ministry of Health and Medical Education, Tehran, Iran, [3] Department of Community and Family Medicine, Preventive Medicine and Public Health Research Center, Iran University of Medical Sciences, Tehran, Iran, [4] Social Welfare Management Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran, [5] Department of Aging, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

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***Correspondence:**
*Ameneh Setareh Forouzan*
*asforouzan@gmail.com*

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**Background:** Responsiveness as a non-medical, non-financial goal of the health system is of special importance to people with physical disability. The current study assessed the experiences of people with physical disabilities when they encounter rehabilitation centers in Tehran.

**Methods:** This cross-sectional study was conducted in Tehran, the capital of Iran. The sample consisted of 610 people with physical disabilities referred to 10 comprehensive rehabilitation centers (CRCs) selected by Quota sampling. Data were collected by a standard responsiveness questionnaire proposed by the World Health Organization (WHO) and were analyzed by a standard protocol. Blinder-Oaxaca analysis was done to explain the inequality in performance of public and private sectors.

**Results:** Study participants included 298 (48.7%) women and 312 (51.3%) men. The mean age of the respondents was 46.3 ($SD$ = 14.3) for women and 45.6 ($SD$ = 15.4) for men. Prompt attention (33.3%) and confidentiality (1.3%) were the most and least important reported domains, respectively. Overall poor responsiveness was reported by 20.9% of respondents. Private rehabilitation centers showed significantly better performance in communication, basic amenities and autonomy compared to public centers ($P \leq 0.05$). Perceived social class explained 76% of the inequality in autonomy in the private and public sector ($P \leq 0.05$).

**Conclusion:** Improving overall responsiveness in domains that are of high importance from the respondents' viewpoint but are performing poorly—areas such as prompt attention and basic amenities—is essential. Additionally, interventions are needed to improve the performance of the public centers and providers in the areas of participation of service users in all social classes in their rehabilitation decisions and procedures, clear communication, and basic amenities.

**Keywords: rehabilitation centers, health status disparities, inequality, responsiveness, Iran**

## INTRODUCTION

Disability is one of the serious issues in the fields of medicine, rehabilitation, and social sciences, and its history dates back to the beginning of humanity (1). The United Nations, as well as many countries, consider disability an important topic on the health agenda (2). There are a billion people living with disabilities around the world, a figure that accounts for approximately 15% of the world's total population (1). People with disability are among the most vulnerable social groups, and they need special attention due to their situation. Physical disabilities, in turn, account for a significant proportion of all disabilities (3). More than 650 million people in the world suffer from physical disabilities, about two thirds of whom live in developing countries, including Iran (1). The World Health Organization (WHO) reported that people with disabilities are twice as likely to be faced with difficulties in access to health services, three times more likely to be neglected and four times more likely to be treated badly compared to people without disabilities (4). Despite the adoption of The Convention on the Rights of Persons with Disabilities, data collection and monitoring mechanisms in international development and global health still largely ignore those with disabilities (5).

Based on Iranian studies, more than 11 million of people in Iran are suffering from disabilities, most of whom are people with physical disabilities (3, 6). Road accidents, one of the main causes of mortality and morbidity in Iran, have had the biggest impact on increasing the rate of disabilities in Iran (7). Aging and chronic diseases are also increasing in Iran, subsequently causing increased rates of disability (8). Tehran, as the capital and the most populous city in Iran, with a population of over 12 million, accounts for the highest proportion of people with disabilities in the country (3).

This increasing prevalence of people with disabilities, in particular physical disabilities, requires continuous care that is mainly provided by health systems (2). The WHO proposes three explicit goals to assess the performance of a health system: improving health, fairness in financial contribution and responsiveness (9). Responsiveness as one of the intrinsic goals of a health system reflects how well that system is responding to the legitimate expectations of individuals regarding non-medical and non-financial issues (10, 11). The WHO Multi-country Survey Study in 2000–2001 produced valuable information about how health systems are responding to the legitimate expectations of populations in many countries around the world (12).

Responsiveness is considered of special importance, as it relates to human rights, has a positive relationship with health outcomes and can be successful achieved by low-cost interventions (13, 14).

Responsiveness is a multidimensional concept with 7 domains for out-patients, including autonomy (involvement in decisions related to health), choice (meeting with the health provider of one's own choice), communication (clarity of information received by the service user), confidentiality (privacy), dignity (respectful interaction), prompt attention (e.g., access, waiting times), and basic amenities (quality of basic facilities). Access to family and community support is only considered for inpatients. Today, autonomy has been globally noticed as a very important domain because service users' participation in decision-makings about their health is a main aspect of patient-centered care. It influences population health outcomes, improves quality and patients' safety and has an important role in patients' welfare and even containing health costs (15).

Responsiveness to people with disabilities becomes even more important, considering their large numbers in the population and their unmet needs in the field of health (16).

Although responsiveness has been studied in general hospitals (17–19) and in special outpatient populations, such as people with mental health disorders (11, 20–22), chronic disease (23), heart disease (24), diabetes (25) or, for inpatient, delivery care (26), there has been very little investigation into the experience of people with disabilities who receive rehabilitation services. Likewise, several studies indicate that there is a significant difference in responsiveness of public and private sector but there are few studies about the socio-economic characteristics that can explain this gap (19, 27–29).

The current study aimed to assess the experience of people with physical disabilities encountering rehabilitation centers in Tehran.

To achieve the objectives of this study, the following key questions were asked:

- How do people with physical disabilities assess rehabilitation service responsiveness?
- Which domains are the best and the worst performing?
- What are the most and least important domains for the service users?
- Is there any difference between the experiences of individuals who used public and private rehabilitation services?
- How do socio-demographic characteristics explain the gap between performance of public and private physical rehabilitation centers in domain of autonomy?

## METHODS

The current study was a cross-sectional study carried out in comprehensive rehabilitation centers of Tehran, the capital city of Iran.

### Setting and Selecting the Comprehensive Rehabilitation Centers (CRCs)

In Iran, designing, planning, and implementing health policies and monitoring and supervising health-related activities in both public and private sectors are the responsibilities of the Ministry of Health and Medical Education (MOHME). Health policies are implemented and supervised through medical universities country-wide (30). Rehabilitation activities and services are mainly provided by public and private rehabilitation centers. All rehabilitation centers must be licensed by the medical universities, which act as the representative of MOHME. In 2016, there were 31 comprehensive rehabilitation centers (CRCs) licensed by three medical universities in Tehran. Comprehensive rehabilitation centers are affiliated with one of the organizations

noted above and provide broad rehabilitation services, including physical, mental and social services.

Physical rehabilitation services include occupational therapy, physiotherapy, orthosis, prosthesis, etc. which are provided under the supervision of specialists in these fields.

## Selecting the Comprehensive Rehabilitation Centers for the Study

Eighteen out of 31 CRCs had licenses in the field of physical rehabilitation during the sampling period. Tehran was divided into five regions (North, South, Center, West, and East) based on division of the municipality. Quota sampling was used to select the centers for the study in order to have centers from public and private sectors as well as representing all regions of Tehran (North, South, Center, West and East) (22). Ten CRCs, including 5 public and 5 private, representing broad geographical coverage, were selected and agreed to participate in the study.

## The Instrument

A standard questionnaire for responsiveness, proposed by WHO, was used to gather data. This questionnaire includes questions related to the use of the service, general health, and responsiveness. As the service users were in the outpatient setting, 7 domains of responsiveness, including prompt attention, dignity, choice, autonomy, confidentiality, clear communication, and basic amenities, were considered (questions are available as a **Supplementary Material**). The questionnaire was previously validated in Iran (14, 31). However, in the current study, internal consistency was examined using Cronbach's alpha. Kappa was also calculated by test-retest on 30 people. Cronbach's alpha of the 7 domains showed a range of at least 0.677 for prompt attention and a maximum of 0.911 for basic amenities. Kappa was at least 0.75 in prompt attention and a maximum of 0.94 in basic amenities. Missing rates for the 7 domains of the questionnaire were within 0.3–1%. Therefore, the WHO standard questionnaire for responsiveness was reliable and feasible to use in this population.

A demographic checklist was completed, including variables such as sex (male/ female based on self-recognition); age (self-reported in two groups as 18–59 and $\geq$60 years); education (self-reported in three groups as elementary with $<$5 years of education, intermediate with 5–12 years of education, and upper with $>$12 years of education); health assessment [self-reported in two groups as good health (very good/good) and bad health (moderate/bad/very bad)], social class [self-reported in three groups as low (very low/ low), middle, and high (very high/high)]. Physical disability was defined as musculoskeletal impairments that could be congenital, due to accidents or diseases, or other causes as specified by the respondent.

## Study Population and Sampling

A formula of the proportion estimation was used to calculate the sample size (32).

$$N = \frac{\left[Z_{1-\frac{\propto}{2}}\right]^2 pq}{d^2} \quad (1)$$

Where $Z_{1-\frac{\propto}{2}}$ is equal to 1.96. Also, "p" and "q" were considered based on previous studies on responsiveness in Iran (18, 30) and "d" was estimated as 0.15p. Finally, based on 5 geographical regions in Tehran the sample size was calculated and rounded as 610. The number of participants for each center was proportional according to the average number of monthly service users (based on a 3-month period). The final sample size by public and private centers was 406 and 204, respectively. People aged 18 years and over who were (1) diagnosed by a physician as having a physical disability, (2) referred to a selected center during the sampling period (from October 2016 through March 2017) and had experience using rehabilitation services in last 12 months, and (3) were mentally and physically capable to answer the questionnaire were included after informed written consent was obtained.

The questionnaire for each service user was completed by face to face interview. To minimize the social bias, two trained interviewers who were not staff members of the rehabilitation center along with the principal investigator, administered the questionnaires in a private area. The participants in the study were assured that their responses were completely confidential and had no effect on the process of receiving the rehabilitation services.

## Data Analysis

Analysis of the data was conducted using the approach of the WHO analytical guideline for Multi-Country Survey (MCSS) (12). There were two to four questions to report experiences of service users and one "rating" question for each domain. The responsiveness score was calculated based on responses to the rating questions. Answers to a 5-point Likert scale were recoded using very good as (5) to very bad as (1). Performance of each domain was assessed as good if the response to the rating question of the domain was very good (5) or good (4) and as poor if the reply was moderate (3), bad (2) or very bad (1).

To determine the overall responsiveness, we summed the scores of each domain and averaged them, then categorized the scores into good (combining the very good and good) and poor (combining moderate, bad and very bad) responsiveness (22).

Based on distribution of data, means, and standard deviation were used to present central values and dispersions in case of symmetrical distribution and median was used if the distribution was asymmetrical.

Comparison of performance of public and private CRCs (as good and poor) was done by a chi-square test. Finally, to decompose the gap between good performance of autonomy in public and private physical rehabilitation centers Blinder-Oaxaca (BO) method was used (33, 34). Outcome of interest was good performance of autonomy domain by center type. The performance of autonomy variable was measured by a question: "Overall, how would you rate your experience of getting involved in making decision about your care or treatment (rehabilitation) as much as you wanted in the last 12 months." The responses then dichotomized in to two groups as good autonomy (combining good and very good) and poor autonomy (combining moderate, bad, very bad).

Explanatory variables which included in the model were age (years), education (years), perceived health status (self-report as good health or bad health), perceived social class (self-report as low, middle, high), economic status [as residential area per capita ($m^2$) -by calculating the ratio of residential area to household size-].

Blinder-Oaxaca decomposition model explains how much of the difference between the two groups in the outcome variables is due to differences in the explanatory variables included in the model, across the groups and how much is due to coefficient effect as well as the other characteristics that have not been included in the model (35).

$$\overline{Y}^U - \overline{Y}^L = \left[\sum_{i=1}^{N^L} \frac{F(X_i^L \beta^H)}{N^L} - \sum_{i=1}^{N^H} \frac{F(X_i^H \beta^H)}{N^H}\right] + \left[\sum_{i=1}^{N^L} \frac{F(X_i^L \beta^L)}{N^L} - \sum_{i=1}^{N^L} \frac{F(X_i^L \beta^H)}{N^L}\right] \quad (2)$$

In Equation (1), $N$ refers to the sample size of public and private center users. In the first bracket, the phrase indicates the portion of the gap in the good performance in autonomy of public and private centers pertaining to differences in the explanatory characteristics that have been included in the model. The second phrase shows the part of the mentioned gap that relates to differences in the effects of these characteristics on the performance of autonomy (unexplained components or coefficient effect).

We used STATA software (V11) for the analysis. The level of statistical significance was considered as ($p \leq 0.05$) in this study.

## Ethics and Consent

This study was conducted after gaining approval from the ethical committee of the University of Social Welfare and Rehabilitation Sciences (ethical code: IR.USWR.REC.1395.86) and receiving permission from the management boards of the private and public rehabilitation centers and from the medical universities responsible for health services in the area. The service users who met the inclusion criteria were instructed about the goals of our study and were assured about confidentiality of data; they were included after providing informed written consent.

# RESULTS

Of the 610 service users with physical disability included in our study, 298 (48.7%) were women and 312 (51.3%) were men. The mean age of the people referred to CRCs was 46.3 years ($SD$ = 14.3) for women and 45.6 years ($SD$ = 15.4) for men. All users had used only a single rehabilitation center during the past 12 months. Approximately one third of people using CRCs during last 12 months were the service users of private centers (34.3%), while public centers accounted for 65.7% of the sample.

Among various rehabilitation services, physiotherapy was the most commonly referred service (60.4%). Other services used were occupational therapy (32.1%), orthosis, and prosthesis (4.8%) and a mixture of physiotherapy and occupational therapy (2.7%).

**TABLE 1 |** Socio-demographic characteristics of the people with physical disability by center type.

| Characteristic | Frequency (%) | | |
|---|---|---|---|
| | Public | Private | Total |
| **SEX** | | | |
| Male | 212 (52.5) | 100 (49.0) | 312 (51.3) |
| Female | 192 (47.5) | 104 (51.0) | 296 (48.7) |
| Total | 404 (100) | 204 (100) | 608(100) |
| **AGE** | | | |
| 18-59 | 322 (79.3) | 153 (75.7) | 475 (78.1) |
| 60≤ | 84 (20.7) | 49 (24.3) | 133 (21.9) |
| Total | 406 (100) | 202 (100) | 608 (100) |
| Mean age | 44.8 ($SD$ = 14.7) | 48.2 ($SD$ = 15.0) | 45.9 ($SD$ = 14.9) |
| **EDUCATION** | | | |
| 5< (Elementary) | 12 (3.0) | 8 (3.9) | 20 (3.3) |
| 5–12 (Intermediate/high school) | 196 (48.3) | 88 (43.4) | 284 (46.6) |
| >12 (Upper) | 198 (48.8) | 107 (52.7) | 305 (50.1) |
| Total | 406 (100) | 203 (100) | 609 (100) |
| Mean years of education | 13.0 ($SD$ = 4.8) | 13.3 ($SD$ = 5.6) | 13.1 ($SD$ = 5.0) |
| **HEALTH INSURANCE COVERAGE** | | | |
| Yes | 369 (91.8) | 193 (97.5) | 562 (93.7) |
| No | 33 (8.2) | 5 (2.5) | 38 (6.3) |
| Total | 402 (100) | 198 (100) | 600 (100) |
| **PERCEIVED SOCIAL CLASS** | | | |
| Low | 113 (28.0) | 26 (12.8) | 139 (22.9) |
| Middle | 289 (65.3) | 144 (70.9) | 408 (67.2) |
| High | 27 (6.7) | 33 (16.3) | 60 (9.9) |
| Total | 404 (100) | 203 (100) | 607 (100) |
| **ECONOMIC STATUS[RESIDENTIAL AREA PER CAPITA ($m^2$)]** | | | |
| Under median | 217 (55.2) | 114 (57.0) | 331 (55.8) |
| Upper median | 176 (44.8) | 86 (43.0) | 262 (44.2) |
| Total | 393 (100) | 200 (100) | 593 (100) |
| Mean of residential area per capita | 38.5 ($SD$ = 20.8) | 44.4 ($SD$ = 35.0) | 40.5 (26.6) |
| **PERCEIVED HEALTH STATUS** | | | |
| Good health | 189 (46.8) | 108 (53.5) | 297 (49.9) |
| Bad health | 215 (53.2) | 94 (46.5) | 309 (51.0) |
| Total | 404 (100) | 202 (100) | 606 (100) |

The socio-demographic characteristics of the people with physical disability are shown in **Table 1**.

As seen in **Table 1**, majority of people in both public and private rehabilitation centers reported themselves as belonging to middle social class. About two third of all people who reported their health status as bad, were the service users of public sector.

## Assessment of Responsiveness

In all centers, a total of 126 respondents (20.9%) assessed overall responsiveness as poor, and the remainder (79.1%), perceived responsiveness as good.

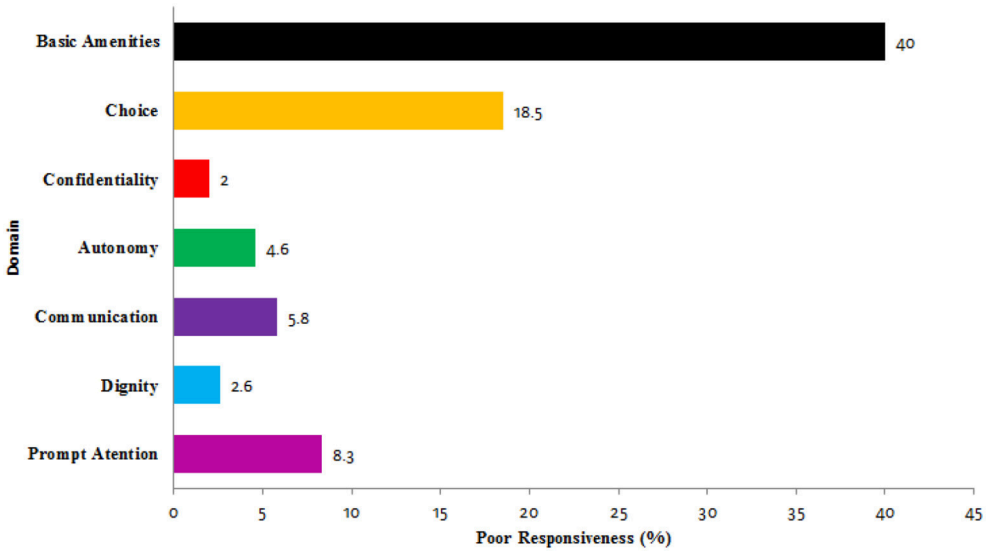


**FIGURE 1 |** Percentage of people perceiving responsiveness as poor in each domain.

The percentage of people who reported responsiveness as poor in each domain is illustrated in **Figure 1**.

It can be determined from **Figure 1** that confidentiality is the best performing domain, followed by dignity. Basic amenities was the poorest domain, followed by the domains of choice and prompt attention.

## Importance of the Domains

The domains of responsiveness selected as the most important by respondents are shown in **Figure 2**.

As seen in **Figure 2**, prompt attention and confidentiality were the most and the least important domains, respectively.

## Responsiveness of Public VS. Private Sector

Among participants, 22.5 and 17.9% of them rated their experience as poor in public and private comprehensive rehabilitation centers, respectively.

Comparison of responsiveness in public and private CRCs showed that people referred to public CRCs had poorer experience in the domains of communication[$x^2(1) = 7.95$, $P = 0.005$], autonomy [$x^2(1) = 9.03$, $P = 0.003$], and basic amenities [$x^2(1) = 23.76$, $P < 0.001$] (**Table 2**).

**Table 2** shows that the experience of people in public and private sector was significantly different in three domains (autonomy communication, basic amenities).

Comparison of responsiveness domains by private and public centers is illustrated in **Figure 3**.

As seen in **Figure 3**, Based on respondents' viewpoint, performance of three domains (autonomy communication, basic amenities,) are poorer in public sector compared to private sector CRCs.

## Performance of Autonomy and the Gap Between Private and Public Sectors

As seen in **Table 3**, in lower perceived social class, lower economic status, bad health status and in age of 60 and over, poor autonomy was reported in a higher percentage.

Decomposition of the gap in autonomy performance between the private and public centers is shown in **Table 4**.

As seen in the **Table 4**, among the explanatory factors (age, education, perceived health status, perceived social class, economic status), perceived social class was the largest contributor in explaining inequality in autonomy performance between public and private physical rehabilitation centers (76%).

# DISCUSSION

The current study was carried out to assess how people with physical disabilities report rehabilitation service responsiveness. To our knowledge (after an extensive literature review), there is a very limited number of studies in the field of physical rehabilitation in Iran. While being a strength of our study, our findings could therefore only be compared with studies conducted in the field of other chronic diseases.

Approximately one out of 5 people experienced poor responsiveness in the current study. Other studies on outpatient services for chronic diseases showed that in patients with mental disorders, poor responsiveness was reported by about one out of 2 service users (22), and in individuals with diabetes (25) and heart diseases (24), this rate was reported by 1 out of 3 respondents. This suggests that rehabilitation centers might have a better responsiveness rate. One possible explanation for this discrepancy is that studies of mental health responsiveness and responsiveness to patients with heart disease were implemented only in the public centers where responsiveness was rated

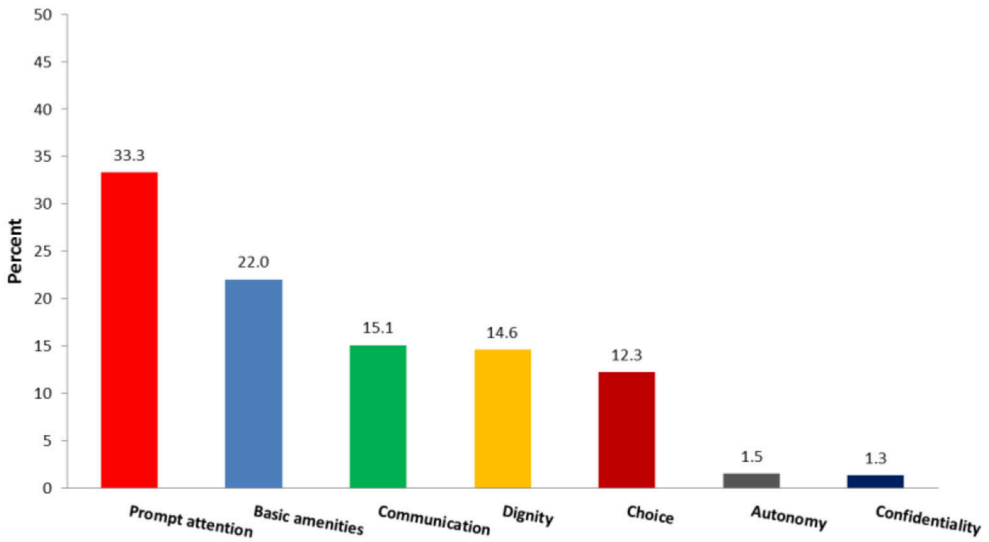


**FIGURE 2 |** Overall responsiveness and importance of domains according to respondents' view.

**TABLE 2 |** Respondents' experiences in public and private rehabilitation centers by responsiveness domains.

| Domain | Performance | Public rehabilitation centers (%) | Private rehabilitation centers (%) | $x^2$ Value | *P*-value |
|---|---|---|---|---|---|
| Prompt attention | Good | 371 (91.8) | 185 (91.6) | 0.011 | 0.91 |
| | Poor | 33 (8.2) | 17 (8.4) | | |
| Dignity | Good | 390 (96.8) | 198 (98.5) | 1.56 | 0.21 |
| | Poor | 13 (3.2) | 3 (1.5) | | |
| Communication | Good | 375 (92.4) | 198 (98.0) | 7.95 | 0.005* |
| | Poor | 31 (7.6) | 4 (2.0) | | |
| Autonomy | Good | 379 (93.6) | 200 (99.0) | 9.03 | 0.003* |
| | Poor | 26 (6.4) | 2 (1.0) | | |
| Confidentiality | Good | 394 (97.8) | 199 (98.5) | 0.387 | 0.53 |
| | Poor | 9 (2.2) | 3 (1.5) | | |
| Choice | Good | 328 (81.0) | 167 (82.7) | 0.254 | 0.61 |
| | Poor | 77 (19.0) | 35 (17.3) | | |
| Basic amenities | Good | 216 (53.2) | 149 (73.8) | 23.76 | 0.001* |
| | Poor | 190 (46.8) | 53 (26.2) | | |
| Overall responsiveness | Good | 307 (77.5) | 165 (82.1) | 1.67 | 0.19 |
| | Poor | 89 (22.5) | 36 (17.9) | | |

**Significant ($P \leq 0.05$).*

lower overall. The other factor that should be considered is the characteristic of disease or disorder in users.

Our findings indicated that people with disabilities receiving services from rehabilitation centers in Tehran, reported their experience regarding confidentiality as the highest, followed by dignity, while they reported basic amenities as the poorest. This suggests that information related to the service users and their medical situation were not divulged, and their privacy was protected. This outcome also suggests that people with disabilities were treated respectfully in CRCs but in a physical environment that was not pleasant. Findings about best performing domains are in agreement with the results of Sajjadi et al. in people with diabetes mellitus in Tehran in 2014 (25) and of Rashidian et al., who conducted a household study about health system responsiveness in district 17 of Tehran city in 2003 (36) and of Peltzer et al. among older adults in South Africa in 2008 (37). But Wang et al. in China in their study on primary care in rural area found confidentiality as worst performing domain (38). This discrepancy could be due to different contexts as Wang studied in rural area where confidentiality may be more of concern in small population compared with large populations such as in Tehran. Results regarding the poorest performing domains supports those of Piroozi et al. in Sanandaj, a western city of Iran in

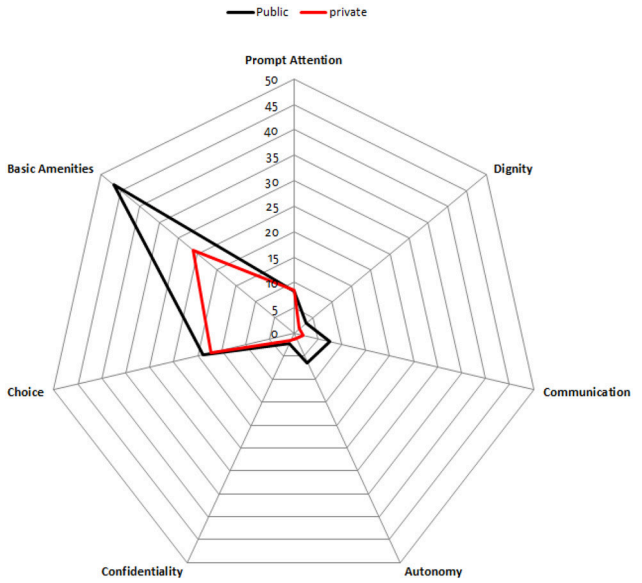


**FIGURE 3 |** Percentages of users' rating their experience as poor by responsiveness domains in public and private CRCs.

2014–2015 (27) and Torabipour et al. that investigated the responsiveness of physiotherapy clinics in Ahvaz in south of Iran in 2014 (39).

In current study, prompt attention was the most important domain from the respondents' viewpoint. This indicates that access to services in a proper waiting time was very important. This finding supports the results of Karami et al. in their study on people with heart disease in Tehran in 2012–2013 (24) as well as an investigation on responsiveness of delivery care in Thailand in 2008 (26). We also found that confidentiality was the least important domain based on respondents' viewpoint. Like vise, confidentiality was reported as the least importance in study of Mohammadi et al. in out-patient clinics of Zanjan in 2013 (40). However, Forouzan et al. found confidentiality to be one of the most important domains reported by people with mental disorders (22). The nature of disease or disorder seems to be the main factor in determining domains of higher priority.

Interestingly, our study indicated that people referred to private CRCs had a better experience than the users of public ones in terms of environment and basic amenities, communication with the health providers, and being involved in their health plans. In a study on responsiveness in Bangladesh in 2017, private rehabilitation centers were more responsive in informing and guiding the service users (41). Also, Adesanya et al. in Nigeria in 2011 found better performance of domains of dignity and prompt attention in private hospitals comparing to public sector (42). Better responsiveness of private centers has also been found in previous studies, both for outpatient and inpatient health care (19, 28, 36, 43). But Wang in rural area in China found the public sector to be more responsive in the primary care centers based on users' viewpoint. Wang reported that characteristics of service users referring to public sector was more equally distributed (38).

In this study we focused on autonomy to find how users' characteristics could explain the difference between public and private sectors. People are expecting for quality of care in domains of communication and especially basic amenities but Autonomy is more than just demanding quality of care. By participating in the decisions-making processes, patients actively exercise their fundamental rights to be involved in the health process and not to be passive about their health decisions as we see in paternalistic models (44). We found that perceived social class was the main factor which explained the gap in autonomy between the public and private rehabilitation centers. It indicates that inequalities in autonomy due to center type could be decreased if the individuals who use these services were more similar in terms of the social class that they perceive they belong to. One probable socio-economical reason could be that people perceived themselves as belonging to lower social class may refer to public centers as seen in the current study. Although responsiveness refers to non-medical, non-financial aspects of health system performance, people's orientation in the selection of public or private centers may be related to their socio-economic situation in Iran. Based on reports, percentage of private expenditure per capita out of total expenditure on health was 59.2% in Iran in 2013 and 88% of private expenditure on health estimated to be out of pocket (45). The out of pocket payments in private rehabilitation centers, may prevent people from lower socio-economic classes from accessing/using them. As a consequence, these people would turn to public rehabilitation centers. In previous study on responsiveness of public mental health centers, Forouzan et al. found that people in lower social class were more likely to report poor responsiveness (22).

Finally it should be emphasized that individual well-being is influenced by the way the person is treated (14). Understanding the experiences and expectations of service users is essential to increase the utilization of health care services, to decrease treatment dropout rates, to encourage earlier seeking of care, to be more open in interactions with health care providers and to better follow the health instructions, thus generating better health outcomes (14, 46). The way patients are treated when they interact with health systems/subsystems is important because it relates to basic human rights (47). Studies that describe and analyze how health systems are performing and how this relates to health system characteristics provide information that helps to identify the gaps in knowledge, to share the information with other countries and populations and to discuss improvements needed for better outcomes. Further investigation on people with other disabilities in terms of mental disability is recommended to assess the responsiveness of health system in the field of rehabilitation to people with disability as a vulnerable group.

## Study Limitations

This study had some limitations. Non-probability sampling in Tehran was one of our limitation in current study, Therefore, generalization to other population and sub-systems should be

**TABLE 3 |** Performance of autonomy domain based on socio-demographic sub-groups' point of view by type of center.

| Characteristic | Autonomy performance frequency (%) | | | | | |
|---|---|---|---|---|---|---|
| | Public | | Private | | Total centers | |
| | Good | Poor | Good | Poor | Good | Poor |
| **SEX** | | | | | | |
| Male | 196(92.9) | 15 (7.1) | 99 (100) | 0 (0) | 295 (95.2) | 15 (4.8) |
| Female | 183 (95.3) | 9 (4.7) | 101 (98.1) | 2 (1.9) | 284 (96.3) | 11 (3.7) |
| **AGE** | | | | | | |
| 18-59 | 301 (93.8) | 20 (6.2) | 152 (99.3) | 1 (0.7) | 453 (95.6) | 21 (4.4) |
| 60≤ | 78 (92.9) | 6 (7.1) | 46 (97.9) | 1 (2.1) | 124 (94.7) | 7 (5.3) |
| Mean age | 45.1 ($SD = 14.5$) | 40.1 ($SD = 16.7$) | 47.9 ($SD = 15.0$) | 55.0 (15.5) | 46.1 ($SD = 14.7$) | 41.2 ($SD = 16.8$) |
| **EDUCATION** | | | | | | |
| 5< (Elementary) | 12 (100) | 0 (0) | 8 (100) | 0 (0) | 20 (100) | 0 (0) |
| 5–12 (Intermediate/high school) | 184 (93.9) | 12 (6.1) | 84 (97.7) | 2 (2.3) | 268 (95.0) | 14 (5.0) |
| >12 (Upper) | 193 (92.9) | 14 (7.1) | 107 (100) | 0 (0) | 290 (95.4) | 14 (4.6) |
| Mean years of education | 13.0 ($SD = 4.8$) | 13.0 ($SD = 4.9$) | 13.4 ($SD = 5.5$) | 8.5 ($SD = 4.9$) | 13.1 ($SD = 5.0$) | 12.6 ($SD = 4.9$) |
| **PERCEIVED SOCIAL CLASS** | | | | | | |
| Low | 102 (90.3) | 11 (9.7) | 25 (96.2) | 1 (3.8) | 127 (91.4) | 12 (8.6) |
| Middle | 249 (94.3) | 15 (5.7) | 143 (100) | 0 (0) | 392 (96.3) | 15 (3.7) |
| High | 26 (100) | 0 (0) | 32 (100) | 0 (0) | 58 (100) | 0 (0) |
| **ECONOMIC STATUS (RESIDENTIAL AREA PER CAPITA) ($m^2$)** | | | | | | |
| Under median | 202 (93.1) | 15 (6.9) | 112 (99.1) | 1 (0.9) | 314 (95.2) | 16 (4.8) |
| Upper median | 165 (94.3) | 10 (5.7) | 85 (100) | 0 (0) | 250 (96.2) | 10 (3.8) |
| Mean of residential area per capita | 38.4 ($SD = 20.9$) | 39.5 ($SD = 20.4$) | 44.5 ($SD = 35.2$) | 22.5 ($SD = 0$) | 40.6 ($SD = 26.9$) | 38.9 ($SD = 20.0$) |
| **PERCEIVED HEALTH STATUS** | | | | | | |
| Bad health | 198 (92.1) | 17 (7.9) | 92 (97.9) | 2 (2.1) | 290 (93.9) | 19 (6.1) |
| Good health | 180 (95.7) | 8 (4.3) | 108 (100) | 0 (0) | 288 (97.3) | 8 (2.7) |

**TABLE 4 |** Decomposition of the gap in domain of autonomy performance by the private and public sectors.

| Variables | Coefficient (95% CI) | *P*-value |
|---|---|---|
| Good status (Good performance) in private | 0.061 (0.037 to 0.085) | 0.0001 |
| Good status (Good performance) in public | 0.005 (−0.004 to 0.015) | 0.3 |
| Differences (total gap) | 0.56 (0.030 to 0.082) | 0.0001 |
| Total :Due to endowments (explained) | 0.013 (0.003 to 0.023) | 0.01 |
| Age | 0.002 (−0.0018 to 0.007) | 0.2 |
| Education | −0.0001(−0.0012 to 0.0009) | 0.7 |
| Perceived health status | 0.002 (−0.001 to 0.001) | 0.2 |
| Economic status (Residential area Per Capita) | −0.002(−0.006 to 0.001) | 0.2 |
| Perceived social class | 0.010 (0.001 to 0.020) | 0.02 |
| Total :Due to coefficients (unexplained) | 0.043 (0.018 to 0.068) | 0.001 |
| Age | −0.067 (−0.154 to 0.20) | 0.13 |
| Education | −0.006 (−0.63 to 0.050) | 0.8 |
| Perceived health status | −0.038 (−0.112 to 0.036) | 0.09 |
| Economic status (Residential area Per Capita) | 0.028 (−0.019 to 0.077) | 0.2 |
| Perceived social class | −0.062 (−0.172 to 0.048) | 0.2 |
| Constant | 0.188 (0.140 to 0.362) | 0.03 |

conservative. However, the geographic location and spread of sample centers was such that we had satisfactory coverage of the service users in Tehran, both in the public and private sectors.

Another limitation was that most of the data especially on socio-demographic variables including health status were gathered based on respondents' self-report so are prone to under-reporting.

## CONCLUSIONS

Since disability is a chronic process and people with disabilities need continuous rehabilitation, the responsiveness of comprehensive rehabilitation centers is critical to successful rehabilitation.

Overall, improvement of responsiveness in domains that are of high importance from the respondents' viewpoint but are performing poorly, such as prompt attention and basic amenities, is essential. Better access to the rehabilitation centers is recommended as most of the CRCs, especially private centers, are in the north of Tehran where people with high socioeconomic status are living. Persons with disabilities should be able to choose their favorite centers and rehabilitation professionals with more freedom.

Public rehabilitation centers should provide high standards in environment, facilities and basic amenities and communicate clearly with the service users. People with disabilities using public rehabilitation centers, especially people who perceive themselves as belonging to the lower social class, should be more involved in the decision-making process regarding their health.

To be most effective, all interventions to improve responsiveness in rehabilitation centers especially public sector should involve policy-makers. Training of service providers, and informing the service users of their own rights when interacting with the health system are also important and recommended.

## AUTHOR CONTRIBUTIONS

MA conception and designing of the study, data collection, analysis of data, interpretation of data and drafting the manuscript. MRKA designing of the study, contribution in planning, implementing the study and coordinating field work, reading, and commenting the manuscript and the revised version. MM-L leading the analysis of data, interpretation of data, reading, and commenting the manuscript and the revised version. HS designing of the study, interpretation of data, reading and commenting the manuscript and the revised version. MS designing of the study, reading, and commenting the manuscript and the revised version. MN analysis of data, interpretation of data, reading and commenting the manuscript and the revised version. ASF designing of the study, analysis of data, interpretation of data and critical revision of the content of manuscript.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2018.00317/full#supplementary-material

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REVIEW
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# Global Inequities in Precision Medicine and Molecular Cancer Research

*Thomas M. Drake*[1]*, *Stephen R. Knight*[1], *Ewen M. Harrison*[1] and *Kjetil Søreide*[1,2,3]*

[1] Department of Clinical Surgery, University of Edinburgh, Edinburgh, United Kingdom, [2] Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway, [3] Department of Clinical Medicine, University of Bergen, Bergen, Norway

Precision medicine based upon molecular testing is heralded as a revolution in how cancer is prevented, diagnosed, and treated. Large efforts across the world aim to conduct comprehensive molecular profiling of disease to inform preclinical models, translational research studies and clinical trials. However, most studies have only been performed in patients from high-income countries. As the burden on non-communicable diseases increases, cancer will become a pressing burden across the world, disproportionately affecting low-middle income settings. There is emerging evidence that the molecular landscape of disease differs geographically and by genetic ancestry, which cannot be explained by environmental factors alone. There is a lack of good quality evidence that characterises the molecular landscape of cancers found in low-middle income countries. As cancer medicine becomes increasingly driven by molecular alterations in high-income settings, low-income settings may become left behind. Further efforts on an international scale must be made by researchers, funders, and policymakers to ensure cancer research addresses disease across the world, so models are not limited to subtypes of disease found in high-income countries. In this review, we discuss differences found in the molecular profiles of tumours worldwide and the implication this has for the future of global cancer care. Finally, we identify several barriers currently limiting progress in this field and innovative solutions, which may address these shortcomings.

**Keywords: cancer, surgery, oncology, genomics, low-income, global health, global surgery, precision medicine**

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*Umberto Malapelle,*
*Università degli Studi di Napoli Federico II, Italy*

***Correspondence:**
*Thomas M. Drake*
*t.drake@ed.ac.uk*
*Kjetil Søreide*
*ksoreide@mac.com*

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## INTRODUCTION

The incidence of cancer across the world is increasing, with the number of new cases set to rise by 70% in the next 20 years (1). This rise in incidence is accompanied by a sharp increase in cancer mortality, which disproportionately affects patients in low-middle income countries (2). As the global burden of communicable disease decreases with improvements in prevention, sanitation and treatment, non-communicable diseases such cancer will become a pressing burden. Whilst low and middle-income countries (LMICs) contend with barriers, such as delays in accessing healthcare, advanced disease at presentation, and limited access to treatment; research, and clinical practice in high income countries (HICs) is aimed toward developing treatment strategies tailored to individual patient characteristics and tumour biology.

Revolutionary polyomic (genomic, epigenomic, transcriptomic, proteomic, **Figure 1**) technologies have become established in clinical research and are increasingly commonplace in clinical practice in HICs. These technologies are set to revolutionise how research is performed and how therapies are selected—bringing precision medicine closer to reality than ever before. Indeed, the pharmaceutical industry are producing new agents designed to target specific molecular subtypes of disease. New prognostic modelling techniques, incorporating molecular data, clinical data and machine learning will provide more information to inform treatment choices for both patients and clinicians.

These evolving capabilities are set to transform outcomes, however, there is little consideration given to how these technologies can improve cancer outcomes across the world and applicability to LMICs. Despite these remarkable advances, most research and clinical trials are conducted on populations within HICs, thus limiting global generalisability. There is clear evidence that basic cellular processes vary across different human populations (3, 4). Despite this, only 3% of genome-wide association studies have been performed in Africans, without considering sequencing studies (5, 6). Evidence in HICs from studies comparing individuals from different ancestries has found that despite controlling for socioeconomic factors and other environmental exposures, there is still a large disparity in cancer incidence and outcomes that remains to be addressed (7, 8). To prevent advances in technologies creating even greater disparity in cancer care across the world, work must now be expanded to include low and middle-income settings.

## CANCER IN LOW AND MIDDLE-INCOME SETTINGS

Across the spectrum of country development and geography, there are marked differences in the burden of cancer-related disease. Compared to well developed countries, LMICs have a higher age-standardised rate of gastric, oesophageal, bladder and liver cancers (**Table 1**). Although LMICs appear at present to have lower rates of lung, colorectal, pancreas and haematological malignancies, the 2016 Global Burden of Disease study has identified sustained rises between 1990 and 2016 of healthy years of life lost to these cancers (2).

This socio-economic and geographical variation in causes of cancer across the world has implications for both clinical practice and future research. This difference in disease profile is multifactorial (**Figure 2**) and includes environmental factors, infectious agents (i.e., hepatitis B (HBV), hepatitis C (HCV), Human Immunodeficiency Virus (HIV), and *Helicobacter pylori*), occupational exposures and other lifestyle factors (smoking, alcohol use) amongst others. In addition to considerable differences in these risk factors, lower levels of resources for healthcare and education result in patients presenting to healthcare facilities with advanced disease in less developed countries.

It is important to consider the context of cancer disease in LMICs can be somewhat different to developed settings and the implications this has. In this review we will explore how the molecular aetiology and epidemiology of cancer in less developed settings may differ and explore the impact this has for the future of clinical practice and research.

## MOLECULAR DIVERGENCE IN CANCER AETIOLOGY

Evidence suggests there is variation in both somatic, germline, and epigenetic alterations found across different human populations (3, 4). What is emerging suggests there are key genetic differences in some solid tumours when disease found in LMIC countries is compared to that in HICs (9–13).

In both African and middle-eastern countries, germline mutations in loci predisposing to breast, ovarian and colorectal cancer have been characterised in a small number of studies (14–19). In breast cancer for example, mutations in the BRCA1 and BRCA2 genes are more commonly found, with one Nigerian study identifying mutation rates of 7.9% for BRCA1 and 3.1% for BRCA2—far higher than in the cancer genome atlas (TCGA), where these are 1.3 and 1.5% respectively (16). Evidence from Tunisia and Morocco is concordant, with a higher rate of BRCA1/BRCA2 mutations, with some found to be novel, previously uncharacterised, of unknown clinical significance (14, 18, 20).

The same holds true for colorectal cancer, where there is little population-level data surrounding the prevalence of germline mutations in common cancer susceptibility genes. Germline mutations reported in the literature from African countries suggest that these variants are typically different from those found in HICs and the clinical significance of these mutations remains poorly characterised (7, 21–23).

Somatic and germline alterations across tumour types are not exclusively limited to low-middle income countries; racial disparity in the molecular composition of tumours also affects patients in HICs. Within the United States, for all cancers combined those of African-American ethnicity have been found to have mortality rates up to 25 percent higher than in Caucasian Americans (24). Several studies from TCGA and others have identified several key alterations in the somatic landscapes of tumours from African-Americans or Asian patients for renal, endometrial, breast, head and neck, colorectal, cervical and prostate cancers (25–29). Frequently, the differences in the mutational landscape of these tumours are in pivotal cancer driver genes, such as the von Hippel-Lindau (VHL) gene in clear cell renal cancer (26).

Furthermore, oncogenes are found to be differentially mutated in different ancestral groups, for example in endometrial cancer where PTEN mutations were found to predominate in those of Caucasian or Asian descent, whereas in African-Americans TP53 mutations are more common. These variations across ancestral groups extend to the nucleotide level, with mutational signatures having significantly divergent nucleotide signatures when compared to mutations found in Caucasian populations (27). Several initiatives are underway to address this, such as the American Association for Cancer Research (AACR) 2020

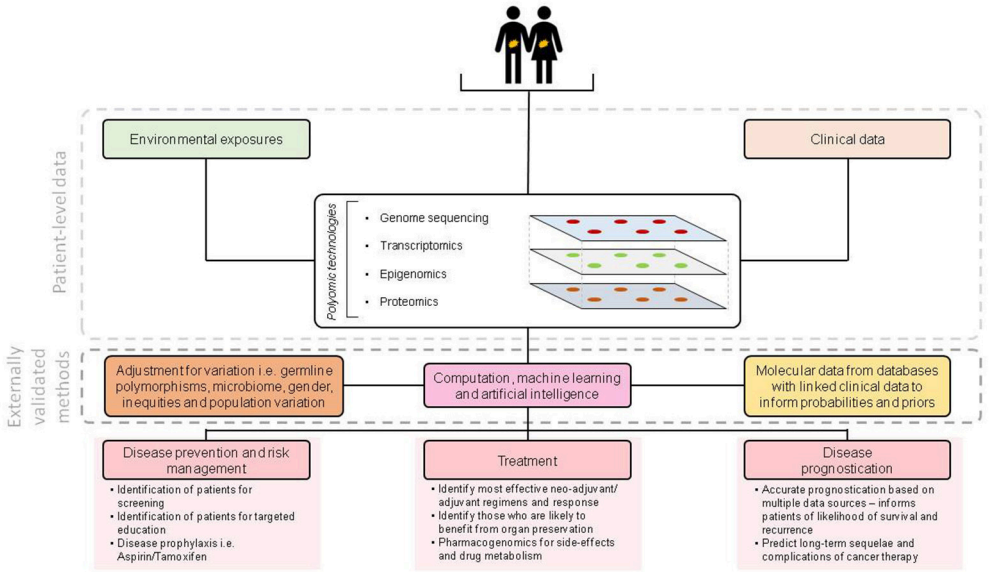


**FIGURE 1 |** Overview of molecular technologies for enabling precision medicine.

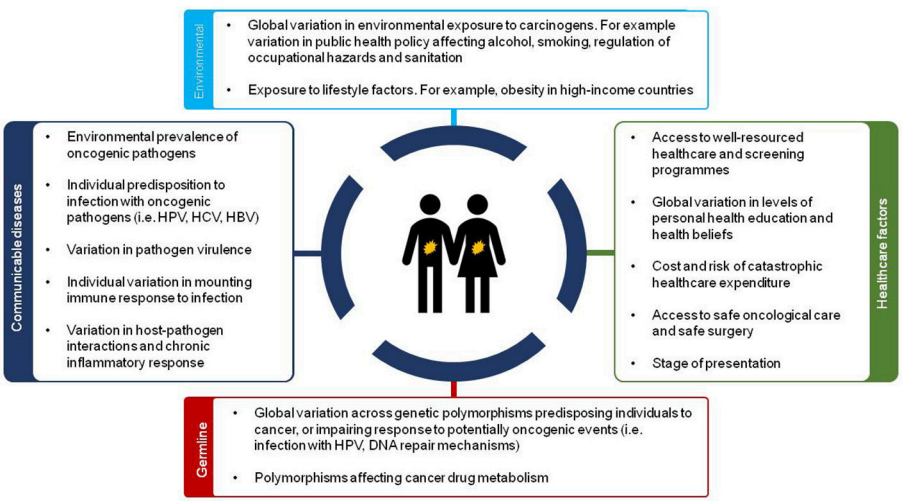


**FIGURE 2 |** Overview of sources of disparity in future cancer care across the world.

by 2020, which aims to sequence matched normal tissue and tumour for 2020 African-American cancer patients by 2020 (30). It is unclear whether the 2020 by 2020 initiative would utilise whole exome or whole genome sequencing. The latter would give a far richer pool of information on which to base further studies upon.

Globally, projects aimed at defining the human genome and cancer biology on a regional basis are beginning to emerge. For example, the International Cancer Genome Consortium (ICGC) is aimed at developing a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 tumour types, with data from 16 countries already included (31). Recent publications have characterised the whole genomes of 560 breast cancers, demonstrating more than 90 mutated cancer genes were implicated in carcinogenesis, and that the mechanisms underlying most mutational signatures are presently unknown (32, 33). Unfortunately, LMICs (i.e., sub-Saharan Africa) are poorly represented within the project, as with many international genome collaborations, which limits conclusions and applicability on a truly global scale.

## Pharmacogenomics

Genetic polymorphisms affecting the metabolism of chemotherapy drugs may also be different across different ancestral groups. Differences in frequencies of functional genetic variants in key drug response and metabolism genes may

**TABLE 1 |** Relative increases in cancer burden by income setting.

| Cancer | HIC number of cases 1990 | LMIC number of cases 1990 | HIC number of cases 2016 | LMIC number of cases 2016 | Fold change HIC | Fold change LMIC |
|---|---|---|---|---|---|---|
| Breast cancer | 467198 | 70634 | 726622 | 190102 | 1.56 | 2.69 |
| Tracheal, bronchus, and lung cancer | 476710 | 72750 | 746752 | 159990 | 1.57 | 2.20 |
| Stomach cancer | 256111 | 98378 | 292833 | 136618 | 1.14 | 1.39 |
| Colon and rectum cancer | 477269 | 47737 | 792174 | 112741 | 1.66 | 2.36 |
| Other neoplasms | 96362 | 39052 | 247574 | 105289 | 2.57 | 2.70 |
| Liver cancer | 80650 | 46993 | 189298 | 91647 | 2.35 | 1.95 |
| Prostate cancer | 419216 | 25137 | 899317 | 74721 | 2.15 | 2.97 |
| Pancreatic cancer | 99603 | 18608 | 192036 | 39197 | 1.93 | 2.11 |
| Bladder cancer | 133992 | 14391 | 213500 | 34771 | 1.59 | 2.42 |
| Kidney cancer | 92384 | 9864 | 160805 | 25876 | 1.74 | 2.62 |
| Uterine cancer | 89318 | 12357 | 188007 | 25635 | 2.10 | 2.07 |
| Malignant skin melanoma | 83987 | 2293 | 211113 | 5763 | 2.51 | 2.51 |

*Global Burden of Disease estimates for cancer incidence (raw case number) in High SDI (HIC) and Low Middle Income (LMIC) countries in 1990 and 2016. Fold change in these is displayed in right hand columns. Considerable rises in cancer incidence in LMICs can be seen.*

significantly influence drug response differences in different populations (34–37).

Evidence from LMICs across the world is sparse, however, studies examining ethnic groups within HICs has identified substantial differences in treatment response and toxicities across ethnic groups. Understanding how these polymorphisms affect treatment response and side effects is important if precision medicine strategies are to be successfully implemented worldwide. These polymorphisms found across different ethnic populations can be beneficial or harmful. For example, African-Americans are more likely to have variants of the DPYD and TYMS genes which predispose this group to haematological toxicities with 5-fluorouracil as compared to Caucasian-Americans (38). Conversely, with 5-fluorouracil, Caucasian-Americans are more likely to suffer diarrhoea, nausea, vomiting, and mucositis when compared with their African-American counterparts. A similar picture is true in the metabolism of Doxorubicin, where African-Americans are more likely to suffer cardiotoxicities than Caucasian-Americans. Polymorphisms found in those of African ancestry may lead to life-threatening toxicities, such as neutropaenia. A fall in neutrophil counts following chemotherapy is more commonly found in patients of African-American and Asian descent when compared with Europeans (39). This may be due to a constitutionally lower neutrophil count (in the absence of cancer therapy), which has been associated with the presence of the Duffy antigen/receptor chemokine gene (DARC) rs2814778 SNP in a study examining 261 healthy volunteers (40). Several small studies examining the cytochrome P450, have identified polymorphisms across ethnic groups (41). Diversity in alleles of P450 is greatest across the African continent, compared to in Europe, and Asia. Where the CYP2B6, CYP2C8, CYP2D6, CYP2D6, CYP2D6, CYP3A5, and CYP3A5 have greatest diversity. Drugs associated with varied metabolism in the presence of polymorphisms affecting these genes include cyclophosphamide (CYP2B6*6), paclitaxel (CYP2C8*2) and $5HT_3$ receptor antagonists (CYP2D6). Despite this, the clinical implications these polymorphisms have for cancer therapy in the context of LMICs are poorly characterised. The polymorphisms found across these populations should be considered in the context of the healthcare infrastructure available. If patients in LMICs have similar diversity in polymorphisms associated with drug metabolism, then consideration must be given to the risk of exposing these patients to serious chemotherapy toxicities. Work is currently underway to try and identify polymorphisms associated with the metabolism of drugs found on the WHO's essential medicines list, beginning with HIV, which could be extended into cancer therapeutics and provide useful information to those administering treatments in LMICs (34, 42). Whole-genome precision medicine approaches to pharmacogenomics at the individual patient level are likely to be some way off, however, a precision medicine approach to public health could have significant advantages. In some ways, this population level consideration of the genetic diversity within a given population has started to occur. For example, in Ethiopia studies have revealed that a high proportion of the population are rapid codeine metabolisers due to CYP2D6 polymorphisms, leading to rapid conversion of codeine to morphine and subsequent overdose at therapeutic doses (100).

## MOLECULAR DIVERSITY AFFECTING COMMUNICABLE CAUSES OF CANCER

Communicable diseases contribute toward a considerable proportion of the cancer burden in LMICs. These are potentially preventable cancers, with infectious agents commonly arising from poor sanitation, vertical transmission (mother to child), horizontal transmission (person to person) and a lack of safe healthcare practices (i.e., needlestick injuries and reused sharps). Examples include infectious agents such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), human papilloma virus (HPV), and Epstein-Barr virus (EBV), which are well known for their oncogenic potential.

Prevention programmes over the past 20 years have increasingly begun to recognise this, and vaccination programmes aimed at preventing hepatitis B have been shown to be effective in reducing the incidence of hepatocellular carcinoma. Similar can be seen for HPV vaccination, where programmes have begun to be rolled out in an increasing number of LMIC settings (43). Despite these initiatives, little is known as to the molecular landscape of these organisms and subsequent host-pathogen interactions.

## Hepatocellular Carcinoma (HCC)

The effects of viral hepatitis on the development of hepatocellular carcinoma is well characterised in HICs. With global vaccination programmes aimed at preventing HBV underway, we may observe a decrease in HBV associated HCC. Despite this, HCC is multifactorial and infection with HCV or other causes of cirrhosis typically contribute to the risk of HCC development. The somatic landscape of HCC has been well characterised in American, European, Chinese and Japanese populations; however, evidence is lacking on disease found in LMICs (44, 45). The practicalities HCC poses to obtain tumour samples in LMICs are challenging, primarily owing to the risks associated with liver surgery and very late stages of presentation.

The distribution of HBV and HCV across the world has substantial variation and drive HCC formation in separate manners. HBV has a higher prevalence in LMICs and is responsible for the majority (%) of virus-induced hepatocellular carcinoma, compared with HCV (%) (46, 47). Dysregulation of key cell-cycle proteins, including cyclin dependent kinase 2 and 4, upregulation of the RAS/MAPK/ERK pathways and maintenance of upregulated canonical Wnt signalling, on the background of chronic inflammation are believed to initiate and drive HCV-related hepatocellular carcinoma (HCC) (48). HBV integrates within the host genome, initiating HCC through the promotion of genomic instability (49, 50).

Different genotypes of the Hepatitis C virus are known to lead to higher risk of HCC (51). Classically, the type 1b genotype has been associated with the highest risk of HCC formation. The global prevalence of HCV genotypes and variation worldwide has been studied in detail. Modelling studies demonstrate a high level of variation across the world in genotype, even within continents (46). Type 1 HCV predominates worldwide, however in central and west Africa, type 4 is more commonly found. Little data is available on why this variation exists and how this may reflect in disparity in HCC rates worldwide (46). In particular, study of genotype 4 and how this type mediates HCC formation in LMICs is missing. Host-pathogen interactions are known to play a crucial role in the clearance of these viruses and hence the subsequent risk of developing virus associated HCC. It is well known that patients of African ancestry have lower viral clearance rates than Caucasians (52). Several genome-wide association studies performed on patients of African descent have identified polymorphisms in alleles near class II Human Leukocyte Antigens on chromosome 6, the IL28B gene and other SNPs (53–56). This evidence draws upon a limited number of participants from LMICs and does not study the subsequent likelihood of HCC development.

The interaction between environmental and genetic factors may have a significant influence on the risk of HCC. The study of these interactions is limited in LMICs, however there are some examples of where this has been proven to be successful. Environmental exposures such as Aflatoxin B1 (found in certain grains and funghi), alcohol use, obesity, amongst others are known to contribute (57, 58). The interaction between Aflatoxin B1 and host genetics is particularly interesting: Aflatoxin B1 exposure is associated with HCC expressing more p53 mutations than in unexposed patients and may lead to greater genomic instability. Aflatoxin B1 has synergy with HBV, promoting HCC formation (59). Strategies to identify ways to abrogate DNA damage exerted by Aflatoxin B1 are under investigation and other environmental exposures are currently under study. Nevertheless, owing to little data on the molecular landscape of HCC in LMICs, it is unclear whether these research findings will have benefit for these patient groups. Similar epidemiological association studies have been done for other cancers, however, the data which provides the basis for disease models and translation to clinical practice in LMICs is lacking.

## Cervical Cancer

Cervical cancer disproportionately affects women in LMICs, with the highest incidence found in sub-Saharan Africa (1, 60). Cervical cancer deaths are higher in LMICs, with 9 out of 10 deaths from cervical cancer worldwide occurring in LMIC settings. At present radiotherapy and surgery are the mainstays of cervical cancer management. The cause for this disparity in cancer incidence across the world is poorly understood and is multifactorial. Availability of radiotherapy in LMICs is also known to be extremely limited (61).

A proportion of cervical cancer cases are preventable, through early identification of dysplastic disease and immunisation against HPV. There are close connections with HIV too, with women who are HIV at a higher risk of developing cervical cancer. The prevalence of HPV is higher in women in LMICs than in HICs (62). There is a particularly high prevalence in Africa and Oceania, with higher exposure at a younger age. This in part accounts for the higher burden of cervical cancer in LMICs and the epidemiological burden of HPV associated cervical cancer is well described. In HIC populations genetic associations have been associated with the development of cervical cancer and are relatively well characterised (63, 64). Host-pathogen interactions between HPV and the immune system are also relatively well-characterised with respect to disease found in HICs. In HICs, genes such as TGF-β, those governing toll-like-receptors (TLRs), MHC genes and expression of cytokines, intricately linked with immune responses are associated with effective clearance of HPV (65–67). The somatic landscape of these tumours in LMICs is poorly characterised.

Evidence in LMICs suggests polymorphisms on the TYMS and RPS19 genes are associated with high-risk infection in Nigerian women, but overall in LMICs evidence is lacking on factors influencing effective HPV clearance (68). Several studies of women in HICs of African ancestry have identified that women of African-American descent despite having a similar prevalence of HPV, take longer to clear the virus (69).

This delayed clearance, combined with known polymorphisms affecting genes responsible for immune response may go some way to explaining the higher rates of cervical cancer in LMICs (70). Further evidence is emerging that the distribution of HPV genotypes differs across separate geographical locations, with HPV 16 predominating worldwide, but HPV 58 and 31 more commonly found across Africa and East Asia. HPV 58 has been associated with increased risk of cervical cancer (71). Despite this work, there are scarce data from studies into virus genotype and genome-wide factors that may drive cervical cancer in LMICs.

## BARRIERS TO GLOBAL RESEARCH IN PRECISION MEDICINE

Genetic variation through germline polymorphisms and somatic mutations associated with cancers in LMIC populations, suggests there may be opportunity for implementing global strategies for more effective individualised treatment and better prognostication. In HICs, molecular testing is already being used to target therapies to specific alterations in tumours. Examples of this include the use of trastuzumab following HER2 testing in breast cancer, use of endocrine therapy in breast cancer and guiding EGFR targeted therapies in colorectal cancer using KRAS testing. In the case of colorectal cancer, both type and location of KRAS mutations are known to predict response to EGFR inhibition in colorectal cancer (72). There is some limited evidence to suggest EGFR/KRAS mutations occur in a similar pattern and distribution in LMICs as compared to HICs (22, 73, 74). However, in African-American populations within HICs, there is an increased frequency of mutations found in genes implicated in EGFR signalling, which may correspond with more aggressive disease (75, 76). Despite this, no clinical trials have aimed to include patients within these settings or sequence tumours to identify predictors of response. Building evidence to support precision medicine at a global level is important, both in terms of providing effective cancer therapies and being able to decide whether targeted therapies are cost effective in LMICs.

Building a sustainable workforce of clinicians, laboratory medicine and scientific leaders in this field is key. At present, in LMICs, implementing effective national programmes for precision cancer therapy and prevention following similar models to examples within HICs is unlikely to be feasible. A lack of trained laboratory medicine workforce, instruments, transportation, finances, and evidence to support the applicability of clinical response are all key factors (77–79). Access to pathology and laboratory medicine services in their current format is a major issue, with some LMICs having no workforce at all (77, 78). To support the implementation of precision medicine approaches to therapies, there is a pressing need to change this and ensure the emerging workforce have the skills to support the transition to precision medicine in these settings. Alongside the development of cancer therapies and research models, delivery of increasingly complex therapies requires major improvements in healthcare infrastructure and resource and it is optimistic to say that workforce development alone will enable this. Establishing infrastructure to support translational research in LMIC settings has challenges. The use of regional biobanks may provide a method to collect tissue samples now, for processing later, when infrastructure is in place, or even to demonstrate feasibility of systematic tissue collection—derisking investments that would otherwise have been spent on building an entire sample handling and sequencing pipeline. Biobanks, however, require large amounts of energy resources to ensure samples are frozen, with some biobanks using liquid nitrogen to freeze samples. Liquid nitrogen transport is difficult in HICs, let alone securing a reliable supply in LMICs. Electricity supplies in some LMIC locations is sporadic too, which would be required to operate freezer systems. Other preservative solutions could be used to preserve nucleic acids in tissues at room temperature as a stop-gap solution, or as a means of extending the time available to transport specimens to a central repository. Transporting biospecimens and tissue is subject to tight United Nations control, thus making international efforts more difficult for countries without existing expertise to contribute. Furthermore, times of epidemic and regional spread of disease has implications for whether it would be safe to transport biospecimens across the world. Further issues surrounding the logistics remain and policy makers should identify solutions to this as a priority.

### Global Cancer Trials

Conducting high-quality cancer trials is challenging in high-income settings and even more so in locations with little clinical trial infrastructure (80). Considerable methodological challenges exist around patient stratification by treatment response. Biomarker identification and sample handling must be robust and timely, together with the requirement for high levels of patient follow-up. In all countries, undertaking follow-up, and transporting biological specimens is challenging. These challenges are amplified in LMIC settings, with many countries lacking postal address systems, patient records and the infrastructure to process clinical specimens. Furthermore, a supply of clinical triallists is short in LMIC settings. Training and exchange programmes with HIC partners may help provide solutions in the sohrt term, however, long term infrastructure building must be given priority.

One example of where this is changing is Rwanda, where electronic patient record systems are being introduced (81). Integrating clinical systems into research in such settings would enable efficient research to be undertaken. In HICs, registry-based trials provide an efficient means of producing follow-up data and this approach could be emulated in LMICs where electronic records exist. A further consideration to any future trials of precision in LMIC settings is whether this can be continued after the trial concludes, should an intervention prove effective. For this reason, details on sequelae of interventions should be collected to ensure health-care systems can handle any treatment related harms. Non-governmental organisations such as the World Health Organisation and other non-governmental organisations (NGOs) often perform scoping studies in LMIC countries, but few cancer specific trials have been iniated. These NGOs should consider whether building research infrastructure

in medicine is a sufficient priority to enable tailored solutions to be led by LMIC investigators independently.

In other areas of medicine (such as malaria, HCV and HIV) have successfully delivered clinical trials that integrate molecular or genotypic testing to enable molecular determinants of disease response to be identified in LMICs (82). Malaria is a good example, where trials often collect data on genotypes and information on microsatellites of malaria parasites from DNA isolated from blood films or spots. The markers used can be tested in a polymerase chain reaction (PCR) assay by research staff at that centre. Malaria trials have used these to investigate markers of treatment resistance and response (83, 84). Similarly, for trials in antiretroviral therapy for HIV and HCV, there are several studies which utilise commercial molecular testing kits at the centre level for identifying genotypes found in disease (85). However, this approach is challenging to adopt and thought must be given to the sustainability of testing when it is attempted to adopt trial findings into routine clinical practice.

## Capacity Building for Precision Medicine

The most notable effort currently underway in LMICs to build evidence and crucially capacity for genomic sequencing is the Human Heredity and Health in Africa initiative (H3Africa) (86). This project is a collaboration of African clinicians, scientists and bioinformaticians who conduct large-scale sequencing and genetic association studies. So far, they have largely focussed on communicable disease such as trypanosomiasis, stroke and other neurological diseases affecting patients across the continent. Relevant to the field of oncology, some work has been undertaken into HPV infection in Nigeria (68), with the women included in this study demonstrating similar genetic susceptibility to infection as other populations. This group are set to expand into the field of breast cancer, which will provide useful data to study the genomic epidemiology of the disease on the African continent. The MRC Centre for Genomics and Global Health in the Gambia has also conducted successful genome wide and sequencing techniques in other disease areas, including in *P. falciparum* (87, 88).

There have been several success stories in LMICs, with some African countries delivering exciting genetic epidemiology studies. The Nigerian Breast Cancer Study, led by the University of Idaban has produced several large studies, underpinning the understanding of breast cancer genetics in Nigerian women (89). Through collaborative support from the University of Chicago, this group has gone on to publish multiple genetic epidemiology studies, and have even attempted randomised clinical trials (90). Building partnerships between institutions with experience in polyomics may help foster knowledge exchange and promote the implementation of best practice.

## Local Lead and Oversight of Research Projects

Any solution must be led and maintained locally, rather than researchers from HICs taking data from local populations. It must also maintain practicality and clinical relevance to the local patient population. The H3Africa initiative has recently published guidelines for researchers wishing to do research in the African continent which are aimed at empowering local scientists and ensuring benefit for African patients (5). Developing home-grown expertise in polyomic technologies in LMICs would also have economic benefits in addition to building the global laboratory medicine workforce of the future. In fact, LMICs may be at some advantage in building competitive platforms for precision medicine as they can adopt new technologies without having to make mistakes or go through the intermediate steps of technological evolution that have been observed in high-income settings.

## Disruptive Near-Future Technologies

New technologies may provide innovative solutions to some of the barriers to precision medicine. Genome sequencing over the past 15 years has fallen by 100,000-fold, yet with the cost of sequencing an entire human genome around the region of $1000, this is still prohibitively expensive for patients and healthcare systems (91). Furthermore, the sample handling and analysis pipelines required to support genome sequencing is logistically challenging. Establishing infrastructure and identifying expert staff to deal with sequencing data and ensure appropriate quality control is a large barrier. Large quantities of computational resource are required and may work as a centralised resource across, if shared across multiple LMICs. Whilst a centralised model may be a more cost and resource effective model, other challenges, including specimen transportation, and political stability could pose barriers to such a model. Furthermore, models of research and practice must be sensitive to resources of countries involved (**Figure 3**). Examples such as nanopore sequencing devices may provide an answer to these logistical challenges, with handheld and smartphone based sequencing devices available which reduce requirements for library preparation (92, 93). This has the potential to enable targeted sequencing of patients, at a far lower cost. With other multiplexing approaches, including developments in nucleotide barcoding, many samples could be rapidly processed at a very low cost.

Targeted sequencing and mutation detection assays (PCR or ligation based methods, **Table 2**) offer a good alternative, but require that there is data to support that these assays bring clinical benefit, often derived from sequencing data. New, more portable approaches to molecular testing are being developed, which may be useful in resource-limited settings. Paper-based oligonucleotide based ligation assays, originally developed to detect HIV genotypes and monitor resistance, could be adapted for use in cancer therapy (94, 95). Paper-based immunochromatography assays, popularised for detection of HIV, could also be adapted for the detection of cancer specific ligands at the point of care. Nevertheless, these approaches lack the ability to resolve molecular alterations at the nucleotide level and rely on these already being known. The potential impact for these assays is great, particularly in the context of cancer diagnosis in limited resource settings, where other common diagnostic tests such as endoscopy or imaging maybe unavailable.

Promising developments are on the horizon for the diagnosis and monitoring of disease, such as liquid biopsy and measurement of circulating nucleic acids (circulating

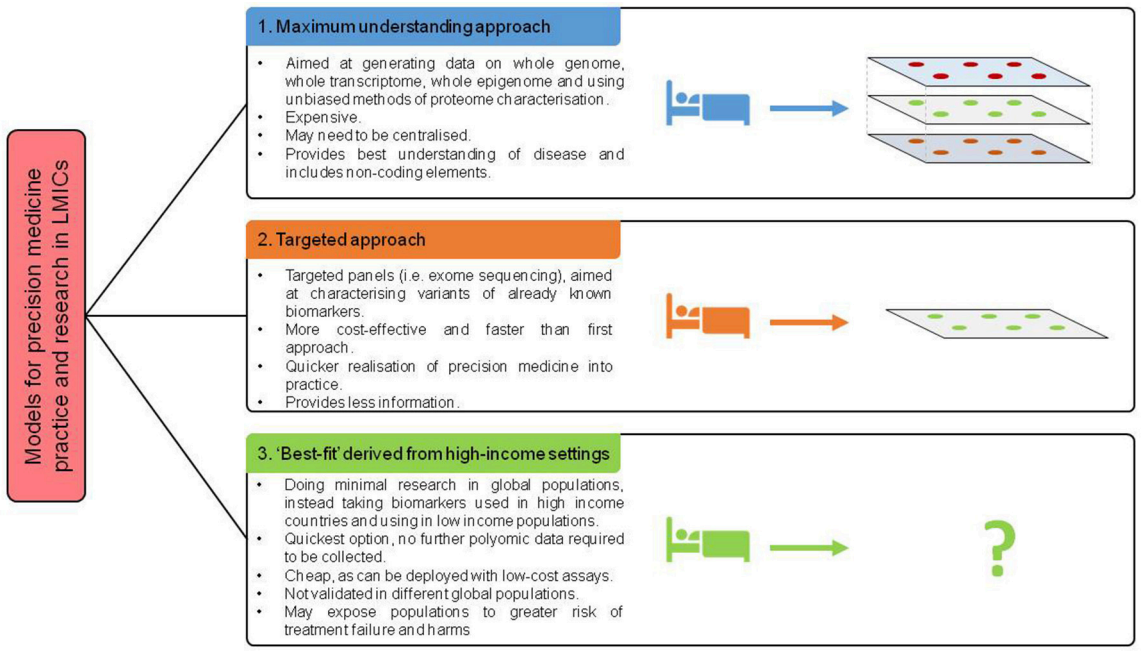


**FIGURE 3 |** Proposed models of future deployment of precision medicine across world.

tumour DNA/ RNA) (96). At present, these technologies rely of measurement of small quantities of nucleic acids, circulating tumour cells or other targets in peripheral blood via sequencing and subsequent computational processing (97). Although a reliable and universal test is yet to be developed based on this methodology, the development of such a test has the potential to improve early diagnosis and reduce reliance on other expensive methods of diagnostic testing in LMICs. However, given the lack of workforce, infrastructure and expertise available in LMICs at present, new technologies may further exacerbate global inequalities. Similarly, for other biomarkers of cancer which could be utilised as substrates to bind ligands to deliver cancer therapies with (such as fluorescence imaging (98), chemotherapeutics, or radiotherapeutics), there is little data to support whether what works in HICs can be translated straight into LMICs safely. Indeed, at present there is very little data that underpins the patient pathway or outcomes after cancer treatment in LMICs.

Collaborative approaches are crucial to ensuring future success (80, 99). Several partnerships between HICs and LMICs have begun to collect prospective, high quality evidence and establish clinical research networks. One such example is the GlobalSurg collaborative, a network of over 5,000 surgeons throughout the world who deliver large multicentre prospective studies (100). Recently, this network has established several trials units in LMIC settings that will deliver cancer trials and test whether new devices being concurrently developed in HICs can be utilised in LMICs. Building sustainable capacity concurrently with new developments will enable local economies to thrive and patients in LMICs to receive cutting edge care. Working with LMIC partners to facilitate global translation should be a priority when developing potentially disruptive technologies for both researchers and industry.

## SUMMARY

Funders, scientists, genome consortia, scientific journals and policy makers have an important role to play in a drive to ensure cancer research is generalisable across the world and will benefit patients in LMICs. Many major journals now mandate that polyomic data is deposited in databases for future use by the scientific community and other interested partners. This has been highly successful, with databases such as RNAcentral containing 13 million sequences and the ICGC Project available to the worldwide scientific community (31, 101). In addition, collaboratives such as the 1,000 genome project, containing 2,500 human genomes and representing 26 populations, demonstrate the growing potential to sequence genomes on a global scale (102). However, most data currently deposited is from HICs and more work is required to increase the availability of data from LMICs. Funders have begun to recognise this, and recent discussions have begun to focus on building precision medicine at a population level in LMICs (5, 103). At present, this initial funding is focussed on precision medicine for communicable disease, despite the rising burden of non-communicable disease.

Precision medicine clearly offers numerous advantages for patients and recent efforts to characterise the landscape of cancers using polyomic technologies is changing research and practice. There is, however, a lack of evidence, data and clear strategy on how this will be used to benefit patients across the world, particularly in LMICs. Emerging evidence suggests there are

**TABLE 2 |** Possible enabling technologies for global precision medicine.

| Technology | Pros | Cons | Barriers to implementation of technologies to LMIC settings |
|---|---|---|---|
| Whole-genome sequencing (Sequencing-by-synthesis or ion semiconductor sequencing) | • High-throughput and high-speed<br>• Well developed technology<br>• Sequencing pipelines can be developed with 'off the shelf' solutions<br>• Large body of global expertise<br>• Provides detailed, pangenome information<br>• Deep sequencing would provide unparalleled information on novel variants (including non-coding) | • High cost<br>• Likely to require centralisation of expertise due to lack of infrastructure currently<br>• Sample preparation and library generation required<br>• Sample logistics may be difficult from the perspective of clinical care and transporting sample to centralised facilities<br>• Short reads | • Current lack of computational infrastructure and expertise in LMICs Likely to require international cooperation - could be sensitive to political instability Sample pipelines would require careful planning and implementation High cost |
| Exome-sequencing (Sequencing-by-synthesis or ion semiconductor sequencing) | • Lower cost than whole-genome<br>• Still captures information on important genes<br>• Typically faster than whole genome sequencing<br>• Could be performed using a more regional model of delivery<br>• Cheaper sequencing instruments to deliver same depth as whole genome<br>• More clinically relevant as same infrastructure could deliver targeted clinical panels | • As above for whole genome sequencing<br>• Still relatively high cost<br>• Offers less coverage and no coverage of non-coding elements | • As above for whole genome sequencing |
| Direct sequencing (Nanopore sequencing) | • Highly transportable<br>• Minaturised versions available that require less computational infrastructure than other sequencing approaches<br>• Lower cost than other sequencing instruments<br>• Less sample and library preparation<br>• Can be used to directly sequence other nucleic acids and proteins<br>• Easily expandable<br>• Very long read lengths | • Currently limited to targeted sequencing studies in humans<br>• Currently marginally lower accuracy than established semi-conductor and sequencing by synthesis approaches<br>• Limited depth at present in humans versus other approaches<br>• Clinically approved devices not yet available | • Would require international collaboration on how data is pooled together and standard operating procedures to ensure quality control if many users and devices used in a distributed model<br>• Current lack of computational infrastructure and expertise in LMICs |
| Other targeted panels (i.e. microarray) | • Lower cost than sequencing<br>• High throughput<br>• Less computationally intensive<br>• Other applications i.e. cytogenetics<br>• Global expertise readily available<br>• Cheap instrumentation | • Biased detection methods<br>• Sequencing becoming increasingly more popular<br>• Lower dynamic range for detection than sequencing methods<br>• Cannot detect novel transcripts | • Would require international collaboration on how data is pooled together and standard operating procedures to ensure quality control if many users and devices used in a distributed model<br>• Technology may be outdated and superceded by sequencing<br>• Current lack of computational infrastructure and expertise in LMICs |
| Oligonucleotide ligation assays/ Polymerase chain reaction | • Very cheap<br>• Can be paper-based<br>• Transportable<br>• Limited scientific skills required<br>• Easily mass-produced | • Can only detect known variants in a very simple fashion<br>• Not quantitative<br>• Requires substantial development<br>• Unclear how may be used with heterogenous samples i.e. solid tumour<br>• Data not easily stored in electronic format | • Would require sequencing or array studies to validate targets of assays prior to deployment |

differences at the molecular level between cancer in HICs and that found in LMICs. To ensure inequity in cancer care between high and LMIC settings is not worsened, steps must be taken to improve the mechanistic understanding of cancer at a global level.

## SUMMARY POINTS

- There is known variation in basic cellular processes such as DNA methylation, epigenomic alterations and frequencies of polymorphisms across different human populations. These are

likely to affect cancer risk, disease behaviour and treatment response.
- LMIC populations are under-represented in large genome wide association studies and sequencing studies. In an era where genomic technologies are driving drug development and targeted therapies, this may result in global inequities for cancer therapy.
- To prevent cancer inequities worsening further, funders, researchers and scientists should aim to include patients from LMICs in international studies. This would ensure that emerging consensus molecular subtypes are representative of disease worldwide.
- New technologies present exciting opportunities to improve cancer care and the representation of LMIC countries in cancer research. Further work should be done to ensure LMIC representation and identify novel ways of implementing cost-effective approaches to precision medicine or precision public health within LMIC settings.

## AUTHOR CONTRIBUTIONS

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

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# Inequality in the Survival of Patients With Head and Neck Cancer in Scotland

*Kate Ingarfield[1]*, Alex Douglas McMahon[1], Catriona M. Douglas[2], Shirley-Anne Savage[3], Kenneth MacKenzie[4] and David I. Conway[1]*

*[1] University of Glasgow Dental School, University of Glasgow, Glasgow, United Kingdom, [2] Department of Otolaryngology – Head and Neck Surgery, Queen Elizabeth University Hospital, Glasgow, United Kingdom, [3] Emergency Care and Medicine Directorate, Victoria Hospital, Kirkcaldy, United Kingdom, [4] Department of Otolaryngology – Head and Neck Surgery, Glasgow Royal Infirmary, Glasgow, United Kingdom*

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*Qian Li,*
*Icahn School of Medicine at Mount Sinai, United States*
*Kun Chen,*
*Zhejiang University, China*

****Correspondence:***
*Kate Ingarfield*
*k.ingarfield.1@research.gla.ac.uk*

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**Background:** Socioeconomic inequalities impact on the survival of head and neck cancer (HNC) patients, but there is limited understanding of the explanations of the inequality, particularly in long-term survival.

**Methods:** Patients were recruited from the Scottish Audit of Head and Neck Cancer between 1999 and 2001 and were linked to mortality data as at 30th September 2013. Socioeconomic status was determined using the area-based Carstairs 2001 index. Overall and disease-specific survival were calculated using the Kaplan-Meier method with 95% confidence intervals (CI's) at 1-, 5-, and 12-years. Net survival at 1-, 5-, and 12-years was also computed with 95% CIs. Cox proportional hazard models with 95% CIs were used to determine the explanations for the inequality in survival by all-cause mortality and disease-specific mortality with 95% CIs.

**Results:** Most patients were from the most deprived group, and were more likely to smoke, drink, have cancer of a higher stage and have a lower WHO Performance Status. A clear gradient across Carstairs fifths for unadjusted overall and disease-specific survival was observed at 1-, 5-, and 12-years for patients with HNC. Following the adjustment for multiple patient, tumor and treatment factors, the inequality in survival for patients with HNC had attenuated and was no longer statistically significant at 1-, 5-, and 12-years.

**Conclusion:** A clear gradient across Carstairs fifths for unadjusted overall, disease-specific and net survival was observed at 1-, 5-, and 12-years for HNC patients in Scotland from 1999 to 2001. This study concludes that explanations for the inequality in the survival of patients with HNC are not straightforward, and that many factors including various patient, tumor and treatment factors play a part in the inequality in the survival of patients with HNC.

**Keywords: head and neck cancer, socioeconomic status, survival, epidemiology, cohort, scotland, long term survival, deprivation**

## INTRODUCTION

Cancer survival often favors those who are from socioeconomically advantaged areas or have a more affluent backgrounds (1), and explanations for these socioeconomic inequalities are complex and difficult to explain. In the 1997 landmark IARC publication *Social Inequalities in Cancer*, Auvinen (2) assessed the socioeconomic factors that are associated with cancer survival, and identified research gaps in understanding the determinants of survival beyond cancer stage. Auvinen concluded that there was "urgent need" to understand the drivers of the inequality in cancer survival, and more than 20 years later, the evidence-base is not much further forward. Woods et al. (3) carried out a comprehensive review to determine the origins of socioeconomic inequalities in all-cancer survival and concluded that stage at diagnosis, access to health services, and comorbidity may explain some of the association.

Previous analyses of the Scottish Audit of Head and Neck Cancer (SAHNC) cohort have presented 5-year overall survival and 5-year disease-specific survival (4–7). In 2010, Robertson et al. (7) reported the impact of socioeconomic status (SES) on survival at 5-years and outlined that socioeconomic status was no longer an independent predictor of survival following the adjustment of multiple covariates. To add to this previous research, the aims of this study are to assess socioeconomic inequality in the survival of head and neck cancer patients assessing short-, mid-, and long-term survival, and to provide an understanding of the explanation of the inequality in the survival of these patients via different measurements of survival including overall, disease-specific and net survival estimates.

## MATERIALS AND METHODS

### Patients

The SAHNC cohort recruited patients between 1st September 1999 and 31st August 2001—the methods have previously been described (4–7). Data were recorded on new HNC patients diagnosed in Scotland during this 2 year period. Quality assurance processes were carried out including cross-checking the data with medical and pathology results.

### Data Linkage and Approvals

The SAHNC cohort was linked to the National Records of Scotland (NRS) mortality data as at 30th September 2013 by ISD Scotland. Records were linked using an established probability matching technique based on the Howard Newcombe principle (8) which matches individual patients to their national Community Health Index (CHI) number—the unique healthcare identifier that is used in the National Health Service (NHS) in Scotland. Data were linked to mortality forms which outlined the primary and secondary causes of death using ICD10 codes. Information governance and data linkage approvals were obtained from the NHS Privacy Advisory Committee (now known as the Public Benefits and Privacy Panel).

### Measurement of Socioeconomic Status

SES was determined using the area-based Carstairs 2001 index (9, 10) which is defined from 2001 Census data consisting of four variables including proportion of unemployed males, those in social classes IV and V, those who do not own a car, and a measurement for overcrowding defined as a density of more than one person per room per private household. The Carstairs index is split at a population level by creating equal fifths using the quintile cut offs—group 1 represents the most affluent patients and group 5 represents the most deprived patients.

### Variables Used for Adjustment

Patient factors (age at diagnosis, sex, smoking behavior, alcohol consumption and patient performance status), tumor factors (stage and anatomical site) and treatment factors (treatment modality and geographic location of treatment) were collected at baseline and no further data was collected afterwards. Smoking behavior and alcohol consumption were determined from questionnaires at the time of diagnosis which allowed the following "tick-box" options for patient selection: "current smoker," "previous smoker" and "never smoked," and "current problem drinker," "previous problem drinker" or "occasionally/never drinks"—no further data were collected on the patients' habits following diagnosis. Patient performance status was classified at diagnosis using the World Health Organization (WHO) Performance Status (11), which groups patients into one of five categories based on their level of physical abilities ("normal activity," "strenuous activity restricted," "up and about for more than 50% of waking hours," "confined to a bed or chair for more than 50% of waking hours," and "confined to a bed or chair for 100% of waking hours"). Tumor stage was determined using the Tumor, Node and Metastases (TNM) Classification of Malignant Tumors (12), and the cohort was grouped into stage I, II, III, or IV. Anatomical site was classified using the International Classification of Disease version 10 (13), grouped into seven categories—lip (C00.9), larynx (C32), nasal cavity (C11.9, C30.0, C31), oral cavity (C02–C04, C05.0, C06, C14), oropharynx (C01, C05.1–, C09, C10), hypopharynx (C12, C13), and other or salivary gland (C07, C08, C30.1, C41, C44, C76, C77). Treatment modality was grouped into five categories: (i) surgery only; (ii) radiotherapy only; (iii) surgery combined with radiotherapy; (iv) chemotherapy only, chemotherapy combined with surgery, chemotherapy combined with radiotherapy, and chemotherapy combined with both surgery and radiotherapy; and (v) no treatment. Location of treatment was based on the service delivered in the Scottish Cancer Networks located in three geographic region—West of Scotland Network (WoSCAN) (which comprises health board areas of Ayrshire and Arran, Forth Valley, Greater Glasgow, Clyde and Lanarkshire); South East Scotland Cancer Network (SCAN) (Borders, Dumfries and Galloway, Fife, Lothian); and North of Scotland Cancer Network (NOSCAN) (Grampian, Highland, Orkney, Shetland, Tayside, Western Isles).

### Statistical Methods

Overall and disease-specific survival were calculated using the Kaplan-Meier method with 95% confidence intervals (CI's).

Overall survival considered all causes of death, whereas disease-specific survival only considered deaths where the patients' primary cause of death on their death certificate was a HNC ICD10 code. Cox proportional hazard models with 95% CIs were used to determine the explanations for the inequality in survival for all-cause mortality and disease-specific mortality with 95% CIs. Overall survival, disease-specific survival, and Cox proportional hazards models for all-cause mortality and disease-specific mortality were calculated using SAS Software, version 9.4 (SAS Institute Inc., USA). Net survival with 95% CIs was calculated by the Pohar-Perme method (14, 15) using the *stns* command in Stata 14 (16, 17), and using life-tables provided by the Cancer Survival Group at the London School of Tropical Hygiene and Medicine (18) These life-tables were standardized by age, sex, and Carstairs 2001 quintile. The Slope Index of Inequality (SII) was calculated based on the regression of the mid-point of survival for mortality for each SES group in each model (19).

# RESULTS

## Cohort Recruitment

The SAHNC cohort recruited 77% ($n$ = 1,910) of HNC cases that were diagnosed and recorded in the Scottish Cancer Registry over the study period from 1st September 1999 to 31st August 2001. Of the 1,910 patients in the baseline cohort, 1,895 were linked to 12-year mortality records−15 patients were excluded as they were unable to be matched to CHI numbers for data linkage follow-up. A further 15 patients were excluded as they could not be matched to Carstairs 2001 fifths, and 60 patients over the age of 85 were also excluded, which was a requirement for the successful computation of net survival for 12-year follow-up. A remaining 1,820 patients were included in the analyses.

## Patient Demographics by SES Carstairs 2001 Fifths

**Table 1** outlines the demographic characteristics broken down by Carstairs 2001 fifths of the 1,820 patients. Most patients were from the most deprived regions of Scotland (29.0%), whereas only 13.2% of patients were from the most affluent areas of Scotland. There were no differences in the distribution of patients in each age category or between males and females across the Carstairs 2001 fifths. As deprivation increased from group 1 (most affluent) to group 5 (most deprived), the proportion of current smokers in each group also increased, and similarly, the proportion of patients with current alcohol problems increased. The number of patients experiencing normal WHO activity decreased across the SES groups, and the most deprived patients had the greatest proportion of Stage IV cancers (40.0%) compared to other groups. There was a slight difference in the treatment modalities used between groups, and the most deprived group had the smallest proportion of patients treated with curative intent. There were no clear trends by Carstairs 2001 fifths for anatomical site, Scottish Cancer Networks, or type of primary cause of death.

## Overall, Disease-Specific, and Net Survival

One-, five-, and twelve-year overall, disease-specific and net survival by Carstairs 2001 fifths are displayed in **Table 2**. The Slope Index of Inequality (SII) for all three methods of survival and at each time point are also displayed in **Table 2**. One-year overall survival for the most deprived patients was 71.8% (67.7%, 75.4%), whereas the most affluent patients' was higher at 83.4% (78.1%, 87.5%). By 5-years, the inequality remained the same, and by 12-years the difference in overall survival had reduced, which can be demonstrated by a similar SII at 5-year [SII = 12.9 (−1.8, 27.5)] and a reduced SII at 12-years [SII = 7.4 (−2.7, 17.5)] compared to the SII at 1-year 12.7 (6.7, 18.8). One-year disease-specific survival for the most deprived patients was 79.1% (75.2%, 82.4%) whereas the most affluent patients' was higher at 88.8% (83.9%, 92.2%). By 5- and 12-years, the gap between the most affluent and most deprived patients for disease-specific survival had widened, and the SII had increased from 9.5 (1.4, 17.7) at 1-year to 12.5 (−1.8, 26.9) and 16.5 (1.5, 31.5) at 5- and 12-years, respectively. Net survival at 1 year for the most deprived patients was 73.7% (69.7%, 77.6%), compared to the most affluent patients at 86.1% (81.3%, 91.0%). The inequality between the net survival results for the most deprived patients and the most affluent patients was strong at 1-year with SII of 13.6 (7.1, 20.1), however this had widened by 5-years with SII of 16.1 (−1.0, 33.3), and by 12-years a weak inequality remained with the SII at 6.6 (−17.2, 30.3).

## Cox Models for All-Cause Mortality

Minimally adjusted and fully adjusted Cox Proportional Hazards models for all-cause mortality are displayed in **Table 3**. Clear trends can be observed following minimal adjustment by age and sex in the models for all-cause mortality at all three time points, and there is statistical evidence to confirm an inequality in all-cause mortality at 1- ($p < 0.001$), 5- ($p < 0.001$), and 12-years ($p < 0.001$). At 1 year, the most deprived patients were 46% more at risk when the model was adjusted by age, sex and patient factors [HR 1.46, (1.02, 2.09)], and there was evidence of a difference between the most affluent patients and those who were in the most deprived group ($p = 0.037$). Following the adjustment for age, sex, tumor and treatment factors, there was no longer any evidence of a difference between the most affluent patients and the patients in other Carstairs 2001 fifth ($p = 0.113$), and this result was also clear when the model was fully adjusted by age, sex, patient, tumor and treatment factors ($p = 0.351$). This was also demonstrated by the SII's which had reduced from 1.1 (0.7, 1.5) in the minimally adjusted model by age and sex, to 0.2 (−0.4, 0.7) in the fully adjusted model. By 5- and 12-years, the gaps between the risk of all-cause mortality for the most affluent and the most deprived patients had narrowed in all models, which can be demonstrated by a reduction in all the models' SIIs between 1-, 5-, and 12-year follow-up—for example, in the model that was minimally adjusted by age and sex, the SII had reduced from 1.1 (0.7, 1.5) at 1-year, to 0.6 (0.1, 1.0) at 5-years, and 0.4 (0.1, 0.7) at 12-years, whereas in the fully adjusted model the SII had reduced from 0.2 (−0.4, 0.7) at 1-year, to 0.03 (−0.6, 0.6) at 5-years, and −0.1 (−0.5, 0.4) at 12-years. There was no longer

**TABLE 1 |** Patient demographic, behavioral, tumor, and treatment characteristics by Carstairs quintiles.

| Variable | Total (Col. %) | Frequencies of Carstairs 2001 quintiles (Col. %) | | | | | Chi-square *p*-value |
|---|---|---|---|---|---|---|---|
| | | 1—Most affluent | 2 | 3 | 4 | 5—Most deprived | |
| Whole cohort (Row %) | 1,820 (100.0%) | 241 (13.2%) | 317 (17.4%) | 325 (17.9%) | 409 (22.5%) | 528 (29.0%) | – |
| **Age at diagnosis** | | | | | | | 0.470 |
| Less than 45 | 99 (5.4%) | 16 (6.6%) | 23 (7.3%) | 16 (4.9%) | 21 (5.1%) | 23 (4.4%) | |
| 45 to 54 | 288 (15.8%) | 35 (14.5%) | 44 (13.9%) | 45 (13.9%) | 68 (16.6%) | 96 (18.2%) | |
| 55 to 64 | 592 (32.5%) | 70 (29.1%) | 105 (33.1%) | 108 (33.2%) | 140 (34.2%) | 169 (32.0%) | |
| 65 to 74 | 551 (30.3%) | 72 (29.9%) | 90 (28.4%) | 111 (34.2%) | 108 (26.4%) | 170 (32.2%) | |
| 75 and over | 290 (15.9%) | 48 (19.9%) | 55 (17.4%) | 45 (13.9%) | 72 (17.6%) | 70 (13.3%) | |
| **Sex** | | | | | | | 0.440 |
| Male | 1,300 (71.4%) | 161 (66.8%) | 227 (71.6%) | 236 (72.6%) | 289 (70.7%) | 387 (73.3%) | |
| Female | 520 (28.6%) | 80 (33.2%) | 90 (28.4%) | 89 (27.4%) | 120 (29.3%) | 141 (26.7%) | |
| **Smoking status** | | | | | | | <0.001 |
| Current smoker | 1,134 (62.3%) | 118 (49.0%) | 173 (54.6%) | 191 (58.8%) | 256 (62.6%) | 396 (75.0%) | |
| Previous smoker | 405 (22.3%) | 60 (24.9%) | 86 (27.1%) | 68 (20.9%) | 100 (24.5%) | 91 (17.2%) | |
| Never smoked | 221 (12.1%) | 56 (23.2%) | 45 (14.2%) | 50 (15.4%) | 41 (10.0%) | 29 (5.5%) | |
| Not recorded | 60 (3.3%) | 7 (2.9%) | 13 (4.1%) | 16 (4.9%) | 12 (2.9%) | 12 (2.3%) | |
| **Alcohol consumption** | | | | | | | <0.001 |
| Current (problem) drinker | 496 (27.3%) | 51 (21.2%) | 77 (24.3%) | 80 (24.6%) | 108 (26.4%) | 180 (34.1%) | |
| Previous (problem) drinker | 212 (11.7%) | 25 (10.4%) | 29 (9.2%) | 49 (15.1%) | 47 (11.5%) | 62 (11.7%) | |
| Occasional/never drank | 891 (49.0%) | 138 (57.3%) | 164 (51.7%) | 150 (46.2%) | 198 (48.4%) | 241 (45.6%) | |
| Not recorded | 221 (12.1%) | 27 (11.2%) | 47 (14.8%) | 46 (14.2%) | 56 (13.7%) | 45 (8.5%) | |
| **WHO performance status** | | | | | | | 0.003 |
| Normal activity | 825 (45.3%) | 137 (56.9%) | 169 (53.3%) | 137 (42.3%) | 177 (43.3%) | 205 (38.8%) | |
| Strenuous activity restricted | 465 (25.6%) | 54 (22.4%) | 66 (20.8%) | 94 (28.9%) | 102 (24.9%) | 149 (28.2%) | |
| Up and about >50% | 137 (7.5%) | 18 (7.5%) | 23 (7.3%) | 17 (5.2%) | 33 (8.1%) | 46 (8.7%) | |
| Confined to bed/chair >50% | 97 (5.3%) | 8 (3.3%) | 18 (5.7%) | 22 (6.8%) | 26 (6.4%) | 23 (4.4%) | |
| Not recorded | 296 (16.3%) | 24 (10.0%) | 41 (12.9%) | 55 (16.9%) | 71 (17.4%) | 105 (19.9%) | |
| **Anatomical site** | | | | | | | 0.470 |
| Lip | 85 (4.7%) | 11 (4.6%) | 17 (5.4%) | 18 (5.5%) | 23 (5.6%) | 16 (3.0%) | |
| Larynx | 584 (32.1%) | 71 (29.5%) | 102 (32.2%) | 103 (31.7%) | 143 (35.0%) | 165 (31.3%) | |
| Nasal cavity | 85 (4.7%) | 12 (5.0%) | 14 (4.4%) | 22 (6.8%) | 15 (3.7%) | 22 (4.2%) | |
| Oral cavity | 506 (27.8%) | 76 (31.5%) | 93 (29.3%) | 78 (24.0%) | 97 (23.7%) | 162 (30.7%) | |
| Oropharynx | 323 (17.8%) | 40 (16.6%) | 53 (16.7%) | 63 (19.4%) | 69 (16.9%) | 98 (18.6%) | |
| Hypopharynx | 119 (6.5%) | 12 (5.0%) | 19 (6.0%) | 20 (6.2%) | 35 (8.6%) | 33 (6.3%) | |
| Other/salivary gland | 118 (6.5%) | 19 (7.9%) | 19 (6.0%) | 21 (6.5%) | 27 (6.6%) | 32 (6.1%) | |
| **Stage** | | | | | | | 0.023 |
| I | 383 (21.0%) | 58 (24.1%) | 85 (26.8%) | 75 (23.1%) | 73 (17.9%) | 92 (17.4%) | |
| II | 369 (20.3%) | 48 (19.9%) | 62 (19.6%) | 65 (20.0%) | 88 (21.5%) | 106 (20.1%) | |
| III | 273 (15.0%) | 37 (15.4%) | 42 (13.3%) | 40 (12.3%) | 80 (19.6%) | 74 (14.0%) | |
| IV | 662 (36.4%) | 79 (32.8%) | 102 (32.2%) | 125 (38.5%) | 145 (35.5%) | 211 (40.0%) | |
| Unknown | 133 (7.3%) | 19 (7.9%) | 26 (8.2%) | 20 (6.2%) | 23 (5.6%) | 45 (8.5%) | |
| **Treatment modality** | | | | | | | 0.064 |
| Surgery only | 477 (26.2%) | 72 (29.9%) | 83 (26.2%) | 86 (26.5%) | 106 (25.9%) | 130 (24.6%) | |
| Radiotherapy only | 507 (27.9%) | 74 (30.7%) | 99 (31.2%) | 98 (30.2%) | 117 (28.6%) | 119 (22.5%) | |
| Surgery + radiotherapy | 458 (25.2%) | 59 (24.5%) | 82 (25.9%) | 73 (22.5%) | 101 (24.7%) | 143 (27.1%) | |
| Chemo ± radio ± surgery | 249 (13.7%) | 23 (9.5%) | 34 (10.7%) | 48 (14.8%) | 56 (13.7%) | 88 (16.7%) | |
| No treatment | 129 (7.1%) | 13 (5.4%) | 19 (6.0%) | 20 (6.2%) | 29 (7.1%) | 48 (9.1%) | |
| **Network** | | | | | | | <0.001 |
| WoSCAN (West Scotland) | 1,001 (55.0%) | 85 (35.3%) | 110 (34.7%) | 149 (45.9%) | 244 (59.7%) | 413 (78.2%) | |

*(Continued)*

**TABLE 1 |** Continued

| Variable | Total (Col. %) | Frequencies of Carstairs 2001 quintiles (Col. %) | | | | | Chi-square *p*-value |
|---|---|---|---|---|---|---|---|
| | | 1—Most affluent | 2 | 3 | 4 | 5—Most deprived | |
| SCAN (East Scotland) | 440 (24.2%) | 83 (34.4%) | 85 (26.8%) | 108 (33.2%) | 108 (26.4%) | 56 (10.6%) | |
| NOSCAN (North Scotland) | 379 (20.8%) | 73 (30.3%) | 122 (38.5%) | 68 (20.9%) | 68 (20.9%) | 59 (11.2%) | |
| **Treatment intent** | | | | | | | 0.053 |
| Curative | 1,355 (74.5%) | 196 (81.3%) | 250 (78.9%) | 239 (73.5%) | 307 (75.1%) | 363 (68.8%) | |
| Palliative | 307 (16.9%) | 29 (12.0%) | 42 (13.3%) | 61 (18.7%) | 69 (16.9%) | 106 (20.1%) | |
| unknown | 158 (8.7%) | 16 (6.6%) | 25 (7.9%) | 25 (7.7%) | 33 (8.1%) | 59 (11.2%) | |
| **Primary cause of death** | | | | | | | 0.063 |
| Cancer—Head and neck | 677 (37.2%) | 78 (32.4%) | 99 (31.2%) | 127 (39.1%) | 157 (38.4%) | 216 (21.6%) | |
| Cancer—Other | 308 (16.9%) | 46 (19.1%) | 54 (17.0%) | 61 (18.8%) | 73 (17.8%) | 74 (14.0%) | |
| Other/unknown | 399 (21.9%) | 59 (24.5%) | 73 (23.0%) | 59 (18.5%) | 81 (19.8%) | 126 (23.9%) | |
| Alive | 436 (24.0%) | 58 (24.1%) | 91 (28.7%) | 77 (23.7%) | 98 (24.0%) | 112 (21.2%) | |

**TABLE 2 |** Overall and disease-specific survival at One-, five-, and twelve-years by Carstairs 2001 quintiles for all patients.

| | 1-year | *p*-value | 5-years | *p*-value | 12-years | *p*-value |
|---|---|---|---|---|---|---|
| **OVERALL SURVIVAL** | | | | | | |
| Whole cohort | 76.0 (74.0, 77.9) | – | 46.1 (43.8, 48.4) | – | 26.3 (24.3, 28.3) | – |
| Carstairs quintile | | 0.007 | | 0.002 | | 0.010 |
| 1 (Most affluent) | 83.4 (78.1, 87.5) | | 49.8 (43.3, 55.9) | | 27.0 (21.5, 32.7) | |
| 2 | 78.6 (73.6, 82.7) | | 52.1 (46.4, 57.4) | | 30.6 (25.6, 35.7) | |
| 3 | 76.3 (71.3, 80.6) | | 44.6 (39.2, 49.9) | | 26.2 (21.5, 31.0) | |
| 4 | 75.1 (70.6, 79.0) | | 47.7 (42.8, 52.4) | | 26.9 (22.7, 31.3) | |
| 5 (Most deprived) | 71.8 (67.7, 75.4) | | 40.5 (36.3, 44.7) | | 22.9 (19.4, 26.6) | |
| Slope Index of Inequality (95% CIs) | 12.7 (6.7, 18.8) | | 12.9 (−1.8, 27.5) | | 7.4 (−2.7, 17.5) | |
| **DISEASE-SPECIFIC SURVIVAL** | | | | | | |
| Whole cohort | 82.3 (80.4, 84.0) | – | 64.1 (61.7, 66.4) | – | 56.9 (54.3, 59.4) | – |
| Carstairs quintile | | 0.031 | | 0.009 | | 0.003 |
| 1 (Most affluent) | 88.8 (83.9, 92.2) | | 69.6 (62.9, 75.3) | | 61.8 (54.4, 68.4) | |
| 2 | 83.2 (78.5, 86.9) | | 69.8 (64.2, 74.8) | | 65.6 (59.6, 70.9) | |
| 3 | 82.2 (77.5, 86.1) | | 61.0 (55.1, 66.4) | | 55.5 (49.2, 61.3) | |
| 4 | 81.8 (77.5, 85.3) | | 64.4 (59.2, 69.1) | | 55.5 (49.9, 60.8) | |
| 5 (Most deprived) | 79.1 (75.2, 82.4) | | 59.6 (54.9, 63.9) | | 51.1 (46.0, 55.9) | |
| Slope Index of Inequality (95% CIs) | 9.5 (1.4, 17.7) | | 12.5 (−1.8, 26.9) | | 16.5 (1.5, 31.5) | |
| **NET SURVIVAL** | | | | | | |
| Whole cohort | 78.3 (76.2, 80.3) | – | 53.9 (51.1, 56.6) | – | 41.4 (37.7, 45.1) | – |
| Carstairs quintile | | N/A* | | N/A* | | N/A* |
| 1 (Most affluent) | 86.1 (81.3, 91.0) | | 58.1 (50.4, 65.8) | | 40.4 (30.7, 50.0) | |
| 2 | 80.9 (76.2, 85.5) | | 61.0 (54.4, 67.6) | | 43.8 (35.0, 52.6) | |
| 3 | 78.6 (73.8, 83.3) | | 52.9 (46.4, 59.3) | | 40.7 (31.5, 49.9) | |
| 4 | 77.2 (72.8, 81.5) | | 55.8 (50.1, 61.6) | | 46.6 (38.4, 54.7) | |
| 5 (Most deprived) | 73.7 (69.7, 77.6) | | 46.6 (41.7, 51.5) | | 35.7 (29.6, 41.8) | |
| Slope Index of Inequality (95% CIs) | 13.6 (7.1, 20.1) | | 16.1 (−1.0, 33.3) | | 6.6 (−17.2, 30.3) | |

**Trend test does not exist for Net survival.*

any evidence of an inequality by all-cause mortality by 5- or 12-years following the adjustment for age, sex and patient, tumor or treatment factors.

## Cox Models for Disease-Specific Mortality

Minimally adjusted and fully adjusted Cox Proportional Hazards models for disease-specific mortality are displayed in **Table 3**.

**TABLE 3 |** One-, five-, and twelve-year all-cause mortality (ACM) and disease-specific mortality (DSM) hazard ratios by Carstairs 2001 quintile for all patients with slope index of inequality (SII) for each measurement and time point.

| Variable | Adjusted by age and sex | | Adjusted by patient factors* | | Adjusted by tumor and treatment factors^ | | Adjusted by patient, tumor and treatment factors+ | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CIs) | *p*-value | HR (95% CIs) | *p*-value | HR (95% CIs) | *p*-value | HR (95% CIs) | *p*-value |
| **1-year ACM** | | <0.001 | | 0.037 | | 0.113 | | 0.351 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 1.35 (0.92, 2.00) | | 1.20 (0.81, 1.78) | | 1.09 (0.74, 1.62) | | 0.99 (0.67, 1.47) | |
| 3 | 1.53 (1.05, 2.25) | | 1.31 (0.89, 1.92) | | 1.42 (0.96, 2.09) | | 1.28 (0.86, 1.89) | |
| 4 | 1.62 (1.12, 2.33) | | 1.30 (0.90, 1.89) | | 1.29 (0.89, 1.88) | | 1.16 (0.79, 1.69) | |
| 5 (Most deprived) | 1.96 (1.38, 2.77) | | 1.46 (1.02, 2.09) | | 1.32 (0.92, 1.91) | | 1.16 (0.80, 1.68) | |
| SII (95% CIs) | 1.1 (0.7, 1.5) | | 0.5 (0.2, 0.8) | | 0.3 (−0.3, 1.0) | | 0.2 (−0.4, 0.7) | |
| **5-year ACM** | | <0.001 | | 0.157 | | 0.065 | | 0.715 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 0.99 (0.78, 1.26) | | 0.89 (0.70, 1.13) | | 0.91 (0.72, 1.16) | | 0.80 (0.63, 1.02) | |
| 3 | 1.22 (0.97, 1.54) | | 1.07 (0.85, 1.35) | | 1.29 (1.02, 1.63) | | 1.11 (0.88, 1.41) | |
| 4 | 1.14 (0.91, 1.43) | | 0.95 (0.76, 1.19) | | 1.07 (0.85, 1.34) | | 0.90 (0.72, 1.14) | |
| 5 (Most deprived) | 1.43 (1.15, 1.76) | | 1.11 (0.89, 1.38) | | 1.17 (0.94, 1.46) | | 0.97 (0.78, 1.22) | |
| SII (95% CIs) | 0.6 (0.1, 1.0) | | 0.2 (−0.2, 0.6) | | 0.2 (−0.5, 0.9) | | 0.03 (−0.6, 0.6) | |
| **12-year ACM** | | <0.001 | | 0.624 | | 0.197 | | 0.465 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 0.94 (0.77, 1.15) | | 0.86 (0.70, 1.04) | | 0.87 (0.71, 1.06) | | 0.79 (0.64, 0.96) | |
| 3 | 1.09 (0.89, 1.32) | | 0.95 (0.78, 1.16) | | 1.14 (0.94, 1.39) | | 0.99 (0.81, 1.21) | |
| 4 | 1.08 (0.89, 1.30) | | 0.89 (0.74, 1.08) | | 1.02 (0.84, 1.23) | | 0.86 (0.71, 1.05) | |
| 5 (Most deprived) | 1.27 (1.06, 1.52) | | 0.99 (0.82, 1.19) | | 1.06 (0.88, 1.27) | | 0.87 (0.72, 1.05) | |
| SII (95% CIs) | 0.4 (0.1, 0.7) | | 0.1 (−0.3, 0.4) | | 0.1 (−0.4, 0.6) | | −0.1 (−0.5, 0.4) | |
| **1-year DSM** | | 0.001 | | 0.162 | | 0.129 | | 0.431 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 1.59 (0.99, 2.54) | | 1.41 (0.88, 2.27) | | 1.23 (0.76, 1.97) | | 1.11 (0.69, 1.80) | |
| 3 | 1.69 (1.06, 2.69) | | 1.42 (0.88, 2.27) | | 1.57 (0.98, 2.52) | | 1.40 (0.87, 2.26) | |
| 4 | 1.72 (1.10, 2.69) | | 1.37 (0.87, 2.16) | | 1.42 (0.90, 2.25) | | 1.24 (0.78, 1.98) | |
| 5 (Most deprived) | 2.09 (1.36, 3.22) | | 1.51 (0.97, 2.34) | | 1.45 (0.92, 2.29) | | 1.23 (0.78, 1.96) | |
| SII (95% CIs) | 1.1 (0.2, 1.9) | | 0.7 (−0.1, 3.5) | | 0.4 (−0.4, 1.3) | | 0.2 (−0.5, 0.9) | |
| **5-year DSM** | | <0.001 | | 0.117 | | 0.046 | | 0.343 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 1.06 (0.77, 1.46) | | 0.96 (0.70, 1.33) | | 0.94 (0.68, 1.29) | | 0.82 (0.59, 1.14) | |
| 3 | 1.41 (1.04, 1.92) | | 1.24 (0.91, 1.68) | | 1.49 (1.10, 2.03) | | 1.29 (0.95, 1.77) | |
| 4 | 1.28 (0.95, 1.72) | | 1.07 (0.79, 1.45) | | 1.21 (0.89, 1.63) | | 1.03 (0.75, 1.40) | |
| 5 (Most deprived) | 1.55 (1.17, 2.06) | | 1.21 (0.91, 1.62) | | 1.27 (0.95, 1.71) | | 1.07 (0.79, 1.45) | |
| SII (95% CIs) | 0.7 (0.1, 1.2) | | 0.3 (−0.3, 0.8) | | 0.3 (−0.7, 1.4) | | 0.1 (−0.7, 1.0) | |
| **12-year DSM** | | <0.001 | | 0.066 | | 0.036 | | 0.359 |
| 1 (Most affluent) | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | | 1.00 (Ref.) | |
| 2 | 0.98 (0.73, 1.33) | | 0.89 (0.66, 1.20) | | 0.88 (0.65, 1.19) | | 0.78 (0.58, 1.06) | |
| 3 | 1.32 (0.99, 1.75) | | 1.16 (0.87, 1.54) | | 1.38 (1.04, 1.85) | | 1.20 (0.90, 1.61) | |
| 4 | 1.27 (0.97, 1.68) | | 1.06 (0.80, 1.40) | | 1.19 (0.90, 1.58) | | 1.02 (0.77, 1.35) | |
| 5 (Most deprived) | 1.51 (1.16, 1.96) | | 1.18 (0.90, 1.55) | | 1.22 (0.92, 1.60) | | 1.02 (0.77, 1.35) | |
| SII (95% CIs) | 0.7 (0.2, 1.2) | | 0.3 (−0.2, 0.7) | | 0.3 (−0.6, 1.2) | | 0.1 (−0.7, 0.9) | |

**Adjusted by age, sex, and patient factors including smoking status, alcohol consumption and WHO Performance Status. ^Adjusted by age, sex, tumor and treatment factors including stage, anatomical site, treatment modality and network of treatment +Adjusted by all factors including smoking status, alcohol consumption, WHO Performance status, stage, anatomical site, treatment modality and network of treatment.*

Similar to the models for all-cause mortality, there were clear trends following minimal adjustment by age and sex in the models for disease-specific mortality at all three time points, and there is statistical evidence to confirm an inequality in disease-specific mortality at 1- ($p = 0.001$), 5- ($p < 0.001$), and 12-years ($p < 0.001$). Following full adjustment for all factors including age, sex, patient, tumor and treatment factors, there was no evidence to support an inequality in excess risk of

disease-specific mortality after 1-year ($p = 0.431$), which can also be demonstrated by the SII which had reduced from 1.1 (0.2, 1.9) in the model minimally adjusted by age and sex, to 0.2 (−0.5, 0.9) in the fully adjusted model. By 5- and 12-years, the gaps between the risk of disease-specific mortality for the most affluent and the most deprived patients had narrowed in all models, which can be demonstrated by a reduction in all the models' SIIs between 1-, 5-, and 12-year follow-up—for example, in the model that was minimally adjusted by age and sex, the SII had reduced from 1.1 (0.2, 1.9) at 1-year, to 0.7 (0.1, 1.2) at 5-years, to 0.7 (0.2, 1.2) at 12-years, whereas in the fully adjusted model the SII had reduced from 0.2 (−0.5, 0.9) at 1-year, to 0.1 (−0.7, 1.0) at 5-years, and −0.1 (−0.5, 0.9) at 12-years. There was statistical evidence of a difference in the risk of disease-specific mortality at 5- and 12-years in the models adjusted by age, sex, tumor and treatment factors which is determined by the patients in group 3 (intermediate affluency) having 49% excess risk of disease-specific mortality [HR = 1.49, (1.10, 2.03)] and 38% excess risk of disease-specific mortality [HR = 1.38, (1.04, 1.85)] at 5- and 12-years, respectively, compared to those who were in the most affluent group. However, there was no evidence of an inequality across the groups from the SIIs at 5- or 12-years [SII = 0.3, (−0.7, 1.4] and 0.3, (−0.6, 1.2, respectively).

## DISCUSSION

This study demonstrates a clear gradient across Carstairs quintiles for minimally adjusted overall, disease-specific and net survival at 1-, 5-, and 12-years for patients with a diagnosis of HNC made between the years of 1999 and 2001 from Scotland. Following full adjustment at 1-, 5-, and 12-years, the inequality was no longer statistically significant suggesting that the inequality in the survival of patients with HNC can be explained by multiple patient, tumor and treatment factors. As an additional analysis, we also investigated the impact of individual co-variates on the inequality in survival, but the inequality remained strong at all three time points for all-cause mortality and disease-specific mortality (**Supplementary Tables 1, 2**), suggesting that the inequality in the survival of patients with HNC is not straightforward, and many factors play a combined effect in the role of the explanation of the inequality in HNC survival. The results for the net survival (unadjusted) analysis demonstrated a clear gradient across the Carstairs fifths at 1- and 5-years, but this gradient disappears by 12-years, suggesting that some of the inequality in long-term survival is partly attributable to background mortality, and since this cohort has such long follow-up, influence from background mortality is to be expected.

There are several limitations to this study. Firstly, SES was measured using the area based Carstairs 2001 Index (9, 10), which is derived from 2001 Census data involving the proportion of male unemployment, those in social classes IV and V, lack of car ownership, and overcrowding in a dwelling. Since this was a clinical cohort study, further data on SES indexes including education level and amount of income, was not collected as part of this study. Carstairs 2001 Index may not accurately represent rural and urban populations as it may be essential for people in these areas to own a car, however as other indices such as education level of income were not available for this analysis, Carstairs 2001 scores were the best measurement available for this analysis.

A further limitation of this study is the use of disease-specific survival which was classified from a patient having a primary cause of death of a form of HNC on their death certificates. Death certificates often contain several causes of death and so an exact cause of patients' death is not usually possible to determine, therefore we advise that these results are interpreted with caution due to the reliability of the reporting of cause of death from death certificates. Due to this, we have included net survival estimates alongside overall and disease-specific survival results to give an additional representation of HNC-specific deaths. Net survival determines the excess hazard of death from HNC, and therefore the impact of background mortality in HNC survival can be assessed. However, net survival cannot be computed in Cox Proportional Hazard analyses to run adjustment for additional confounders, and so all-cause and disease-specific mortality models together with net survival estimates provide a thorough insight into the burden of disease in HNC patients.

There has been an increase in the incidence of HPV-associated HNC over the last 20 years (20–22), which mostly involves cancers of the oropharynx. Around two-thirds of oropharynx cancers may be explained by HPV (23), and patients have substantially better prognoses than those with non-HPV-driven tumors, suggesting that one limitation of this study is the absence of HPV data (24, 25). These data were collected between the years of 1999 and 2001, which was before the discovery of the significant difference in survival between HPV-positive and HPV-negative HNC tumors (26), and thus HPV data was not collected as part of this study. Smoking and alcohol consumption are the main risk factors for non-oropharyngeal HNC tumors, and apart from tumors of the oropharynx, most HNCs are HPV-negative (27, 28). The marked improvement of in the survival of patients with HPV-positive oropharyngeal tumors was not observed in this study (data not shown), suggesting that these tumors are likely to be HPV-negative and therefore mostly explained by the high prevalence of smoking and alcohol consumption in this cohort (27, 28). HPV status, smoking behavior and alcohol consumption are three independent risk factors of survival (29, 30), and therefore we believe that the majority of cancers in this study are smoking and alcohol related and thus we believe that our findings are relevant despite missing HPV data.

Socioeconomic inequalities are present in HNC survival and are observed between and within countries. There are global inequalities in the incidence and mortality of HNC, and around two thirds of cases and three-quarters of deaths occur in low- or middle-income countries[1]. Paterson et al. (31) reported that the initial differences in survival (up to 18 months from diagnosis) may be explained by an advanced stage at diagnosis in the patients who were most deprived, and once this effect was eliminated, deprivation was no longer a predictor of patient prognosis for those who survive beyond 18 months. Ellis et al.

[1] http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

(32) confirmed that there was a gap in relative survival by deprivation at both 1 and 5 years in favor of the patients from socioeconomically advantaged areas and concluded that the origins of the inequalities were unclear, although it was likely that comorbidities and healthcare access were contributing toward the differences.

This study adds to the understanding of the inequality in survival for head and neck cancer patients. The SAHNC cohort represented 77% of all HNC cases on the Scottish Cancer Registry over a 2-year period and is therefore a good representation of HNC cases in Scotland. In unadjusted models, a clear gradient across Carstairs quintiles for overall, disease-specific and net survival was observed at 1-, 5-, and 12-years for this cohort of HNC patients. Following adjustment for multiple patient, tumor and treatment factors the inequality was no longer present for all-cause and disease-specific mortality. This study concludes that explanations for the inequality in survival of patients with HNC are not straightforward. Many factors, including various patient, tumor and treatment factors, play a part in the inequality of survival in patients with HNC.

## ETHICS STATEMENT

Research ethics committee advice was sought using the online tool from the NHS health research authority and Medical Research council website and was not required.

## AUTHOR CONTRIBUTIONS

KI statistical analysis and wrote paper; AM statistical analysis and supervision; DC supervision; CD supervision; KM supervision; S-AS supervision.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00673/full#supplementary-material

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SYSTEMATIC REVIEW
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# Socioeconomic Differences and Lung Cancer Survival—Systematic Review and Meta-Analysis

*Isabelle Finke*[1,2], *Gundula Behrens*[1], *Linda Weisser*[1,2], *Hermann Brenner*[1,3,4] *and Lina Jansen*[1]*

[1] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany, [2] Medical Faculty Heidelberg, University of Heidelberg, Heidelberg, Germany, [3] Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany, [4] German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

**Background:** The impact of socioeconomic differences on cancer survival has been investigated for several cancer types showing lower cancer survival in patients from lower socioeconomic groups. However, little is known about the relation between the strength of association and the level of adjustment and level of aggregation of the socioeconomic status measure. Here, we conduct the first systematic review and meta-analysis on the association of individual and area-based measures of socioeconomic status with lung cancer survival.

**Methods:** In accordance with PRISMA guidelines, we searched for studies on socioeconomic differences in lung cancer survival in four electronic databases. A study was included if it reported a measure of survival in relation to education, income, occupation, or composite measures (indices). If possible, meta-analyses were conducted for studies reporting on individual and area-based socioeconomic measures.

**Results:** We included 94 studies in the review, of which 23 measured socioeconomic status on an individual level and 71 on an area-based level. Seventeen studies were eligible to be included in the meta-analyses. The meta-analyses revealed a poorer prognosis for patients with low individual income (pooled hazard ratio: 1.13, 95 % confidence interval: 1.08–1.19, reference: high income), but not for individual education. Group comparisons for hazard ratios of area-based studies indicated a poorer prognosis for lower socioeconomic groups, irrespective of the socioeconomic measure. In most studies, reported 1-, 3-, and 5-year survival rates across socioeconomic status groups showed decreasing rates with decreasing socioeconomic status for both individual and area-based measures. We cannot confirm a consistent relationship between level of aggregation and effect size, however, comparability across studies was hampered by heterogeneous reporting of socioeconomic status and survival measures. Only eight studies considered smoking status in the analysis.

**Conclusions:** Our findings suggest a weak positive association between individual income and lung cancer survival. Studies reporting on socioeconomic differences in lung cancer survival should consider including smoking status of the patients in their

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***Edited by:***
*Dana Hashim,*
*Cancer Registry of Norway, Norway*

***Reviewed by:***
*Marie-Elise Parent,*
*Institut National de la Recherche Scientifique (INRS), Canada*
*Colin Robert Muirhead,*
*Independent Researcher, Newcastle upon Tyne, United Kingdom*

***Correspondence:**
*Lina Jansen*
*l.jansen@dkfz.de*

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analysis and to stratify by relevant prognostic factors to further explore the reasons for socioeconomic differences. A common definition for socioeconomic status measures is desirable to further enhance comparisons between nations and across different levels of aggregation.

**Keywords: socioeconomic status, lung cancer, cancer survival, area-based, education, income, occupation, index**

# INTRODUCTION

## Rationale

With 34.2 and 13.6 lung cancer cases per 100,000 per year for men and women around the world, respectively, lung cancer has the highest incidence rate for men and the fourth highest incidence rate for women (1). Regarding mortality, lung cancer has the highest rate in men and the second highest rate in women worldwide (1). Five-year survival rates vary considerably across countries with estimates between 10 and 20 % (2). These differences were even observed when comparing countries of similar structures in health care and access to care, such as the Scandinavian countries Sweden, Norway, and Denmark (3). Variations in the distribution of prognostic factors, such as stage, are likely to at least partly explain these differences (3). Numerous other prognostic factors have been investigated which include tumor-related factors like lung cancer subtype but also patient-related factors, such as age, gender, and comorbidities as well as smoking status and cancer treatment (4). For example, a later stage at diagnosis, male gender and current smoking at diagnosis have been shown to predict poor prognosis in lung cancer patients (5–7).

Another well-established prognostic factor for various cancer sites is socioeconomic status (SES) (8). Socioeconomic differences in cancer survival have been investigated and summarized by systematic reviews for different cancer types, such as breast (9, 10), colorectal (11), and prostate cancer (12). A recent meta-analysis reported lower breast cancer survival for women with lower SES even after adjustment for tumor characteristics, treatment, comorbidity or lifestyle-factors (10). Manser and Bauerfeind (11) reported in their systematic review significantly lower 1- and 5-year colorectal cancer survival rates for the lowest socioeconomic group compared to the highest socioeconomic group. Generally for all cancer types, neither stage at diagnosis nor treatment factors could entirely explain the association between SES and cancer survival (13).

For lung cancer, socioeconomic differences in incidence, mortality and treatment patterns have been summarized in systematic reviews, meta-, and pooled-analyses. A meta-analysis reported an increased risk in lung cancer incidence for lower socioeconomic groups with similar effect estimates in studies adjusting and not adjusting for smoking status (14). These results were confirmed by a recent international pooled analysis of case-control studies including detailed information on occupations and smoking behavior of around 17,000 cases and 20,000 controls (15). An analysis including 16 European populations reported higher lung cancer mortality rates in groups with lowest educational attainment (16). Another systematic review focused on lung cancer and showed higher lung cancer incidence and mortality in socioeconomically deprived areas (17). Tumor stage was not found to be associated with deprivation. However, stage might still confound associations between deprivation and lung cancer survival (18). Regarding treatment of lung cancer (19), the probability of receiving any type of treatment, surgery, and chemotherapy was lower in more deprived groups compared to the least deprived groups (19). To date, a systematic summary of findings regarding socioeconomic differences and lung cancer survival outcomes has not yet been provided.

SES can be measured for each patient individually (for example via questionnaire) or by using an ecological approach, meaning that a particular SES level is assigned to the residential area of each study participant (20). The latter can be called area-based studies which are often conducted if no individual SES data are available or if the effect of the area-based SES on health-related outcomes of a study participant is investigated (20). In such area-based studies, the aggregation level might be important. For patients with a diagnosis of breast cancer resident in England, it has been shown that the difference in crude survival between the most and the least deprived groups was 25 % smaller when using larger geographic units compared to smaller units (21). This dilution effect is caused by an increase in social heterogeneity the larger the area-level is (21). Another example from Australia reported stronger associations between socioeconomic disadvantage and the risk of cancer death and a more consistent socioeconomic gradient for the smaller geographical unit (22). However, this effect has not been investigated for lung cancer and has often been neglected in systematic reviews and meta-analyses. Furthermore, detailed meta-analyses regarding prognostic factors and their potential confounding in the association between socioeconomic measures and lung cancer survival have not yet been provided.

## Objectives

In our systematic review and meta-analysis, we provide a comprehensive summary on the current literature on socioeconomic differences in lung cancer survival with a focus on the impact of aggregation and adjustment level. The results of our review may inform health care planners about disparities in the prognosis of lung cancer patients and might help to more precisely identify socioeconomic deprived groups to counteract these differences.

## Research Question

We investigated three research questions:

1) What is the current state of research on socioeconomic differences in lung cancer survival with regard to studies measuring individual or aggregated socioeconomic status?

2) To what extend does a potential gradient in lung cancer survival by socioeconomic status vary by level of exposure definition (e.g., individual level, community level)?
3) Which prognostic factors have an impact on differences in socioeconomic status, particularly regarding the association with lung cancer survival?

# METHODS

## Systematic Review Protocol

The systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (23) and the extended version for equity-focused systematic reviews PRISMA-E 2012 (24). This review is registered in the international prospective register for systematic reviews PROSPERO (www.crd.york.ac.uk/PROSPERO, registration number: CRD42017072607).

## Literature Search

The main information sources for the literature search were four databases: Medline/PubMed (1966 to December 6, 2017), Web of Science (Science Citation Index Expanded, Social Science Citation Index, 1945 to December 7, 2017), The Cochrane Library (1992 to December 6, 2017), and GESIS Sowiport (1910 to December 8, 2017). The online portal Sowiport is organized by the GESIS Leibniz Institute for the Social Sciences (25) and included several social science related databases until its termination in December 2017. For our search strategy, a combination of key words regarding lung cancer survival and SES was applied. Key words related to SES were for example: socioeconomic, deprivation, disparit*, segregation, education, income, occupation, [social AND (status OR class OR position OR inequality*)]. The detailed search strategies for all databases including the respective thesaurus terms are displayed in **Table S1**. In addition, reference lists of included papers have been searched.

## Inclusion and Exclusion Criteria—Population

To be eligible, studies had to investigate a population of patients with a primary diagnosis of lung cancer. If other cancer sites were additionally investigated, studies were only included if results for lung cancer patients were reported separately.

## Inclusion and Exclusion Criteria—Exposure(s)

We focused our search on the main socioeconomic factors education, income and occupation as explanatory variable, measured either on an individual or area-based level. As many area-based studies used combined SES measurements, also called indices, we additionally included all combined measures or indices. Categorical and continuous measurements of socioeconomic measures were included.

## Inclusion and Exclusion Criteria—Outcome

The primary outcome of interest is survival after lung cancer diagnosis reported stratified by socioeconomic group. We focused on effect estimates from survival regression models (Cox or Poisson), 1-, 3-, or 5-year survival rates and median survival time after diagnosis. Other measures of survival were additionally included. The description of our results in the text focused on the regression models and 5-year survival rates.

## Inclusion and Exclusion Criteria—Types of Studies

Observational studies published in a peer-reviewed journal in English or German language were eligible for inclusion in our review. Non-original articles, such as guidelines, comments, book-chapters, editorials, reviews, and methods-papers were excluded. There was no further restriction regarding the period of publication or the study design.

## Inclusion and Exclusion Criteria—Meta-Analysis

To be eligible for inclusion in our meta-analysis, included studies had to fulfill further criteria. First, a study had to report hazard ratios including respective 95 % confidence intervals. Second, the studies should report on the same socioeconomic measure in a comparable manner to be able to combine the results in a meta-analysis. Third, socioeconomic measures had to be reported as categorical variables to identify low SES and high SES groups. Lastly, studies had to have a quality score of at least 6 out of 8 stars (for definition of the score see quality assessment below). This criterion was defined after writing the review protocol but before study results were summarized and interpreted. A cut-off of 6 was chosen by trading off the aim to include as many studies as possible against the aim to guarantee a high quality of the included studies. However, we additionally conducted sensitivity analyses including all studies irrespective of the quality score. In case of overlapping populations, we decided to hierarchically include the study with the most comprehensive inclusion of all stage groups, the longest period of diagnosis, and the longest follow-up period.

## Study Selection and Data Extraction/Screening

Titles, abstracts, and full texts retrieved were screened by one reviewer (IF). If no full text was available, studies were excluded if published before 1980, otherwise retrieved from The German National Library of Medicine (ZB MED) (26). EndNote software X7 was used to remove duplicates, retrieve full text articles, and manage citations. Data extraction of relevant information from included studies was performed by at least two reviewers for each study (IF, LW, and GB). Disagreements were resolved through discussion with a fourth member (LJ) of the review team. If relevant information was not reported in a study, the corresponding author was contacted via email. Sixteen authors were contacted and 10 answered to our request. Data items extracted from articles included the following: First author, publication year, country, study type, study setting, sample characteristics (n, age, gender), measure of SES (education, income, occupation, index), level of measurement (individual/area-based), outcome measure, prognostic factors,

risk of bias evaluation and main results. If a study used two different SES measurements separately, results for both measures were extracted. Model results were reported for the full model including all adjustments.

## Quality Assessment

To assess the methodologic and reporting quality of included studies, a modified version of the Newcastle-Ottawa-Scale (NOS) was used (27). The NOS consists of seven items to judge the quality of a study regarding the selection and comparability of study groups and ascertainment of the outcome (cohort studies) or exposure (case-control studies). One star was awarded for each item, except the comparability item which was modified so studies controlling for age in their analysis were awarded with one star and one additional star if any other factor was controlled for. In total, a study could be awarded with a maximum of 8 stars. We did not restrict the coding manual to a specific follow-up length, as the assessment of an adequate follow-up period refers to the study aim of the respective article. For example, if a study reported 3 months survival rates, the follow-up period had to be at least 3 months. The coding manual of our modified NOS can be found in the **Supplementary Material**.

## Statistical Analysis and Sensitivity Analysis

We computed random effects models and assessed heterogeneity across studies by using $I^2$ and Q statistics (28). The inverse variance method was used to assign the weight of each study in the analysis. For each study, we compared hazard ratios of the lowest SES group with the highest SES group as a reference. This was necessary as the categorizations of socioeconomic measures were very heterogeneous between the studies. Subgroup analyses were performed if possible by adjustment for smoking status, stage, and treatment. To assess the possible risk of bias and heterogeneity across studies included in our meta-analyses, we generated funnel plots and performed Begg's and Egger's test of plot asymmetry. All analyses were performed in the R statistical software (version 3.3.1) by using the metafor library (version 2.0-0).

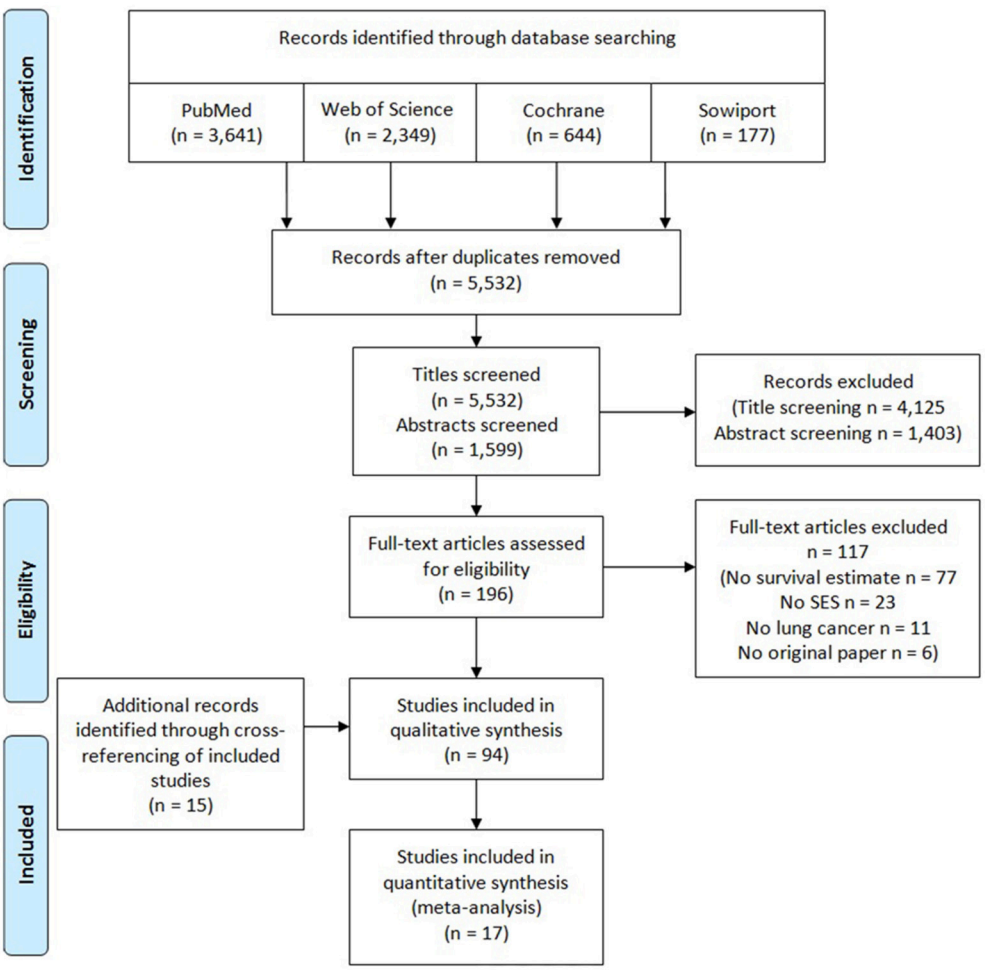


**FIGURE 1 |** PRISMA flow diagram of study selection process for a systematic review and meta-analysis on socioeconomic differences and lung cancer survival.

# RESULTS

## Study Selection and Characteristics

Based on our search strategy, the initial search resulted in 5,532 publications potentially relevant for the systematic review (**Figure 1**). After title and abstract screening, 196 articles were selected for full-text screening. Assessment of the full-texts led to the exclusion of 117 articles, mainly due to not investigating survival after lung cancer or not using a measure of education, income, occupation or an index. Fifteen publications were identified by reviewing of reference lists of included articles (29–43). In total, 94 articles (5, 6, 22, 29–119) were included in the qualitative synthesis and 17 (44–48, 54–56, 60–62, 88, 90, 98, 112, 114, 115) of these were eligible to be included in the meta-analyses.

Characteristics of included studies are shown in **Tables 1** and **2**. There were 23 studies (30, 32, 39, 42, 44–62) reporting on socioeconomic measures on individual level (**Table 1**), 70 studies (5, 6, 22, 29, 31, 33, 35–38, 40, 41, 43, 63–119) reporting on area-based level (**Table 2**) and one study reporting on both levels (34) (**Table 2**). One study included both individual and aggregated measures and performed a multilevel analysis (34) (**Table 2**). Most studies have been published within the last 10 years. Studies on individual SES measures used mostly data from Scandinavia, the United States (US) and Italy, while the majority of studies including area-based SES measures used data from the US, Great Britain and Australia/New Zealand. Data sources for cancer survival were usually national cancer registries but also cohort studies and clinical trials (50, 53). Most studies reported on all types of lung cancer, but 20 studies restricted analyses to non-small-cell lung cancer (NSCLC) patients (5, 34, 44, 45, 50, 56, 63, 66, 68, 72, 76, 80, 88–90, 93, 96, 97, 101, 112, 115) and three studies were restricted to small-cell lung cancer (SCLC) patients (6, 92, 114).

Regarding individual socioeconomic status, 16 studies measured educational attainment, eight studies measured income and eight studies assessed the occupation of the patients. Studies investigating area-based SES most often used an index (42 studies) or income measures (30 studies) with diverse levels of aggregation from postal codes in The Netherlands (∼8–17 households) (63, 94, 106) to comparisons of whole countries (77, 113). More details and definitions of socioeconomic measures and aggregated levels are provided in **Table S2**.

## Association of Individual SES and Survival—Modeling Results

Detailed modeling results for all studies with individual measures are displayed in **Table S3**. The majority of studies adjusted for age, gender, stage, and treatment. Three studies adjusted for smoking (44, 45, 47) (**Table 1**). Overall, there was no consistent difference in survival between studies with different levels of adjustment for prognostic factors (**Figure 2**).

For individual education (**Figure 2**), nine studies (44, 45, 47, 48, 54–56, 60, 61) were included in the meta-analysis. The summary estimate from the random effects model revealed no association between education and lung cancer survival (hazard ratio (HR) 1.03, 95 % confidence interval (CI): 0.96–1.10). The results of these studies were rather heterogeneous ($I^2 = 54.76$ %, $p = 0.02$). A stratified meta-analysis by stage at diagnosis was possible with three studies (45, 48, 56), but no significant associations were observed (early stage: HR 1.03, 95 % CI 0.92–1.15; late stage: HR 0.94, 95 % CI 0.81–1.08; **Figure S1**). We conducted stratified meta-analyses for studies that included stage, smoking or treatment in Cox models (**Figures S2–S4**). These analyses showed smaller effect estimates in studies that adjusted for stage (stage adjustment: HR 1.00, 95 % CI 0.92–1.08; no stage adjustment: HR 1.14, 95 % CI 1.05–1.23, **Figure S2**) or smoking status (smoking adjustment: HR 0.91, 95 % CI 0.72–1.14; no smoking adjustment: HR 1.04, 95 % CI 0.97–1.12, **Figure S3**), but confidence intervals were wide and overlapping. Stratified meta-analyses by studies that included treatment in Cox models did not suggest a difference in effect estimates (**Figure S4**). Three studies (50, 51, 53) were not included in the meta-analysis because of low scores for quality assessment. We conducted a sensitivity analysis by including these three studies into the meta-analysis. Results were similar to the main analysis (HR 1.05, 95 % CI 0.99–1.12, **Figure S5**).

For individual income (**Figure 2**), five studies (45–48, 62) were included in the meta-analysis showing a lower survival after lung cancer diagnosis for patients in the lowest income group compared to patients in the highest income group (HR 1.13, 95 % CI: 1.08–1.19). The studies were homogeneous ($I^2 = 0.00$ %, $p = 0.81$). All studies included in the meta-analysis of individual income adjusted for stage (**Table 1**). A stratified meta-analysis by smoking adjustment gave similar estimates as for the main analysis (smoking adjustment: HR 1.12, 95 % CI 1.03–1.22; no smoking adjustment: HR 1.14, 95 % CI 1.07–1.20, **Figure S6**). Exclusion of one study not adjusting for treatment (62) resulted in a marginal change of estimate (HR 1.13, 95 % CI 1.08–1.18, **Figure S7**). One study was not included in the meta-analysis because of reporting on a continuous scale (34) and indicated an association between higher income and lower risk of death after lung cancer diagnosis (**Table S3**).

Individual occupation was investigated in three studies (32, 45, 55) (**Table S3**). As the measures were very heterogeneous, a meta-analysis was not possible. In summary, no lower survival with decreasing SES was reported for occupational groups. Fujino (32) conducted analyses stratified by gender and reported a higher risk of dying after lung cancer diagnosis for housewives (women) and unemployed women compared to employed women but he did not consider other confounding factors besides gender. Kravdal (55) stratified occupational groups by education and reported for the low educational group a lower risk of death in non-manual occupations and a lower survival in farmers compared to manual occupations within the same educational group (**Table S3**). High-level non-manual occupations with medium education had a lower risk compared to low educated manual occupations (55).

No study reported hazard ratios for the association between an individually measured SES index and lung cancer survival (**Table 1**).

**TABLE 1 |** Characteristics of included studies with individual measurements of socioeconomic status.

| Paper, Data source[1] | Country | Years of diagnosis, Follow-up length, Age (range) | Sample size[2] | SES indicator(s)[3] | | | | Outcome | | | | | | Adjustment[4] | | | | | QS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Survival | | | | | | | | | | |
| | | | | Education | Income | Occupation | Index | HR | Median | Year | OS | RS | CSS | Age | Sex | Stage | Smoking | Other | |
| **EUROPE, NORTH** | | | | | | | | | | | | | | | | | | | |
| Dalton et al. (49), PBC (REG) | Denmark | 1994–2003, FU: 2006, 30–79 yrs | 21,492 | 3 | 3 | 3.6[5] | | | | 1,5,KM | | X | | X | X | | | | 8 |
| Dalton et al. (48), PBC (REG) | Denmark | 2004–2010, FU: 2011, 51–81 yrs | 13,045 | 3 | 3 | | | X | | | X | | | X | X | X | | X[a] | 8 |
| Pokhrel et al. (39), PBC (REG) | Finland | 1971–2005, FU: 2005, ≥25 yrs | 66,014 | 3 | | | | | | 5 | X | X | X | X | X | | | | 8 |
| Kravdal (55), PBC (REG) | Norway | 1955–1986, FU: 1960–1991, 50–79 yrs | NA[6] | 4 | | 14[7] | | X | | | | | | X | X | X | | X[b] | 7 |
| Skyrud et al. (58), PBC (REG) | Norway | 2002–2011, FU: 2013, ≤30 yrs | 24,565 | 3 | 3 | | | | | | | X[8] | | X | X | X | | X[c] | 8 |
| Berglund et al. (45), PBC (REG) | Sweden | 1996–2004, FU: 2006, 30–94 yrs | 3,370 (NSCLC) | 3 | 2 | 2 | | X | | 1,3 | | | X | X | X | X | X | X[d] | 8 |
| Hussain et al. (54), PBC (REG) | Sweden | 1990–2004, FU: 2004, 30–64 yrs | 17,936 | 4 | | | | X | | | | | X | X | X | | | X[e] | 7 |
| Vågerö et al. (59), PBC (REG) | Sweden | 1961–1979, FU: 1979, 20–64 yrs | 7,817 | | | 3 | | | | 5,KM | | X | | | X | | | | 7 |
| **EUROPE, OTHER** | | | | | | | | | | | | | | | | | | | |
| Grivaux et al. (52), PCo | France | 2000, FU: 2005–2006, all ages | 5,447 | | | 7 | | | | 5 | X | | | | | | | | 4 |
| Di Maio et al. (50), CT | Italy | 1996–2005 (conduction of trials), FU: median 26.3 mths, 29–86 yrs | 1,680 (NSCLC) | 2 | | | | X | X | KM | X | | | | X | X | | X[f] | 4 |
| Pagano et al. (56), PBC (REG) | Italy | 2000–2003, FU: 2006, all ages | 2,259 (NSCLC) | 3 | | | | X | | | X | | | X | X | X | | X[g] | 8 |
| Pastorino et al. (57), PBC (REG) | Italy | 1976–1979, FU: ≥ 9 yrs, 34–85 yrs | 222 | | | 3 | | | | 5 | X | | | | | | | | 6 |
| Smailyte et al. (42), PBC (REG) | Lithuania | 2001–2009, FU: 2009, 30–74 yrs | 8,812 | 3 | | | | | | 5 | | X | | X | X | | | | 8 |
| Aarts et al. (44), PBC (REG) | NL | 1991–2008, FU: 2009, 15–75 yrs | 274 (NSCLC) | 4 | | | | X | | 1,3,KM | X | | | X | X | X | X | X[h] | 7 |
| **USA** | | | | | | | | | | | | | | | | | | | |
| Chirikos et al. (30), PBC (REG) | USA | 1977–1981, FU: NA, Age: NA | NA[9] | | 2 | 2 | | | | 1,3,KM | | | X | | | X | | | 8 |
| Clement-Duchene et al. (47), PCo | USA | 2003–2005, FU: 2012, all ages | 3,410 | 3 | 4 | | | X | | | | | | X | X | X | X[10] | X[i] | 8 |
| Herndon et al. (53), CT | USA | 1988–2001[11], FU:2005, all ages | 1,577 | 5 | | | | X | X | KM | X | | | | | | | | 1 |
| **ASIA** | | | | | | | | | | | | | | | | | | | |
| Yeole et al. (61), PBC (REG) | India | 1987–1991, FU: until 1996, all ages | 1,995 | 4 | | | | X | | 5 | | X | | X | | X | | X[j] | 8 |
| Yeole et al. (60), PBC (REG) | India | 1992–1994, FU: until 1999, all ages | 1,230 | 4 | | | | X | | 5 | X | | | X | | X | | X[k] | 8 |
| Fujino (51), CoS | Japan | 1988–1990[12], FU: 2003, 40–79 yrs | 1,098 | 3 | | | | X | | | | | | X | X | | | X[l] | 5 |
| Fujino (32), CoS | Japan | 1988–1990[12], FU: 2003, 40–79 yrs | NA | | | 6,3,4[5] | | X | | | | | | X | X | | | X[l] | 5 |
| Yim et al. (62), RCo | Korea | 2000, FU: ≤48 mths, all ages | 261 | | 3 | | | X | | 3,KM | X | | X | X | X | X | | X[m] | 7 |
| Chang et al. (46), PGB (INS) | Taiwan | 2002, FU: 5 years, all ages | 4,698 | | 6 | | | X | | 5,KM | X | | | X | X | X | | X[n] | 8 |

*CSS, Cause-specific survival; CoS, Cohort study; CT, Data from clinical trials; FU, Follow-up length; HR, Hazard ratio; mths, months; INS, Insurance; KM, Study provided Kaplan-Meier-Curve(s) or other survival curves stratified by SES; NA, Not available; NL, The Netherlands; NSCLC, Non-small cell lung cancer; OS, Overall survival; PBC, Population-based cohort; PCo, Prospective cohort; QS, Quality score; RCo, Retrospective cohort; REG, Registry; RS, Relative survival; SEER, Surveillance, Epidemiology, and End Results Program; SES, Socioeconomic status; Yrs, years of age;* [1]*Data sources for survival data;* [2]*Only lung cancer patients;* [3]*Numbers indicate number of groups, excluding unknown/missing, more detail in* ***Table S2****;* [4]*Adjustment by stratification and standardization was also considered; if both model and survival rates were calculated, only model adjustments are reported;* [5]*Study assessed two (three) indicators for occupation;* [6]*Sample size: 114,000 (all cancers);* [7]*Combination of education and occupation;* [8]*Study reported relative excess risk;* [9]*Sample size: 1,180 (all cancers, only men);* [10]*Study included only non-smokers;* [11]*Enrollment dates;* [12]*Study start;* [a]*Comorbidities, first-line treatment, performance status, period;* [b]*Histologic type/grade, period/year, sub-site;* [c]*Health services region, radiotherapy, surgery;* [d]*Histopathology, performance status, treatment;* [e]*Period;* [f]*Birth cohort, histology, performance status;* [g]*Comorbidity, marital status, pattern of care;* [h]*Alcohol, comorbidities, period, physical activity;* [i]*Race, comorbidity, insurance, health care setting, histology, surgery, chemotherapy, radiotherapy;* [j]*Marital status, treatment;* [k]*Marital status, religion, treatment;* [l]*Area of study;* [m]*Family history, out-patient-visits per month, performance status;* [n]*Comorbidities, hospital characteristics, treatment modality.*

**TABLE 2 |** Characteristics of included studies with aggregated measurements of socioeconomic status.

| Paper, Data source[1] | Country | Years of diagnosis, Follow-up length, Age (range) | Sample size[2] | SES indicator(s)[3] | | | | SES Level[4] | Outcome | | | | | | Adjustment[5] | | | | | QS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Survival | | | | | | | | | | | |
| | | | | Education | Income | Occupation | Index | | HR | Median | Year | OS | RS | CSS | Age | Sex | Stage | Smoking | Other | |
| **EUROPE** | | | | | | | | | | | | | | | | | | | | |
| Chouaid et al. (70), RCo | France | 2011, FU: 2013, all ages | 41,115 | | | | 4 | Com-mune | X | | 1,2 | X | | | X | X | | | X[a] | 7 |
| Jansen et al. (35), PBC (REG) | Germany | 1997–2006, FU: 2006, ≥15 yrs | 105,688 | | | | 5 | District | | | 5 | | X[6] | | X | | X | | | 8 |
| Aarts et al. (63), PBC (REG) | NL | 2001–2012, FU: 2014, all ages | 5,428 NSCLC stage IV | | | | 4 | PC | X | X | 1 | X | | | X | X | | | X[b] | 8 |
| Louwman et al. (94), PBC (REG) | NL | 1997–2006, FU: NA, all ages | 12,945 | | | | 3 | PC | X | | 1 | X | | | X | X | | | X[c] | 8 |
| Schrijvers (106), PBC (REG) | NL | 1980–1989, FU: 1991, all ages | 4,591 | | | | 5 | PC | X | | 5 | | X | | X | | X | | X[d] | 8 |
| Pollock and Vickers (102), PBC (REG) | England | 1987–1992, FU: 1992, 40–99 yrs | 22,842 | | | | 10 | ED | | | 5, KM | | X | | X | X | | | | 8 |
| Schrijvers (107), PBC (REG) | England | 1980–1989, FU: 1992, 30–99 yrs | 40,279 | | | | 5 | ED | X | | 5 | | X | | X | X | X | | X[e] | 8 |
| Berglund et al. (64), PBC (REG) | England | 2006–2008, FU: 2009, 0–80+ yrs | 15,582 | | 5 | | | LSOA | X | | 3, KM | X | | | X | X | X | | X[f] | 8 |
| Nur et al. (99), PBC (REG) | England | 2001–2005, FU: 2011, 15–99 yrs | 145,532 | | | | 5 | LSOA | | | 1,5, 10, KM | | X[6] | | X | X | | | | 8 |
| Rachet et al. (40), PBC (REG) | England | 1996–2006, FU: 2007, 15–99 yrs | 303,422 | | | | 5 | LSOA | | | | | X[7] | | X | X | | | X[g] | 8 |
| Riaz et al. (104), PBC | England | 2003–2007, FU: 2008, all ages | 150,939 | | 5 | | | LSOA | | | 1 | X | | | | X | | | X[h] | 7 |
| Rich et al. (105), PBC | England | 2004–2008 (data entry), FU: 2008, all ages | 60,059 | | | | 5 | LSOA | X | | | | | | X | X | X | | X[i] | 8 |
| Coleman et al. (71), PBC (REG) | England/Wales | 1971–1990, FU: 1995, all ages | 144,604 | | | | 5 | ED | | | 1,5 | | X | | X | | | | | 7 |
| Rachet et al. (103), PBC (REG) | England/ Wales | 1986–1999, FU: 2001, 15–99 yrs | 392,000 | | 5 | | | LSOA | | | 5 | | | | | X | | | X[g] | 6 |
| Sloggett et al. (41), PBC | England/Wales | 1981–1997, FU: 2000, ≥45 yrs | 4,271 | | | 6 | 5 | Ward/IND | | | | | X[6] | | X | X | | | X[j] | 8 |
| Coleman et al. (31), PBC (REG) | England/Wales | 1986–1990, FU: 2001, 15–99 yrs | 107,317 | | | | 5 | Electoral ward | | | | | X[7] | | | X | | | | 7 |
| Campbell et al. (29), PBC (REG) | Scotland | 1991–1995, FU: 1995, all ages | 19,449 | | | | 5 | OA | | | 1 | X | | | | | | | | 8 |
| Shack et al. (108), PBC (REG) | Scotland | 1986–2000, FU: 2004, 15–99 yrs | 20,851 | | | | 5 | Postcode sector | | | 5 | | X | | X | X | | | | 8 |
| Iyen–Omofoman et al. (86), PCo | UK | 2000–2009, FU: 2009, all ages | 12,135 | | | | 5 | OA | X | X | 1,5 | X | | | | | | | | 6 |
| O'Dowd et al. (100), PCo | UK | 2000–2013, FU: 3 mths, ≥30 yrs | 20,142 | | | | 5 | OA | | | 1,3 mth | X | | | | | | | | 6 |
| Cheyne et al. (69), RCo | UK | 2008–2010, FU: NA, 31–97 yrs | 1,432 | | | 5 | 5 | LSOA | | X | 1 | X | | | | | | | | 4 |
| Ellis et al. (75), PBC (REG) | UK | 2001–2005, FU: 2009, ≥35 yrs | 145,206 | | | | 5 | LSOA | | | 1,5 | | X[7] | | | X | | X | | 8 |
| Forrest et al. (78), PBC (REG) | UK | 2006–2009, FU: ≥ 2 yrs, all ages | 22,967 | | 5 | | | LSOA | | | 2 | X | | | | | | | | 8 |
| Jack et al. (87), PBC (REG) | UK | 1998, FU:NA, all ages | 695 | | | | 5 | Ward | | | 1 | X | | | | | | | | 8 |
| Vercelli et al. (113), PBC (REG) | Europe | 1990–1994, FU: ≥ 5 yrs, 65–84 yrs | 657,541 | | X[8] | | | Country | | | 5 | | X | | | X | | | | 7 |
| Evans and Pritchard (77), PBC | Europe/USA | Europe: 1983–1985, USA: 1983–1989, FU: 1995,0–84 yrs | 10 countries | | X[8] | | | Country | | | 5 | | X | | X | X | | | | 8 |
| **CANADA/USA** | | | | | | | | | | | | | | | | | | | | |
| Mackillop et al. (95), PBC (REG) | Canada | 1982–1991, FU: NA, Age: NA | 357,530 all cancers | | 5 | | | Postal code | X | | 5,KM | | | X | X | X | | | X[k] | 8 |
| Booth et al. (66), PBC (REG) | Canada | 2003–2007, FU: ≥ 1 year, Age: NA | 12,276 NSCLC | | 5 | | | Com–munity | X | | 3,5 | X | | X | X | | X | | | 8 |
| Dabbikeh et al. (73), PBC (REG) | Canada | 1993–2009, FU: 2013, all ages | 122,889 | | 5 | | 5 | EA/DA | X | | 5 | | | X | X | X | | | | 8 |
| Boyd et al. (67), PBC (REG/SEER) | Canada/USA | 1987–1992, FU: 1994, ≥20 yrs | NA[9] | | 5 | | | USA: CeT, Canada: EA | X | | 5,KM | | | X | X | X | | | X[g] | 8 |

*(Continued)*

**TABLE 2** | Continued

| Paper, Data source[1] | Country | Years of diagnosis, Follow-up length, Age (range) | Sample size[2] | SES indicator(s)[3] | | | | SES Level[4] | Outcome | | | | | | Adjustment[5] | | | | | QS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Survival | | | | | | | | | | | |
| | | | | Education | Income | Occupation | Index | | HR | Median | Year | OS | RS | CSS | Age | Sex | Stage | Smoking | Other | |
| Gorey et al. (33), PBC (REG/SEER) | Canada/USA | Canada:1986–1992, FU: 1993, ≥25 yrs USA:1984, FU: 1991, ≥25 yrs | Canada: 58,202 USA: 76,055 | | 3 | | | CeT | | | 1,5[10] | | | | | X | | | | 8 |
| Zhang–Salomons et al. (43), PBC (REG/SEER) | Canada/USA | Canada:1989–1993, FU: 1998, ≥25 yrs USA: 1988–1992, FU: 1997, ≥25 yrs | Canada: 8,209, USA: 15,261 | | 5 | | | CeT | X | | 5 | | | X | X | X | | | | 8 |
| Gomez et al. (79), PBC (REG) | USA | 2000–2010, FU: 2012, all ages | 3,832 Chinese ethnicity | | | | 5 | CBG | X | X | | X | | | X | X | X | | | X[l] | 8 |
| Hastert et al. (82), PBC (SEER) | USA | 2000–2002, FU: 2010, 50–76 yrs | 52,186 | 4 | 5 | | 5 | CBG | X | | | | | | X | X | | | | X[m] | 8 |
| Lara et al. (92), PBC (REG) | USA | 1998–2012, FU: 2013, all ages | 22,863 SCLC | | | | 2 | CBG | X | | | | | X | X | X | X | | | X[n] | 8 |
| Ou et al. (5), PBC (REG) | USA | 1989–2003, FU: median 53 mths, all ages | 19,702[14] NSCLC, stage I | | | | 5 | CBG | X | | | | | | X | X | X | | | X[N] | 8 |
| Ou et al. (101), PBC (REG) | USA | 1989–2003, FU: median 53 mths, all ages | 19,702[14] NSCLC, stage I | | | | 5 | CBG | X | X | 5,KM | X | | | X | X | | | | X[o] | 8 |
| Ou et al. (6), RCo | USA | 1991–2005, FU: ≥77 mths, all ages | 3,428 ED-SCLC | | | | 5 | CBG | X | X | 1,2 | X | | | X | X | | X | | X[p] | 7 |
| Caposole et al. (68), PBC (REG) | USA | 1998–2012, FU:>12 yrs, all ages | 3,531 NSCLC | | 4 | | | CeT | | X | | X | | | | | | | | | 6 |
| Erhunmwunsee et al. (76), PBC (REG) | USA | 1995–2007, FU: ≥2 yrs, 20–105 yrs | 4,820 NSCLC | 2 | 2 | | | CeT | | X | 6,KM | | | X | | | | | | | 5 |
| Greenwald et al. (34), PBC (REG) | USA | 1980–1982, FU: 1987, Mean age 67.6 yrs | 78 (NSCLC, stage II) | | X | | | Multi-level (CeT+ IND) | X | | | | | | X | X | | | | | 8 |
| Greenwald et al. (80), PBC (SEER) | USA | 1978–1982, FU: ≥10 yrs, ≤75 yrs | 5,132 NSCLC | | 10 | | | CeT | X | | 5 | X | | | X | X | | | | X[q] | 8 |
| Johnson et al. (88), PBC (REG) | USA | 2000–2009, FU: 2011, 50–85 yrs | 32,711 NSCLC | 4 | 4 | | | CeT | X | | | X | | | X | X | X | | | X[r] | 8 |
| Johnson et al. (89), PBC (REG) | USA | 2000–2009, FU: 2012, 30–85 yrs | 8,322 early stage NSCLC | 4 | 4 | | | CeT | X | | | | | | X | X | | | | X[s] | 8 |
| Lara et al. (93), PBC (REG) | USA | 1998–2009, FU: 2011, all ages | 114,451 NSCLC | | | | 3 | CeT | X | X | | | | X | X | X | X | | | X[t] | 8 |
| Lipworth et al. (38), PBC (REG) | USA | 1959–1963, FU: 3 yrs, all ages | 246 | | 2 | | | CeT | | | 1,3 | | X | | | X | | | | | 5 |
| Niu et al. (98), PBC (REG) | USA | 1986–1999, FU: 2004, all ages | 64,206 | | 4 | | | CeT | X | | 5 | | | X | X | X | X | | | X[u] | 8 |
| Shugarman et al. (109), PBC (SEER) | USA | 1995–1999, FU: NA, ≥65 yrs | 26,073 | | 3 | | | CeT | X | | | | | | X | X | X | | | X[v] | 7 |
| Tannenbaum et al. (112), PBC (REG) | USA | 1996–2007, FU: ≥3 yrs, 18–104 yrs | 98,541 NSCLC | | 4 | | | CeT | X | X | 1,3,5, KM | X | | | | X | X | X | | X[w] | 8 |
| Yang et al. (117), PBC (REG) | USA | 1998–2002, FU: 2006, all ages | 97,046 | | 4 | | | CeT | X | X | KM | X | | | X | X | X | X | | X[x] | 8 |
| Yu et al. (118), PBC (SEER) | USA | 2000–2002, FU: ≥5 yrs, Age: NA | 97,046 | | | | 5 | CeT | | | | | | X | | | | | | | 7 |
| Khullar et al. (90), PBC (NCDB) | USA | 2003–2006, FU: NA, Mean 66.0 yrs ± SD 10.33 yrs | 92,929 NSCLC | 4 | 4 | | | Zip code | X | | KM | X | | | X | X | X | | | X[y] | 8 |
| McMillan et al. (96), PBC (NCDB) | USA | 2004–2012, FU: 2013, all ages | 14,154 NSCLC, stage III | | 2 | | | Zip code | X | | | X | | | X | X | | | | X[z] | 8 |
| Melvan et al. (97), PBC (NCDB) | USA | 2003–2011 (resection date), FU: 30 days, ≥60 yrs | 215,645 NSCLC | 4 | 4 | | | Zip code | | | 30day | X | | | | | | | | | 6 |
| Wen and Christakis (116), PBC (REG) | USA | 1993, FU: 1999, all ages | NA | | | | X[11] | Zip code | X | | | | | X | | | | | | | 6 |
| Wang et al. (114), PBC (SEER) | USA | 1983–2012, FU: NA, 30–75+ yrs | 293,471 NSCLC | | 3 | | | County | X | | 1 | | X | | X | X | | | | X[u] | 8 |
| Wang et al. (115), PBC (SEER) | USA | 1983–2012, FU: NA, all ages | 56,220 SCLC | | 3 | | | County | X | | 1,2,3,5 | | X | | X | X | | | | X[u] | 8 |

*(Continued)*

**TABLE 2** | Continued

| Paper, Data source[1] | Country | Years of diagnosis, Follow-up length, Age (range) | Sample size[2] | SES indicator(s)[3] | | | | SES Level[4] | Outcome | | | | | | Adjustment[5] | | | | | QS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Survival | | | | | | | | | | | |
| | | | | Education | Income | Occupation | Index | | HR | Median | Year | OS | RS | CSS | Age | Sex | Stage | Smoking | Other | |
| **AUSTRALIA/NEW ZEALAND** | | | | | | | | | | | | | | | | | | | | |
| Bonett et al. (65), PBC (REG) | Australia | 1977–1982, FU: 1983, all ages | 2,934 | | X | | | CD | X | | | | | X | | | | | | 8 |
| Hall et al. (81), PBC | Australia | 1982–1996, FU: ≥ 5 yrs, all ages | 9,080 | | | | 5 | CD | X | | 5 | | X | | X | X | | | $X^{A}$ | 8 |
| Tervonen et al. (22), PBC (REG) | Australia | 2000–2008, FU: 2008, all ages | 26,415 | | | | 5 | CD/SLA | X | | | | | | X | X | X | | $X^{B}$ | 8 |
| Currow et al. (72), PBC (REG) | Australia | 2003–2007, FU: 2008, all ages | 3,040 NSCLC | | | | 5 | POA | X | | | | | | X | X | | | $X^{D}$ | 8 |
| Denton et al. (74), PCo | Australia | 2001–2014 (case discussion), FU: NA, Mean age 68 ± 11 (SD) yrs | 2,369 | | | | 5 | POA | X | | 5 | | X | | X | X | X | | $X^{E}$ | 7 |
| Hui et al. (84), PBC (REG) | Australia | 1996, FU: ≥ 4 yrs, 32–91 yrs | 526 | | | | 5 | POA | | X | KM | | X | X | | | | | | 6 |
| Stanbury et al. (110), PBC (REG) | Australia | 1991–2008, FU: 2008, 15–89 yrs | 33,942 | | | | 5 | LGA | | | 5 | | | $X^{6}$ | X | X | X | | $X^{F}$ | 8 |
| Yu et al. (119), PBC (REG) | Australia | 1992–2000, FU: 2001, 15–89 yrs | 15,251 | | | | 5 | LGA | | | 5 | | | $X^{6}$ | X | X | X | | $X^{F}$ | 8 |
| Jeffreys et al. (36), PBC (REG) | NZ | 1994–2003, FU: 2004, 15–99 yrs | 13,643 | | | | 4 | MB | | | | | | $X^{7}$ | X | | | | | 7 |
| Sutherland and Aitken (111), RCo | NZ | 1997–1999, FU: ≥ 5 yrs,27–92yrs | 102 | | | | 10 | MB | | | $X^{12}$ | X | | | | | | | | 4 |
| Haynes et al. (83), PBC | NZ | 1994–2001, FU: 2004, Mean age 69 yrs | 12,420 | | | | 4 | CAU | X | | | | | | X | X | X | | $X^{G}$ | 8 |
| **ASIA** | | | | | | | | | | | | | | | | | | | | |
| Ito et al. (85), PBC (REG) | Japan | 1993–2004, FU: ≥ 5 yrs,Age:NA | 39,621 | | | | 5 | Cho-Aza | | | 1,5 | | | $X^{13}$ | | X | | | $X^{H}$ | 7 |
| Kwak and Kim (91), PBC (REG) | Korea | 2010–2011, FU: 2014, all ages | 1,426 | | | | 4 | Dong | X | | 1,3,5 | X | | | X | X | X | X | $X^{L}$ | 8 |
| Kwak (37), PBC (REG) | Korea | 2000–2011, FU: 2013, all ages | 13,801 | | | | 4 | Dong | X | X | 1,2,3, KM | X | | | X | X | | | | 8 |

*BMI, Body mass index; CAU, Census Area Unit; CBG, Census block group; CD, Census Collection District; CeT, Census tract; CSS, Cause-specific survival; DA, Dissemination area; EA, Enumeration area; ED, Enumeration district; ED-SCLC, Extensive disease small-cell lung cancer; FU, Follow-up length; HR, Hazard ratio; IND, Individual; IQR, Inter quartile range; KM, Study provided Kaplan-Meier-Curve(s) or other survival curves stratified by SES; LGA, Local Government Area; LSOA, Lower Super Output Area; MB, Meshblock; mth(s), month(s); NA, Not available; NCDB, National Cancer Data Base (American Cancer Society); NL, The Netherlands; NSCLC, Non-small cell lung cancer; NZ, New Zealand; OA, Output area; OS, Overall survival; PBC, Population-based cohort; PC, Postal code; PCo, Prospective cohort; POA, Postal code area; QS, Quality score; RCo, Retrospective cohort; REG, Registry; RS, Relative survival; SCLC, Small-cell lung cancer; SEER, Surveillance, Epidemiology, and End Results Program; SES, Socioeconomic status; SLA, Statistical Local Area; UK, United Kingdom; wks, Weeks; yrs, Years of age; [1]Data sources for survival data; [2]Only lung cancer patients; [3]Numbers indicate number of groups, excluding unknown/missing; [4]More details about SES levels in **Table S2**; [5] Adjustment by stratification and standardization was also considered; if both model and survival rates were calculated, only model adjustments are reported; [6]Study reported relative excess risk; [7]Study reported deprivation gap; [8]Rank order of % Gross domestic product expenditure on health; [9]Sample size for all cancers: USA n = 486,327, Canada n = 187,650; [10]Study reported survival rate ratios; [11]SES index has been measured on a continuous scale; [12]Survival rate: 6 weeks, 3 and 6 months, 1, 2, and 5 years, according to correspondence with author; [13]Study reported net survival; [14]Studies included same patient population; [a]Comorbidities, population density; [b]Chemotherapy, comorbidity, grade, histology, location of metastasis, period; [c]Presence of concomitant diseases; [d]Follow-up period, histology, treatment; [e]Follow-up period, period of diagnosis; [f]Comorbidity, resection, radiotherapy, chemotherapy; [g]Year of diagnosis; [h]Urban/rural; [i]Histology, performance status; [j]Marital status, north/south geographic zone, period of diagnosis, year of follow-up; [k]Cancer center catchment area, year of diagnosis; [l]Cancer center, chemotherapy, health insurance, histologic subtype, marital status, nativity, neighborhood ethnic enclave, radiation, surgery type, urban/rural, year of diagnosis; [m]Race/ethnicity, marital status; [n]Race, treatment, urban/rural, year of diagnosis; [o]Chemotherapy, ethnic origin, histologic grade, histology, marital status, radiation, surgery, tumor lobar location; [p]Chemotherapy, ethnicity, marital status, radiation, surgery; [q]Race, surgery; [r]Race, treatment, tumor grade; [s]Elderly concentration, place of residence, race, racial segregation, random census tract effect, surgery, tumor grade; [t]Histology, race, treatment, urban/rural, year of diagnosis; [u]Race; [v]Urban/rural, race, marital status, Medicaid, comorbidity, year of diagnosis, treatment, English speaking, health professional shortage area, health care provider supply characteristics; [w]Comorbidities, geographic location, grade, histological type, hospital volume, insurance status, lymph node status, marital status, race/ethnicity, teaching hospital, treatment; [x]Comorbidities, grade, insurance, lymph node status, race/ethnicity, tumor size, histology, surgery, radiation, chemotherapy; [y]Comorbidity, facility type, grade, histology, insurance, lymph nodes, primary tumor site, race, radiation before surgery, surgery, urban/rural, year of diagnosis; [z]Comorbidity, distance between residence and hospital, facility type, grade, histology, insurance, race, TN classification, tumor location, tumor size, chemotherapy, radiation fractions, radiation treatment time; [A]Calendar period, comorbidity, histology, indigenous status, insurance status, location/status of hospital, marital status, remoteness, surgical status; [B]Country of birth, remoteness, year of diagnosis; [D]Comorbidity, country of birth, histology, insurance status, local health districts, lung location, remoteness, resection; [E]Place of residence; [F]Follow-up year; [G]Ethnic group, travel to primary care, travel to cancer center; [H]Period of diagnosis; [L]BMI, diagnosis path (by regular checkup, by chance, by symptom), drinking; [N]Chemotherapy, ethnic origin, histologic grade, histology, radiation, surgery, tumor lobar location, tumor size, period of diagnosis.*

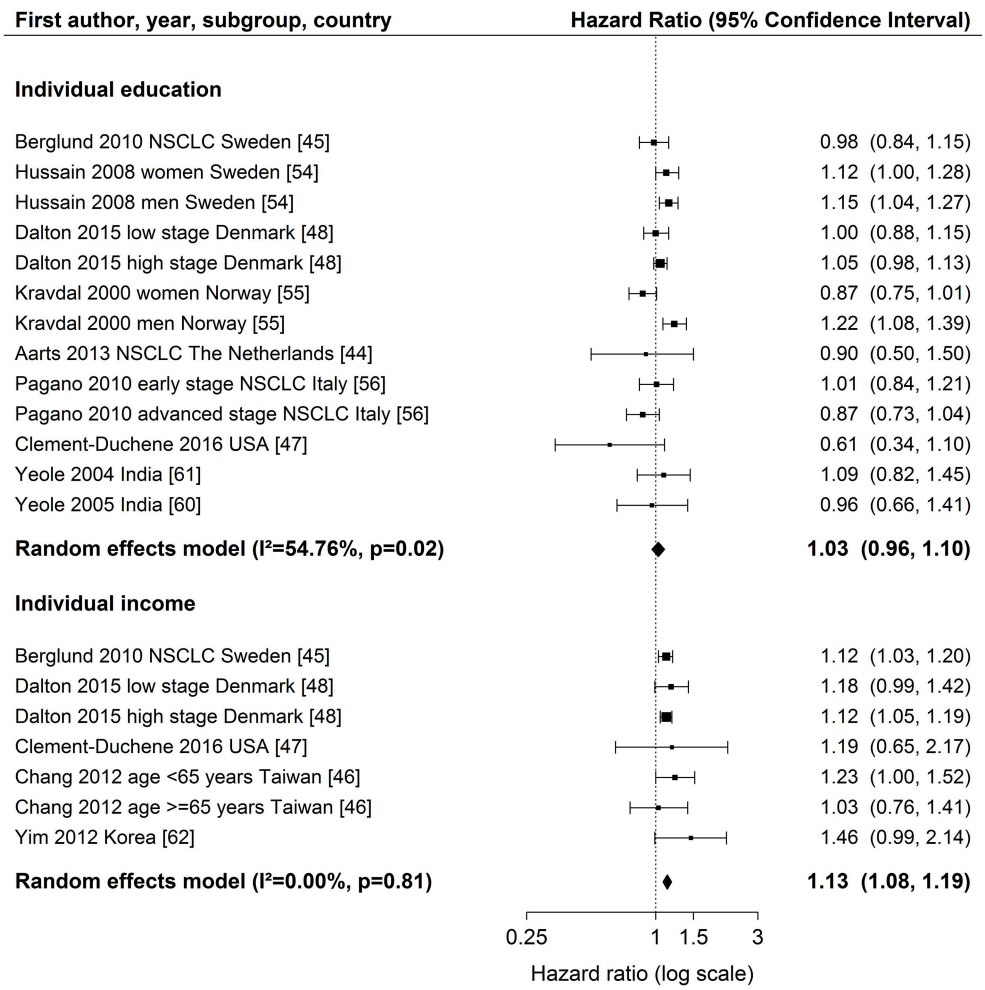


**FIGURE 2 |** Meta-analyses of studies on the association of individual education / income (reference: high income/education) and survival after lung cancer. NSCLC, non-small cell lung cancer. Kravdal (55): highest educational group, men = 17+ years, women = 13–17+ years. Chang et al. (46): high income category = high individual AND high neighborhood income (reference), low income category = low individual AND low neighborhood income.

## Association of Area-Based SES and Survival—Modeling Results

Characteristics of SES exposure of most studies on area-based SES measurements were too heterogeneous to conduct meta-analyses. However, for studies reporting hazard ratios for SES group comparisons, the hazard ratios for low SES vs. high SES (reference) are shown in **Figure 3** (education), **Figure 4** (income) and **Figure 5** (index), sorted by region and area-level (small to large). **Figure 6** additionally displays a meta-analysis for studies on area-based income from the US. Ten studies were not displayed in figures because they did not report confidence intervals (43, 73, 83, 109), did not show results (65), assessed SES on a continuous scale (6, 34, 80, 116) or did not use low or high SES as reference category (67). Results of all studies are reported in detail in **Table S4**.

Three studies (88–90) investigated area-based measurements of education and all reported a lower survival after lung cancer diagnosis in areas with the lowest education levels (**Figure 3**, **Table S4**). All studies adjusted for age, sex, and stage at diagnosis and included patients diagnosed with NSCLC residing in the US. The extent of the association did not depend on the size of area-level (**Figure 3**). Results of area-based studies were more homogeneous and reported stronger associations compared to studies investigating individual education.

The association between area-based income and lung cancer survival was investigated in 19 studies (34, 43, 64–67, 73, 80, 88–90, 95, 96, 98, 109, 112, 114, 115, 117). Twelve studies (64, 66, 88–90, 95, 96, 98, 112, 114, 115, 117) displayed in **Figure 4** in general show a lower survival for the lowest income group compared to the highest group (range: HR 1.03–1.24, **Figure 4**). Estimates of seven studies (64, 88–90, 98, 112, 117) adjusting for stage at diagnosis were similar to estimates of studies not adjusting for stage (**Table 2**, **Figure 4**). The meta-analyses of six US studies (88, 90, 98, 112, 114, 115) revealed a slightly larger summary estimate for the smaller area-level of census tracts (HR 1.15, 95 % CI 1.09–1.21, **Figure 6**) than for the two larger area-levels zip

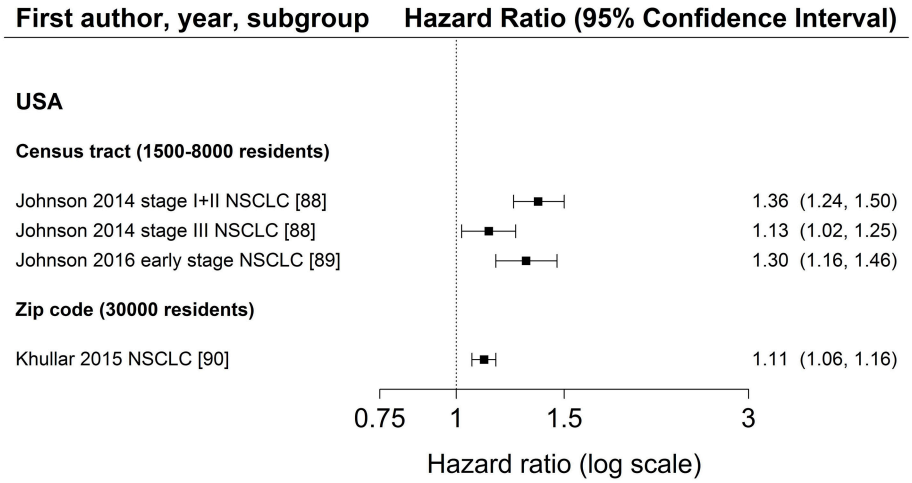


**FIGURE 3 |** Association of area-based education (reference: high education) and survival after lung cancer. Order: small to large area level. NSCLC, non-small cell lung cancer.

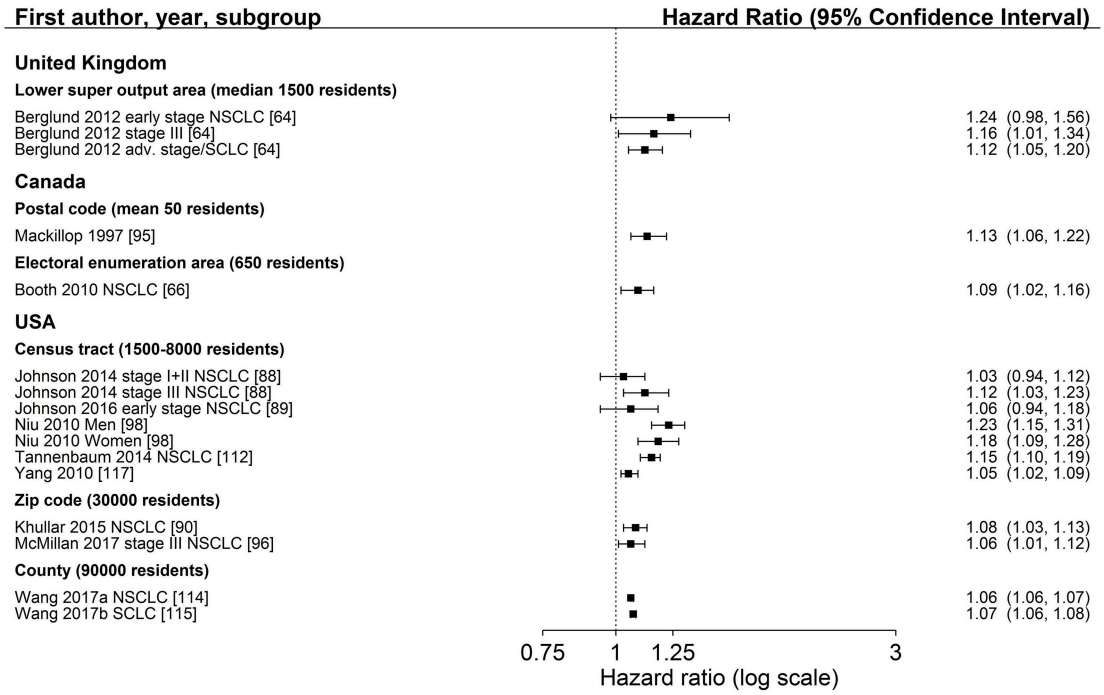


**FIGURE 4 |** Association of area-based income (reference: high income) and survival after lung cancer. Order: small to large area level. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

code and county (zip code: HR 1.08, 95 % CI 1.03–1.13; county: HR 1.06, 95 % CI 1.06–1.07, **Figure 6**). However, not all of these studies adjusted for stage, which hampers their comparability. Two studies had been excluded from this meta-analysis due to overlapping study populations. The study by McMillan et al. (96) has overlapping population with the study by Khullar et al. (90). We decided to include Khullar et al. (90) in our meta-analysis as all stages were analyzed compared to McMillan et al. (96) which included solely patients diagnosed with stage III. We excluded the study by Yang et al. (117) because there is overlapping population with the study by Tannenbaum et al. (112). Although Tannenbaum et al. (112) included solely patients diagnosed with non-small cell lung cancer, they included a longer period of diagnosis compared to Yang et al. (117).

The majority of studies reported lower survival in lower income areas (**Table S4**).

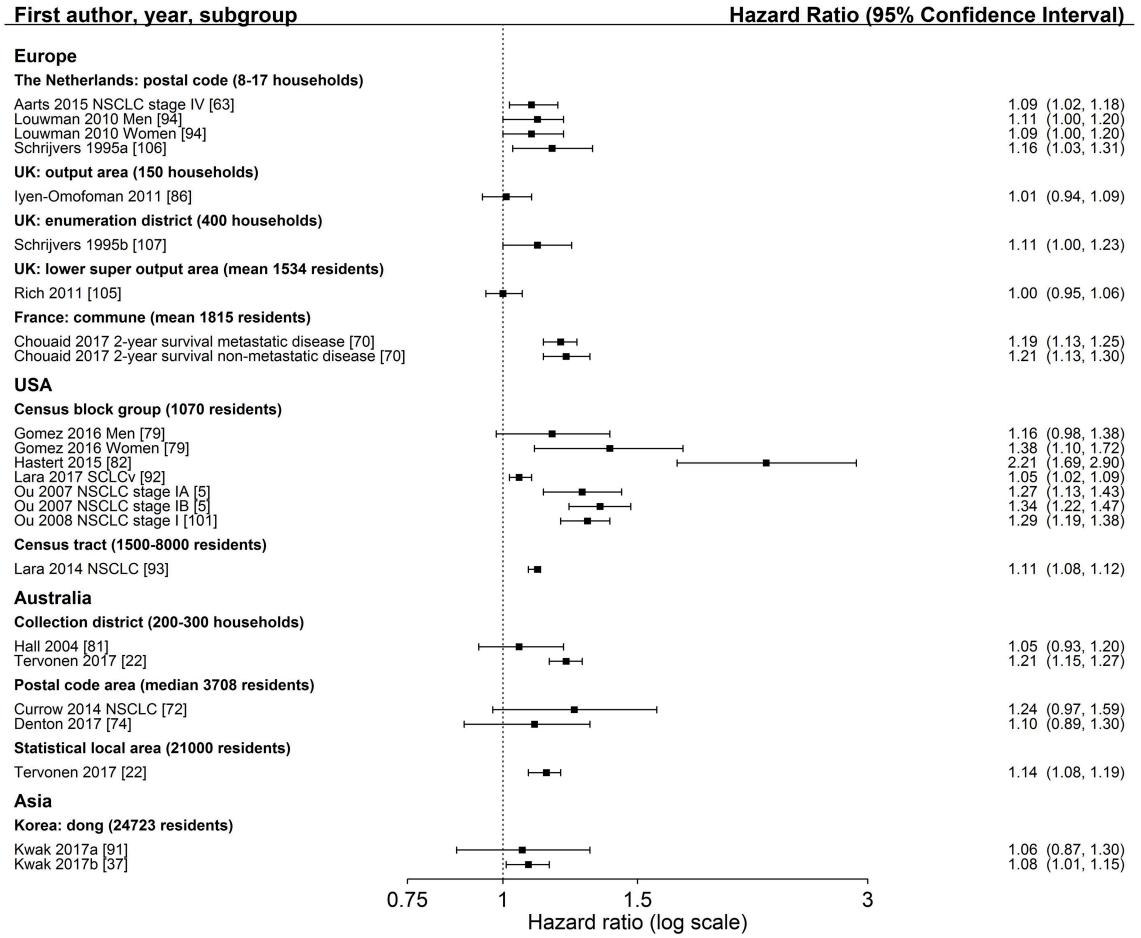


**FIGURE 5 |** Association of area-based index measures (reference: high socioeconomic group) and survival after lung cancer. Order: region and small to large area level. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; UK, United Kingdom.

Twenty-two studies reported hazard ratios on the association between an area-based SES index measure and lung cancer survival (5, 6, 22, 37, 63, 70, 72–74, 79, 81–83, 86, 91–94, 101, 105–107, 116) (**Table S4**). Group comparisons of 18 studies (5, 22, 37, 63, 70, 72, 74, 79, 81, 82, 86, 91–94, 101, 105–107) showed significant associations between lower income areas and a lower survival after lung cancer diagnosis in 10 studies (5, 22, 37, 70, 79, 82, 92, 93, 101, 106), with a range of HR 1.05–2.21 (**Figure 5**). Nine studies (5, 22, 74, 79, 91–93, 105, 107) adjusted for stage at diagnosis (**Table 2**). Notably, no study reported a hazard ratio below 1.00. Within-country comparisons did not reveal a tendency for larger or smaller estimates depending on the size of the area-level (**Figure 5**).

The majority of studies adjusted for age, gender and stage. Two income studies (112, 117) and two SES index studies (6, 91) included smoking status in their models (**Table 2**). The latter two studies reported slightly lower estimates than studies without adjustment for smoking (**Table S4**).

## Combined Effects of Individual and Area-Based SES—Modeling Results

Two studies investigated both individual and area-based SES (34, 82). However, only one study investigated directly combined effects of individual and area-based income (34). These analyses are based on a population size of $N = 78$ patients with stage II NSCLC and showed a significantly lower survival only for higher individual income. In the combined model, the area-level variable did not add any explanatory power to the model including individual income (34) (**Table S4**). The other study analyzed area-based SES with adjustment for individual SES in the Cox model (82). The study reported a significant association between lower area-level SES and lung cancer survival in both models with and without adjustment for individual SES (82). The estimate of the model including individual SES adjustment was considerably smaller (including individual SES: HR 1.43, 95 % CI 1.07–1.91; without individual SES: HR 2.21, 95 % CI 1.69–2.90).

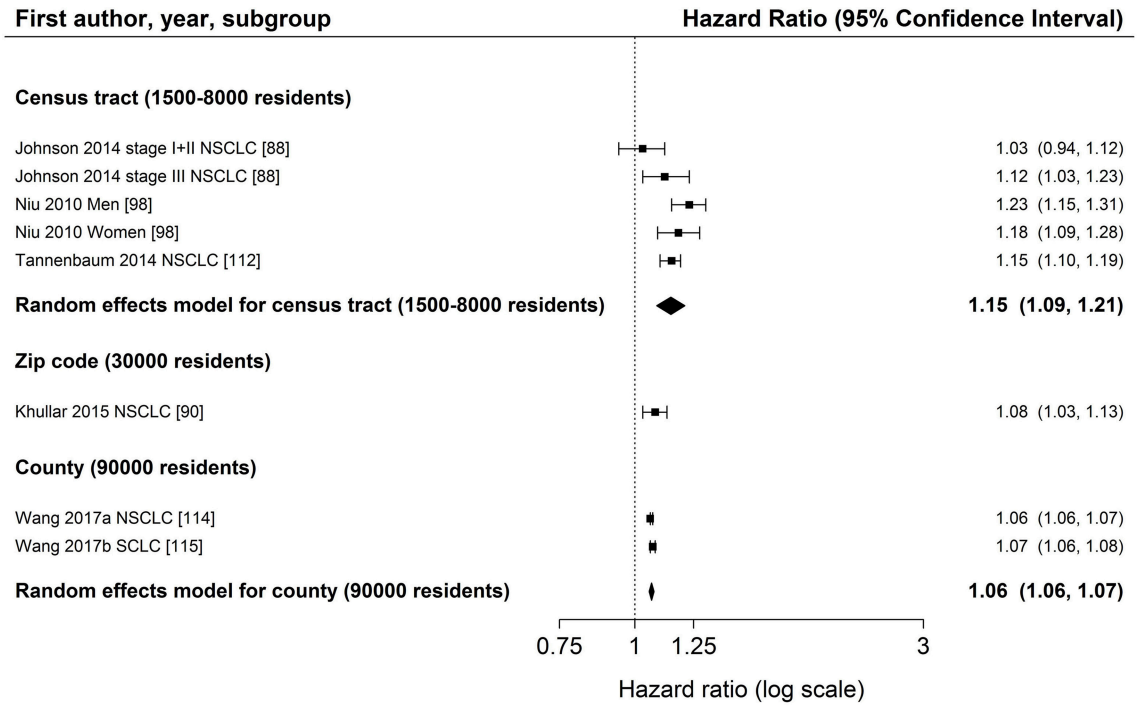


**FIGURE 6 |** Meta-analysis of studies from the United States on the association of area-based income (reference: high income) and survival after lung cancer. Order: small to large area level. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

## SES and Survival Time, Survival Rate, and Other Survival Measures

Overall, 67 studies (6, 30, 33, 35, 37–39, 42–46, 49, 50, 52, 53, 57, 59–64, 66–71, 73–81, 84–87, 90, 91, 93–95, 97–104, 106–108, 110–115, 117–119) reported median survival time or survival rates after lung cancer stratified by SES (**Tables S5**, **S6**). Fifteen (30, 39, 42, 44–46, 49, 50, 52, 53, 57, 59–62) and 52 studies (6, 29, 33, 35, 37, 38, 43, 63, 64, 66–71, 73–81, 84–87, 90, 91, 93–95, 97–104, 106–108, 110–115, 117–119) used an individual or area-based SES measure, respectively. Nine individual (30, 39, 42, 45, 46, 49, 50, 59, 62) and 45 area-based (6, 29, 33, 35–38, 43, 63, 64, 66–69, 73–76, 78–81, 84–87, 90, 93–95, 97–101, 104, 106, 107, 110–112, 114, 115, 117, 118) SES studies reported lower lung cancer survival in lower SES groups (**Tables S5**, **S6**). The remaining 6 individual (44, 52, 53, 57, 60, 61) and 9 area-based (36, 70, 71, 77, 91, 103, 108, 113, 119) studies reported no difference or no gradient across socioeconomic categories in survival time or survival rates.

Forty-one studies (33, 35, 36, 39, 42, 43, 46, 49, 52, 57, 59–61, 66, 67, 71, 73–77, 80, 81, 85, 86, 90, 91, 95, 98, 101–103, 106, 107, 110–114, 118, 119) reported 5-year survival after lung cancer diagnosis and 30 (33, 35, 36, 39, 42, 43, 46, 49, 59, 66, 67, 71, 73–76, 80, 81, 85, 90, 95, 98, 101, 106, 107, 110–112, 114, 119) of these showed lower survival rates in lower SES groups (**Tables S5**, **S6**). The range of differences between survival rates for lowest and highest SES groups was larger in studies considering area-based SES than in studies assessing individual SES (Individual SES: range 1.0–12.8 % units; area-based SES: range 0.9–22.9 % units, **Tables S5**, **S6**) but did not depend on the SES measure or the population size of the area. When we compared area-based US studies, studies using the smaller census tract level (33, 43, 67, 76, 80, 98, 112) reported larger differences in 5-year survival between high and low income areas. But those studies also observed a larger range of differences in survival rates (1.0–22.9 %) than studies assessing SES by zip codes (90) and counties (114) (range 1.2–7.7 %, **Table S6**).

Differences in survival between highest and lowest SES groups were similar when comparing studies reporting 1 or 3-year survival rates (1-year survival: range 1.4–11 %; 3-year survival: range 0.4–11 %, **Tables S5**, **S6**). In general, there was no distinct pattern regarding higher effect sizes in studies showing shorter survival rates.

One individual study (58) and four area-based studies (35, 41, 110, 119) calculated the relative excess risk (RER) and indicated a lower risk for higher SES groups (**Tables S5**, **S6**). Eight area-based studies (31, 36, 40, 71, 75, 85, 103, 108) used the deprivation gap which indicates the survival difference between the highest and lowest SES group and is mostly used in the UK. All of these studies reported a negative deprivation gap, meaning that the highest SES group has a higher survival rate than the lowest SES group (**Table S6**).

## Risk of Bias

**Table S7** displays the risk of bias assessment for included studies according to a modified Newcastle-Ottawa-Scale. Overall, the mean quality scores of individual and area-based studies were

rather in line, both ranging from 7 to 8 out of 8 points. As the majority used data of national or regional cancer registries, many studies scored high within the categories selection and outcome, representing for example adequacy of follow-up or representativeness of study population.

Both funnel plots for the meta-analyses of individual education and income studies did not reveal any asymmetry (Education: Begg's test $p = 0.13$, Egger's test $p = 0.07$, **Figure S8**; income: Begg's test $p = 0.38$, Egger's test $p = 0.34$, **Figure S9**). The funnel plot of individual education analysis appeared to be cylindrical which might be due to the larger heterogeneity between these studies (**Figure 2** and **Figure S8**).

## DISCUSSION

This systematic review provides a comprehensive overview of the current literature on socioeconomic differences in lung cancer survival by including both individual and area-based measurements of socioeconomic status. Meta-analyses for individual SES and lung cancer survival revealed a weak association for studies using income measures but no consistent association for education measures. For studies using individual income measures, no consistent difference across level of adjustment for smoking status was observed and stratified meta-analyses by stage and treatment were not possible. For individual education, results indicated that adjusting for stage and smoking status might result in smaller effect estimates. Studies using occupational measures did not report lower lung cancer survival with decreasing SES. Group comparisons for hazard ratios of area-based studies indicated lower survival for lower SES irrespective of the socioeconomic measure. Meta-analyses for US studies reporting on area-based income showed a slightly larger estimate for the smaller geographical unit census tract compared to zip code and county level. However, comprehensiveness of adjustment was different across these studies. For the remaining area-based studies, the extent of association did not depend on the size of area-level but most studies reported a hazard ratio above 1.00. Compared to model results of individual SES studies, area-based studies in general reported stronger associations between SES and survival. Most studies reporting on survival time and survival rates revealed lower lung cancer survival in lower socioeconomic groups, not depending on individual or different area levels.

Compared to results for other cancer types, the association between individual income and survival after lung cancer diagnosis was weak. Cancers occurring in lung tissue are mostly detected in later stages (120) which limits opportunities for cancer therapy (121). Nevertheless, despite good treatment options for some patients, survival is still rather low (121). Given these circumstances, the effect of SES on differences in lung cancer survival might be not as relevant as for other cancer types. The smaller effect estimates for individual education studies adjusting for stage at diagnosis supports this assumption, as this cancer type is mainly diagnosed at later stages (120). For cancers of intermediate or good prognosis, such as colorectal or breast, higher relative risks were observed (10, 122).

Results of meta-analyses including individual education compared to income were rather different. This was an unexpected finding as other systematic reviews reported lower survival in low educational groups for several cancer types (20), such as breast (10) and prostate cancer (12). Furthermore, educational attainment influences occupational status which as well determines income (20). One explanation might be that many income studies were conducted in countries where income has a higher impact on access to and quality of health care; however, significant associations were as well reported in Scandinavian countries with universal health care systems.

Summary estimates of meta-analyses for individual and area-based income were similar, especially in studies using the smaller geographical unit US census tract. This was an unexpected finding as all area-based studies included in the meta-analyses were conducted in the US, a country with a non-universal health care system, and individual income studies included both types of health care systems. Therefore, we would have expected larger effect sizes for studies conducted in the United States but due to area-based measurements of income, effects might have been diluted. The comparisons of different area-level income studies revealed a slightly higher summary estimate for the smaller US census tract unit. However, not all of these studies adjusted for stage at diagnosis. Our results partly confirm results of a study comparing SES measures for different geographical units in two US states in which census tract SES measures detected gradients in all-cause mortality more consistently compared to zip code level SES measures (123). In contrast, another study examining area-based SES variables at census tract and zip code level reported small differences in effect estimates of self-rated health (124). In other countries, we could not observe larger effect sizes for studies using smaller areas consistently, but studies reported rather heterogeneously. Group comparisons of area-based studies using composite measures of SES did not reveal stronger or more consistent associations depending on the size of the geographical unit, although no study reported a HR below 1.00. This result does not confirm the discussion about the importance of the use of smaller area-levels to minimize or avoid ecological fallacy (20, 125). Due to the lack of individual index studies, it was not possible to compare area-based index studies with individual studies, thus we cannot exclude ecological bias.

One study (34) included in our systematic review investigated directly combined effects of individual and area-based income and reported the aggregated median income on US census tract level to not add any explanatory power to the model including individual income. In this study, area-based income was not valuable as proxy measure for individual income, however, it might be reasonable to interpret area-based income as its own concept, for example regarding access to health care. The study by Greenwald and colleagues (34) included only a small number ($N = 78$) of patients diagnosed with stage II lung cancer resident in the US. To further explore differences and relationships between individual and aggregated SES measures in the context of lung cancer survival, larger studies conducted in different countries are required.

The level of adjustment for prognostic factors was very heterogeneous across studies. Most studies adjusted for age,

gender, and stage and many studies additionally included variables for treatment and comorbidity. Although strongly associated with lung cancer incidence, mortality, and survival (126), smoking was only considered by three individual (44, 45, 47) and five area-based studies (6, 75, 91, 112, 117). Our meta-analyses stratified by adjustment for smoking suggested lower effect estimates for individual education studies adjusting for smoking status which indicates the importance of controlling for this prognostic factor. A recent analysis confirmed the contribution of smoking to socioeconomic inequalities in mortality among 14 European countries (127). Since many individual studies, especially in Scandinavia, used cancer registry data and linked these data to other registries for the socioeconomic status, there might be no information on individual smoking status. Area-based studies using census data could have linked their data to area-based information on smoking status by other censuses or administrative sources. Such an approach should be considered in future studies.

Mechanisms that might lead to socioeconomic differences in lung cancer survival can include factors related to diagnosis, treatment modalities, and patients themselves (20). Access to health care can be both influenced by the affluence of a country or a residential area and the individual. More deprived areas can have less health care resources which could result in a delay in diagnosis and delay in start of treatment (20). However, a meta-analysis on the effect of SES on stage at lung cancer diagnosis did not reveal an association (18). The stratified meta-analysis of individual education studies in the present review did as well not show any differences which confirm the results of Forrest and colleagues (18). For cancer therapy, socioeconomic differences have been reported regarding the administration of specific treatments as well as the referral to specialists or to oncology centers (20). For instance, lung and breast cancer patients belonging to deprived groups were less frequently treated by surgery in a study from England (128). Due to the lack of studies stratifying by treatment in the present review we could not investigate this issue.

Our study has important strengths and some limitations. The current literature search was conducted in four databases, which might have missed out relevant articles. We restricted our search terms to only "lung cancer" due to the large amount of search results when using the term "cancer." This might be the reason why the number of articles found through searching reference list of included papers was high. Nevertheless, the amount of detected literature through database search was still rather large and it was possible to include databases specialized to the social sciences to assure inclusion of articles not only indexed in biomedical science focused databases. In addition, we enhanced the quality of extracted data by contacting authors if results were not reported clearly or incompletely to give a comprehensive view of all included studies. While we cannot completely rule out the presence of a publication bias, which would lead to an overestimation of socioeconomic differences in cancer survival, our funnel plots for the meta-analyses did not reveal asymmetries suggesting that the probability of publication bias is rather low.

In general, studies were very heterogeneous, not only in the use of socioeconomic measures and aggregated levels but also in reporting of survival measures and in the level of adjustment. The studies have been conducted in several countries around the world including very different settings. The adjustment for key prognostic factors such as stage was often not possible. Thus, like in most epidemiologic studies, we cannot rule out that findings might be influenced by confounding. Furthermore, our comparisons of summary estimates across subgroups (e.g., by adjustment and aggregation level) were not based on statistical tests and observed trends might be chance findings. Thus, comparison of results across studies and the conclusions derived from this review must be interpreted with caution.

The generalizability of our results to low-income countries is limited, as they were highly underrepresented and no study from Africa or South America was found. One reason for this might be the restriction to publications in English or German language in our literature search. In our study, most individual studies were conducted in Scandinavian countries and most area-based studies were conducted in the US or United Kingdom. For other European countries as well as Asian countries, further studies are needed.

We did not carry out meta-analyses stratified by gender. Considering papers with the largest study populations included in our review, studies reported in general a higher survival in women compared to men. However, the majority of these studies also reported similar results for women and men regarding a potential gradient according to SES. This was true for both individual and aggregated SES measurements.

Although the Newcastle-Ottawa-Scale (NOS) is a tool for quality assessment of studies which is widely used, there is some critique about its validity (129). However, the NOS gives an overview of the quality of included articles and helps to exclude studies that are not suitable to be included in a meta-analysis. We excluded three studies from our meta-analyses because of a low quality score. These studies were also less comparable to the other studies due to other reasons: The first study used data from clinical trials (50) and was therefore not representative of the underlying population, the second study only reported univariate hazard ratios without adjustment (53) and the third study used data of 24 institutions which could voluntarily participate in the study (51). As the cut-off quality score was not set a priori, a sensitivity analysis including these three studies was conducted and revealed similar estimates. Another limitation was that there is no specific NOS coding manual for studies relying on registry data. We used the manual for cohort studies, therefore many registry studies were rated too low in the outcome section because they did not describe how mortality data were collected although it could be assumed that these data were retrieved by administrative sources with good quality (130). On the other hand, studies using registry data might be awarded too many points (stars) in the comparability section as their quality of measurement of potential confounders might not be as high as in usual cohort studies.

The interpretation and summary of both model and survival rate results among studies remained difficult due to diversity in SES measurements used, in particular across different countries or continents. In their review on socioeconomic differences and the risk of lung or colorectal cancer, Kuznetsov and Mielck (17)

already found very heterogeneously reported SES measurements and therefore could not conduct a meta-analysis. However, we were still able to perform meta-analyses by using hazard ratios of the lowest and highest socioeconomic group which was reported by most studies. Furthermore, we focused on model results of the studies, as most studies that reported survival rates showed age-standardized rates without any further adjustment for other prognostic factors. Our restriction of using the highest and lowest SES categories for comparing the model results enabled us to conduct meta-analyses with studies assessing the SES on different categories like tertiles or quintiles. The downside of this approach is that we compared different levels of SES (e.g., the lower quintile might correspond to a lower SES as compared to the lower tertile). However, as studies reported SES measures heterogeneously, this was the only way to show summarized measures for the effect of SES on lung cancer survival.

Another limitation was that it was not possible to perform stratified meta-analyses by subtypes of lung cancer because no individual study reported on SCLC patients only. Nevertheless, meta-analyses of other important prognostic factors (stage, treatment, and smoking) were conducted and revealed no major differences compared to the main analyses.

In conclusion, the body of evidence in this review provides some support for the hypothesis that lower individual income is associated with a lower survival after lung cancer diagnosis. There was no evidence for an association between individual education or occupation and lung cancer survival. Group comparisons for hazard ratios of area-based studies indicated lower survival for lower SES groups, irrespective of the socioeconomic measure. However, effect sizes are generally smaller than and not as consistent as found for other cancer types. Future research should focus on a combined analysis of individual and aggregated SES measures, for example by constructing aggregated measures from individual data. This approach would allow to investigate associations between survival and both individual and aggregated measures, whilst also taking prognostic factors such as stage and smoking into account. Furthermore, a standardized socioeconomic measure would be desirable to enhance comparability across nations and across different levels of aggregation.

## AUTHOR CONTRIBUTIONS

Study designed by IF, LJ, and HB. Literature search performed by IF. Data extraction and quality check completed by IF, GB, and LW. Data synthesis of selected studies completed by IF. Meta-analyses performed by IF, GB, and LJ. Abstract, cover letter and manuscript drafted by IF and LJ. Abstract, cover letter, and manuscript reviewed and edited by HB, GB, and LW.

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## SUPPLEMENTARY MATERIAL

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# Survival After Childhood Cancer–Social Inequalities in High-Income Countries

*Hanna Mogensen[1]*, Karin Modig[1], Giorgio Tettamanti[1], Friederike Erdmann[2,3], Mats Heyman[4] and Maria Feychting[1]*

*[1] Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2] Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France, [3] Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark, [4] Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden*

Despite substantial improvements in survival from childhood cancer during the last decades, there are indications that survival rates for several cancer types are no longer improving. Moreover, evidence accumulates suggesting that socioeconomic and sociodemographic factors may have an impact on survival also in high-income countries. The aim of this review is to summarize the findings from studies on social factors and survival in childhood cancer. Several types of cancer and social factors are included in order to shed light on potential mechanisms and identify particularly affected groups. A literature search conducted in PubMed identified 333 articles published from December 2012 until June 2018, of which 24 fulfilled the inclusion criteria. The findings are diverse; some studies found no associations but several indicated a social gradient with higher mortality among children from families of lower socioeconomic status (SES). There were no clear suggestions of particularly vulnerable subgroups, but hematological malignancies were most commonly investigated. A wide range of social factors have been examined and seem to be of different importance and varying between studies. However, potential underlying mechanisms linking a specific social factor to childhood cancer survival was seldom described. This review provides some support for a relationship between lower parental SES and worse survival after childhood cancer, which is a finding that needs further attention. Studies investigating predefined hypotheses involving specific social factors within homogenous cancer types are lacking and would increase the understanding of mechanisms involved, and allow targeted interventions to reduce health inequalities.

**Keywords: childhood neoplasms, leukemia, nervous system neoplasms, socioeconomic factors, survival, review**

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*Lorenza Scotti,*
*Università degli studi di Milano Bicocca, Italy*

****Correspondence:***
*Hanna Mogensen*
*hanna.mogensen@ki.se*

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## INTRODUCTION

From low survival rates in the 1970's and earlier, overall 5 years survival from childhood cancer is now exceeding 80% in most of Europe (1, 2). Nonetheless, despite these advances a significant number of children with cancer fail to reach this milestone, with varying proportions according to cancer type (2). Moreover, reports from the US and Europe indicate that survival improvements for several childhood cancer types have leveled off during recent years (2, 3). At the same time, evidence

accumulates suggesting that socioeconomic and sociodemographic factors may be associated with survival even in high-income countries where children are presumed to have equal access to health care services, see for example (4–7). This does not only highlight a potential inequality that needs attention, but might imply a possibility of improving childhood cancer survival rates overall, by addressing this potential gap. However, even though several studies support an association between higher parental socioeconomic status (SES) and better survival, findings differ between countries, cancer types, and SES indicator studied. Some of the differences might be explained by inconsistent methodology between studies, but might also indicate different mechanisms in which parental SES affects survival. For example, differences in treatment and prognosis between cancer types are likely to influence.

Gupta et al. (8) conducted a systematic review evaluating the association between SES and childhood cancer survival, including studies published until 2012. This review indicated that in high income countries, parental income is not the driver of the association but instead other SES indicators such as education, having insurance, or place of residence seemed to be of importance (8). However, parental income was only assessed in few studies. Since 2012, there have been several studies examining the association between parental SES and survival from childhood cancer in high income countries, and these are the focus of the current review.

The objectives of this review are (i) to summarize the findings from studies on social factors and survival from childhood cancer in high-income countries, by cancer type, and (ii) to elucidate the role of different socioeconomic and sociodemographic factors (parental education, income, social status based on occupation, cohabitation, and marital status, place of residence, number of siblings, and birth order) on the association, in order to shed light on potential mechanisms and to identify particularly affected groups.

## METHODS

A literature search was conducted in PubMed (the 15th of June 2018) and included articles published from December 2012 until mid-June 2018, this corresponds to the time period following the previous systematic review (8). The search included terms related to cancer, survival, children, and socioeconomic and sociodemographic factors (for details see **Supplementary Table 1**). Titles, abstracts and full-texts were screened for relevance by one of the authors (HM). *A priori* defined inclusion criteria were: non-ecological, original articles, conducted in high-income countries, that restricted analyses to childhood cancer of any type and assessed the association with at least one socioeconomic or sociodemographic factor in relation to overall survival, relative survival or event-free survival. Studies focusing on cancer types primarily affecting adults were excluded. Included individual measures of SES were parental education, parental income, parental occupation, parental cohabitation and marital status, place of residence, number of siblings and birth order. Also studies using area-based measures of SES were included. No restrictions on language were applied.

From all included studies information on setting, cancer diagnoses, study size and diagnostic period, source of identification of cancer cases, socioeconomic, and sociodemographic measurements of relevance, outcome of relevance, as well as main results of interest were extracted by one of the authors (HM). Also results of the association between specific social factors and survival, from each of the included studies, were extracted and included in tables by cancer type, most often in terms of hazard ratios (HR) and corresponding 95% confidence intervals (CI). Similar to the previous review in this field (8), no quantitative meta-analysis was considered due to the diversity of social factors included, but findings were summarized in a narrative synthesis.

## RESULTS

Twenty-four of the 333 articles identified by the literature search met the inclusion criteria and were included in this review (**Table 1**). Exclusions were made based on titles (179 articles), abstracts (98 articles), and full-texts (32 articles), **Figure 1** shows the reasons for exclusion in a flow diagram. **Tables 2A**,**B** summarize the main results of the included studies.

### All Diagnoses Combined

Combining all types of childhood cancer make the study population diverse but provides an overall pattern of potential inequalities. Four recent European register studies have looked at such associations. In Switzerland and Sweden, lower parental education was associated with higher mortality among children with cancer (5, 6), and a similar tendency was seen in Denmark (9). In Finland such an association was seen for the most recent years (7). An association between lower income and higher mortality was observed in Finland (7) and suggested in Denmark (9), but not found in Sweden (6). Furthermore, worse survival was observed for children with siblings, single parents, or poor living conditions (5, 9).

### Hematological Malignancies

Hematological malignancies are the most common types of childhood cancer, and were also most frequently investigated regarding the association between SES and survival; 16 of the studies examined these diagnoses. In addition, one meta-analysis has been published (30), but due to its broader scope, the individual studies of relevance for this review will be discussed separately.

Various findings are reported regarding the association between parental SES and survival from hematological malignancies; while some studies found no association, others reported a gradient with lower survival among disadvantaged children, although the SES indicators of importance differed between studies. Overall, SES differences seemed to be less pronounced in hematological malignancies compared to childhood cancer overall. For leukemia and acute lymphoblastic leukemia (ALL), the associations with both parental education and income were inconclusive (5, 6, 12, 13). Disadvantaged

**TABLE 1 |** Description of included studies.

| References | Setting | Included diagnoses | Study size and diagnostic period | Source of identification of cancer cases | Socioeconomic and sociodemographic measurements of relevance | Outcome of relevance |
|---|---|---|---|---|---|---|
| (9) | Denmark | All diagnoses combined; hematological malignancies– ALL, CNS tumors, non-CNS solid tumors | 3,797 children, diagnosed <20 years old during 1990-2009 | Danish cancer registry | Individual level: Maternal and paternal education, maternal income, parents' cohabitation status, and number of full siblings <19 years, based on registries | Overall survival |
| (5) | Switzerland | All diagnoses combined; leukemia-ALL, lymphoma, CNS tumors, bone and soft tissue tumors, embryonal tumors | 1,602 children, diagnosed <16 years old during 1991– 2006 | Swiss childhood cancer registry | Individual level: Maternal and paternal education, and living conditions (number of rooms per person, living space), based on census. Area-based: SES-index | 5 year cumulative mortality |
| (6) | Sweden | All diagnoses combined; leukemia-ALL, tumors of the nervous system- brain tumors, lymphoma | 4,723 children, diagnosed 1-14 years old during 1991–2010 | Swedish cancer registry | Individual level: Parental education, and household income, based on registries | Overall survival, follow-up for maximum 10 years |
| (7) | Finland | All diagnoses combined; ALL and LBL, CNS tumors, all other malignant neoplasms | 4,437 children diagnosed <20 years old during 1990–2009 | Finnish cancer registry | Individual level: Combined parental income, highest parental education, maternal and paternal employment status, based on registers | Cause specific mortality (death from primary cancer) and childhood cancer specific survival, follow-up for maximum 5 years |
| (10) | Northern England | Leukemia; ALL, acute non-lymphocytic leukemia | 1,007 children, diagnosed 0-14 years old during 1968-2010 | Northern region young persons malignant disease registry | Individual level: Paternal occupational social class, based on birth certificate | Overall mortality |
| (11) | U.S | Hematologic malignancies, CNS tumors, solid tumors | 36,337 children, diagnosed 0-19 years old during 1992–2011 | SEER | Area-based: Poverty, education, unemployment, language isolation, foreign-born, and income, based on census | Death within one month of diagnosis |
| (12) | West Germany | ALL | 647 children, diagnosed <15 years old during 1992–1994 | German childhood cancer registry | Individual level: Maternal and paternal education, family income, and residential area, based on telephone interviews (response rate 82%) | Overall survival and event-free survival, follow-up for maximum 10 years |
| (13) | Greece | ALL, AML | 994 children, diagnosed 0–14 years old during 1996–2010 | Nationwide registry for childhood hematological malignancies | Individual level: Parental marital status, parental socioprofessional category, maternal education, number of children, place of living, and travel distance, based on questionnaires | Overall mortality |
| (14) | West Germany | ALL | 647 children, diagnosed <15 years old during 1992–1994 | The German childhood cancer registry | Individual level: Birth order, number of siblings, place of residence, based on questionnaires (response rate 82%) | Overall survival and event-free survival, follow-up for maximum 10 years |
| (15) | Canada | ALL | 1,541 children diagnosed <18 years old during 1995–2011 | Pediatric oncology group of ontario networked information system | Individual level: Rurality, distance from tertiary center Area-based: Neighborhood income, based on census | Event-free survival |

*(Continued)*

**TABLE 1 |** Continued

| References | Setting | Included diagnoses | Study size and diagnostic period | Source of identification of cancer cases | Socioeconomic and sociodemographic measurements of relevance | Outcome of relevance |
|---|---|---|---|---|---|---|
| (16) | California, U.S. | ALL | 9,295 children diagnosed 0–19 years old during 1988–2011 | California cancer registry | Area-based: Neighborhood SES, based on census | Overall survival |
| (17) | Texas & Florida, U.S. | ALL | 4,719 children diagnosed 1–18 years old during 1995–2008 | Florida cancer data system and the Texas cancer registry | Area-based: Neighborhood-level poverty rate, based on census | Overall survival |
| (18) | U.S. | ALL | 8,516 children, diagnosed <19 years old during 1999–2009 | Pediatric health information system | Area-based: ZIP-code based median household income, based on census | Inpatient mortality, death during the induction period. The children were followed from the first day of chemotherapy (in inpatient care) until maximum 60 days |
| (19) | U.S. | AML | 3,651 children diagnosed 0–19 years old during 1973–2012 | SEER | Area-based: SES factors and clusters constructed from 23 socioeconomic variables, based on census | Overall mortality |
| (20) | Denmark | Hematological malignancies; ALL, AML, non-Hodgkin lymphoma | 1,819 children diagnosed <20 years old during 1973–2006 | Danish cancer registry | Individual level: Birth order, number of full and half siblings, place of residence, based on registers | Overall survival, follow-up for maximum 10 years |
| (21) | Ontario, Canada | Lymphoma; Hodgkin lymphoma, non-Hodgkin lymphoma | 692 children diagnosed 0–14 years old during 1985–2006 | Pediatric oncology group of ontario networked information system database | Area-based: Neighborhood income and material deprivation, based on census | Overall survival and event-free survival |
| (22) | Denmark | CNS tumors; astrocytomas and other gliomas, embryonal CNS tumors | 1,261 children diagnosed <20 years old during 1973–2006 | Danish Cancer Registry | Individual level: Birth order, number of siblings, number of children living in the household, place of residence, parental cohabitation, maternal education, based on registries | Overall survival, follow-up for maximum 10 years |
| (23) | Texas, U.S. | Primary CNS solid tumors | 2,421 children diagnosed <19 years during 1995 and 2009 | Texas cancer registry | Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census | Overall survival |
| (24) | Texas, U.S. | Non-CNS solid tumor | 4,603 children diagnosed <19 years old during 1995-2009 | Texas cancer registry | Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census | Overall survival |
| (25) | Texas, U.S. | Melanoma | 235 children diagnosed <19 years old during 1995–2009 | Texas cancer registry | Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census | Overall survival |

*(Continued)*

**TABLE 1** | Continued

| References | Setting | Included diagnoses | Study size and diagnostic period | Source of identification of cancer cases | Socioeconomic and sociodemographic measurements of relevance | Outcome of relevance |
|---|---|---|---|---|---|---|
| (26) | Northern England | Renal tumors combined: Wilms tumors | 209 patients (183 in SES analysis) diagnosed 0–24 years old during 1968–2012 Multivariate analyses are performed only among children diagnosed 0–14 years old with Wilms' tumor | Northern region young persons' malignant disease registry | Individual level: Paternal occupational social class based on birth certificate | Overall survival |
| (27) | U.S. | Well-differentiated thyroid cancer | 9,585 children <22 years old from the register 1998–2012 | National cancer database | Area-based: ZIP-code based median income and education, categorized by census data | Overall mortality |
| (28) | U.S. | Disseminated Langerhans cell histiocytosis | 145 children diagnosed 0–19 years old during 2000–2009 | SEER | Area-based: Crowding, educational attainment, poverty level, and rural/urban county, based on census | 5 year relative survival |
| (29) | U.S. | Retinoblastoma | 830 children 0–9 years old diagnosed 2000–2010 | SEER | Area-based: County-level poverty, educational attainment, crowding, unemployment, immigration, language isolation, and SES-index, based on census | 5 year relative survival |

*ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CNS, Central nervous system; LBL, Lymphoblastic lymphoma; SEER, The Surveillance, Epidemiology, and End Results.*

parental SES, based on occupation, was associated with worse leukemia and ALL survival (10, 13), while no pattern was detected when the association between parental employment and survival was assessed in Finland (7). However, two studies reported point estimates suggesting an opposite gradient between parental education and survival from leukemia (5) and ALL (13), but these results were imprecise and not consistent between maternal and paternal education (5). Based on area-level indicators of SES, worse ALL and AML survival among children from low SES areas was observed in the US (16, 17, 19), also when insurance status was controlled for (16), while no association with event-free survival in ALL was seen in Canada (15). For lymphoma, higher parental education was suggested to be associated with better survival (5, 6), while findings for area-based SES indicators are inconclusive (5, 21).

An association between a larger number of siblings or higher birth order, and poorer survival from subtypes of hematological malignancies was suggested by studies conducted in Denmark (9, 20), while those pattern were not seen in Germany or Greece (13, 14).

Two US studies have looked at mortality close to a diagnosis of a hematological malignancy (11) or ALL (18). While one study reported an increased risk of death within the first month for children from lower SES neighborhoods (11), the other found no association between area-based income and inpatient mortality during the first period of chemotherapy (18).

## Tumors of the Nervous System

The association between parental SES and survival after tumors of the nervous system were examined in seven of the included studies. Three studies suggest lower mortality among children of higher educated parents (5–7), while others did not find similar associations (9, 22). Individually measured parental income was assessed in three of the studies and these did not detect any statistically significant associations (6, 7, 9). Studies on other individually measured SES indicators suggested lower mortality among children of cohabitating parents (9, 22), or better living conditions (5), while no association with the number of siblings or birth order was found (9, 22). In addition, results of area-based indicators pointed toward an association between lower SES and higher mortality; in Texas children with the lowest SES-index had a higher risk of advanced stage disease and worse overall survival, although these associations were diluted in adjusted analyses (23). Another study from the US reported an association between several markers of disadvantaged SES areas and a higher risk of early deaths in CNS tumors, in univariate analyses (11).

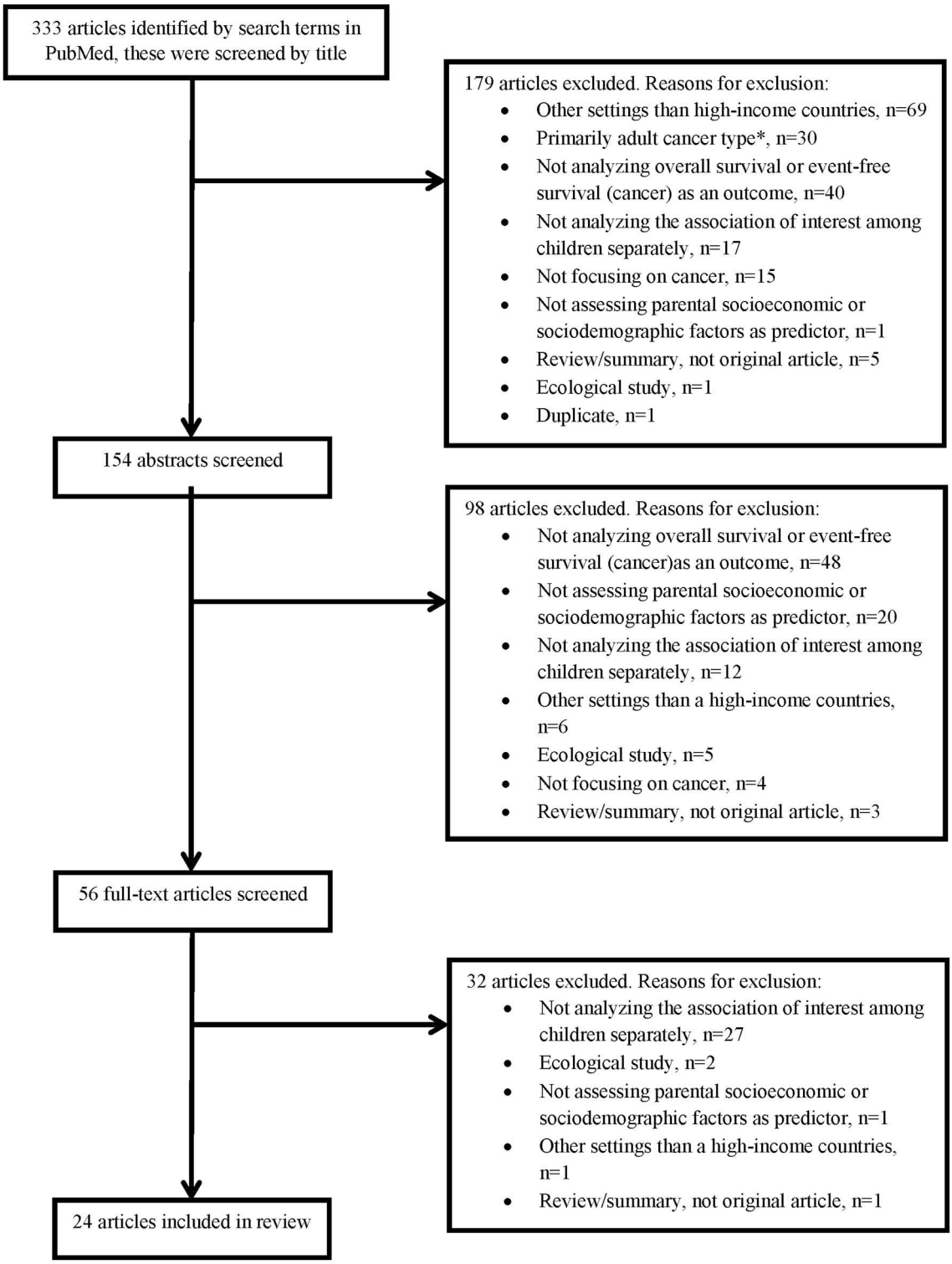


**FIGURE 1 |** Flow chart of title, abstract and full-text screening.

**TABLE 2A |** Main results of the included studies regarding the associations between socioeconomic factors and survival.

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) |
| **ALL DIAGNOSES COMBINED** | | | | | | | | |
| (9) | **Maternal** | | **Maternal, quartiles** | | | | | |
| | Basic | 1 (ref) | 1st (lowest) | 1 (ref) | | | | |
| | Vocational | 0.93 (0.75–1.15) | 2nd | 1.01 (0.84–1.21) | | | | |
| | Higher | 0.88 (0.69–1.13) | 3rd | 0.92 (0.75–1.14) | | | | |
| | Unknown | 1.05 (0.74–1.49) | 4th | 0.84 (0.66–1.08) | | | | |
| | **Paternal** | | | | | | | |
| | Basic | 1 (ref) | | | | | | |
| | Vocational | 0.90 (0.74–1.10) | | | | | | |
| | Higher | 0.89 (0.70–1.13) | | | | | | |
| | Unknown | 1.05 (0.75–1.46) | | | | | | |
| (5) | **Maternal** | | | | | | **SES index, tertiles** | |
| | Compulsory | 1 (ref) | | | | | Lower | 1 (ref) |
| | Secondary | 0.81 (0.65–1.02) | | | | | Medium | 0.93 (0.71–1.20) |
| | Tertiary | 0.67 (0.45–0.98) | | | | | Upper | 0.95 (0.73–1.24) |
| | **Paternal** | | | | | | | |
| | Compulsory | 1 (ref) | | | | | | |
| | Secondary | 0.85 (0.64–1.11) | | | | | | |
| | Tertiary | 0.72 (0.53–0.98) | | | | | | |
| (6) | **Parental** | | **Household, quartiles** | | | | | |
| | Postsecondary | 1 (ref) | 4th (highest) | 1 (ref) | | | | |
| | Upper secondary | 1.17 (1.00–1.38) | 3rd | 0.85 (0.69–1.04) | | | | |
| | Compulsory or less | 1.28 (1.03–1.59) | 2nd | 0.96 (0.79–1.18) | | | | |
| | | | 1st | 1.03 (0.85–1.26) | | | | |
| (7) | **Parental** | | **Combined parental, quartiles** | | **Maternal employment status** | | | |
| | Primary or less | 1 (ref) | 1st (lowest) | 1 (ref) | Employed | 1 (ref) | | |
| | Secondary | 1.00 (0.79–1.27) | 2nd | 0.83 (0.63–1.09) | Unemployed | 0.84 (0.64–1.09) | | |
| | Post-secondary | 0.84 (0.66–1.06) | 3rd | 0.76 (0.58–1.00) | Student | 1.39 (0.98–1.98) | | |
| | | | 4th | 0.68 (0.52–0.89) | Pensioner | 0.91 (0.51–1.62) | | |
| | | | Information missing | 0.93 (0.61–1.41) | Other non-working | 1.10 (0.90–1.35) | | |
| | | | Structural missing | 0.78 (0.53–1.15) | Information missing | 1.61 (0.98–2.66) | | |
| | | | | | **Paternal employment status** | | | |
| | | | | | Employed | 1 (ref) | | |
| | | | | | Unemployed | 1.14 (0.89–1.47) | | |
| | | | | | Student | 1.31 (0.80–2.15) | | |
| | | | | | Pensioner | 1.00 (0.65–1.54) | | |
| | | | | | Other non-working | 1.41 (0.87–2.29) | | |
| | | | | | Information missing | 1.26 (0.91–1.75) | | |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) |
| **HEMATOLOGICAL CANCERS** | | | | | | | | |
| (9) | **Maternal** | **Maternal, quartiles** | | | | | | |
| | Basic | 1 (ref) | 1st (lowest) | 1 (ref) | | | | |
| | Vocational | 1.05 (0.71–1.56) | 2nd | 1.17 (0.85–1.60) | | | | |
| | Higher | 1.10 (0.70–1.73) | 3rd | 0.81 (0.55–1.20) | | | | |
| | Unknown | 1.00 (0.54–1.86) | 4th | 0.82 (0.53–1.28) | | | | |
| | **Paternal** | | | | | | | |
| | Basic | 1 (ref) | | | | | | |
| | Vocational | 1.14 (0.78–1.66) | | | | | | |
| | Higher | 0.95 (0.60–1.50) | | | | | | |
| | Unknown | 1.94 (1.07–3.49) | | | | | | |
| (11) | | | | | | | **Education[b]** | |
| | | | | | | | Univariate | |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.43 (1.12–1.83) |
| | | | | | | | **Income[b]** | |
| | | | | | | | Univariate | |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.66 (1.30–2.12) |
| | | | | | | | Adjusted | |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.51 (1.07–2.14) |
| **LEUKEMIA** | | | | | | | | |
| (5) | **Maternal** | | | | | | **SES index, tertiles** | |
| | Compulsory | 1 (ref) | | | | | Lower | 1 (ref) |
| | Secondary | 1.06 (0.69–1.61) | | | | | Medium | 0.90 (0.56–1.42) |
| | Tertiary | 1.05 (0.58–1.91) | | | | | Upper | 1.06 (0.66–1.71) |
| | **Paternal** | | | | | | | |
| | Compulsory | 1 (ref) | | | | | | |
| | Secondary | 1.39 (0.81–2.38) | | | | | | |
| | Tertiary | 1.45 (0.82–2.58) | | | | | | |
| (6) | **Parental** | | **Household, quartiles** | | | | | |
| | Postsecondary | 1 (ref) | 4th (highest) | 1 (ref) | | | | |
| | Upper secondary | 1.28 (0.95–1.74) | 3rd | 1.05 (0.72–1.53) | | | | |
| | Compulsory or less | 1.39 (0.93–2.08) | 2nd | 1.06 (0.72–1.56) | | | | |
| | | | 1st | 1.22 (0.83–1.78) | | | | |
| (10) | | | | | **Paternal social class based on occupation** | | | |
| | | | | | I/II (most advantaged) | 1 (ref) | | |
| | | | | | IIIN/M | 1.66 (1.20–2.29) | | |
| | | | | | IV/V | 1.96 (1.35–2.86) | | |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator |
|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | HR[a] (95% CI) |
| **ALL and LBL** | | | | | | | |
| (7) | **Parental** | | **Combined parental, quartiles** | | **Maternal employment status** | | |
| | Primary or less | 1 (ref) | 1st (lowest) | 1 (ref) | Employed | 1 (ref) | |
| | Secondary | 1.12 (0.66–1.88) | 2nd | 0.91 (0.49–1.71) | Unemployed | 0.66 (0.35–1.28) | |
| | Post-secondary | 0.82 (0.48–1.40) | 3rd | 0.76 (0.40–1.44) | Student | 2.02 (0.88–4.64) | |
| | | | 4th | 0.86 (0.47–1.57) | Pensioner | 0.50 (0.07–3.58) | |
| | | | Information missing | 0.60 (0.18–2.08) | Other non-working | 1.24 (0.82–1.89) | |
| | | | Structural missing | 1.08 (0.45–2.60) | Information missing | 1.72 (0.54–5.50) | |
| | | | | | **Paternal employment status** | | |
| | | | | | Employed | 1 (ref) | |
| | | | | | Unemployed | 1.43 (0.85–2.42) | |
| | | | | | Student | 0.85 (0.21–3.46) | |
| | | | | | Pensioner | 0.81 (0.26–2.59) | |
| | | | | | Other non-working | 1.20 (0.38–3.80) | |
| | | | | | Information missing | 1.13 (0.50–2.58) | |
| **ALL** | | | | | | | |
| (6) | **Parental** | | **Household, quartiles** | | | | |
| | Postsecondary | 1 (ref) | 4th (highest) | 1 (ref) | | | |
| | Upper secondary | 1.26 (0.86–1.87) | 3rd | 1.20 (0.74–1.94) | | | |
| | Compulsory or less | 0.98 (0.55–1.74) | 2nd | 0.95 (0.57–1.59) | | | |
| | | | 1st | 1.24 (0.76–2.04) | | | |
| (10) | | | | | **Paternal social class based on occupation** | | |
| | | | | | I/II (most advantaged) | 1 (ref) | |
| | | | | | IIIN/M | 1.68 (1.20–2.36) | |
| | | | | | IV/V | 1.86 (1.24–2.77) | |
| (12) | **Maternal** | | **Family** | | | | |
| | No degree | 1.07 (0.38–3.04) | <2,000 DM | 1.21 (0.60–2.44) | | | |
| | Low degree | 1 (ref) | 2,000–4,000 DM | 1 (ref) | | | |
| | Intermediate degree | 0.69 (0.41–1.17) | 4,000–6,000 DM | 0.80 (0.47–1.38) | | | |
| | High degree | 0.92 (0.52–1.62) | 6,000–8,000 DM | 1.27 (0.52–3.06) | | | |
| | | | >8,000 DM | 1.11 (0.37–3.29) | | | |
| (13) | **Maternal** | | | | **Parental socioprofessional category** | | |
| | Four categories, per increase of one level | 1.11 (0.90–1.37) | | | Three categories, per increase of one level | 0.71 (0.54-0.94) | |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|---|
| | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | |
| (15) | | | | | | | **Neighborhood median income, quintiles** | |
| | | | | | | | 1st (lowest) | Ref |
| | | | | | | | 2nd | 0.93 (0.62–1.40) |
| | | | | | | | 3rd | 1.03 (0.69–1.54) |
| | | | | | | | 4th | 1.09 (0.74–1.62) |
| | | | | | | | 5th | 1.09 (0.72–1.64) |
| (16) | | | | | | | **Neighborhood SES, quintiles** | |
| | | | | | | | 1st (lowest 20%) | 1.39 (1.18–1.64) |
| | | | | | | | 2nd | 1.15 (0.97–1.35) |
| | | | | | | | 3rd | 1.13 (0.95–1.33) |
| | | | | | | | 4th | 1.17 (0.99–1.39) |
| | | | | | | | 5th | 1 (ref) |
| (17) | | | | | | | **Neighborhood-level poverty rate (% of households living in poverty)** | |
| | | | | | | | 0-<5 | 1 (ref) |
| | | | | | | | 5-<20 | 1.29 (1.03–1.61) |
| | | | | | | | 20–100 | 1.80 (1.41–2.30) |
| (18) | | | | | | | **Median household income based on ZIP-code** | |
| | | | | | | | Univariate | |
| | | | | | | | For every $10,000/year increase | 0.95 (0.84–1.07) |
| **AML** | | | | | | | | |
| (10) | | | | | **Paternal social class based on occupation** | | | |
| | | | | | Unadjusted | | | |
| | | | | | I/II (most advantaged) | 1 (ref) | | |
| | | | | | IIIN/M | 1.47 (0.57–3.80) | | |
| | | | | | IV/V | 2.05 (0.77–5.44) | | |
| (13) | **Maternal** | | | | **Parental socioprofessional category** | | | |
| | Four categories, per increase of one level | 0.99 (0.65-1.52) | | | Three categories, per increase of one level | 0.89 (0.49-1.62) | | |
| (19) | | | | | | | **SES factors and clusters** | |
| | | | | | | | One unit increase in the average score of each factor | |
| | | | | | | | Factor 1 (economic and educational disadvantage) | 1.07 (1.02–1.12) |
| | | | | | | | Factor 2 (immigration) | 0.99 (0.94–1.04) |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | HR[a] (95% CI) | | HR[a] (95% CI) |
| | | | | | | Factor 3 (housing instability) | 1.05 (1.00–1.10) |
| | | | | | | Factor 4 (low rates of moving within the state) | 0.98 (0.93–1.03) |
| | | | | | | Clusters were formed based on factors and compared. Lowest AML mortality was seen in Cluster 1 which reflected low Factor 1, 2, & 3. | |
| **LYMPHOMA** | | | | | | | |
| (5) | **Maternal** | | | | | **SES index, tertiles** | |
| | Compulsory | 1 (ref) | | | | Lower | 1 (ref) |
| | Secondary | 0.71 (0.30–1.66) | | | | Medium | 1.09 (0.38–3.09) |
| | Tertiary | 0.40 (0.05–3.19) | | | | Upper | 1.51 (0.55–4.16) |
| | **Paternal** | | | | | | |
| | Compulsory | 1 (ref) | | | | | |
| | Secondary | 0.40 (0.16–1.02) | | | | | |
| | Tertiary | 0.26 (0.08–0.85) | | | | | |
| (6) | **Parental** | | **Household, quartiles** | | | | |
| | Postsecondary | 1 (ref) | 4th (highest) | 1 (ref) | | | |
| | Upper secondary | 1.35 (0.69–2.64) | 3rd | 0.67 (0.28–1.56) | | | |
| | Compulsory or less | 1.13 (0.46–2.77) | 2nd | 1.36 (0.63–2.94) | | | |
| | | | 1st | 1.37 (0.62–3.02) | | | |
| (21) | | | | | | **Material deprivation, quintiles** | |
| | | | | | | Hodgkin lymphoma | |
| | | | | | | 1st | 0.63 (0.13–3.17) |
| | | | | | | 2nd | 1.16 (0.38–3.52) |
| | | | | | | 3rd | 1.41 (0.52–3.83) |
| | | | | | | 4th | 0.99 (0.30–3.27) |
| | | | | | | 5th (least deprived) | 1 (ref) |
| | | | | | | Non-hodgkin lymphoma | |
| | | | | | | 1st | 1.26 (0.49–3.24) |
| | | | | | | 2nd | 1.45 (0.57–3.68) |
| | | | | | | 3rd | 1.37 (0.57–3.29) |
| | | | | | | 4th | 2.33 (1.03–5.30) |
| | | | | | | 5th (least deprived) | 1 (ref) |
| **CNS TUMORS/TUMORS OF THE NERVOUS SYSTEM** | | | | | | | |
| (9) | **Maternal** | | **Maternal, quartiles** | | | | |
| | Basic | 1 (ref) | 1st (lowest) | 1 | | | |
| | Vocational | 1.20 (0.79–1.82) | 2nd | 0.92 (0.66–1.28) | | | |
| | Higher | 1.17 (0.73–1.89) | 3rd | 0.84 (0.58–1.22) | | | |
| | Unknown | 1.42 (0.73–2.78) | 4th | 0.86 (0.55–1.34) | | | |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) |
| | **Paternal** | | | | | | | |
| | Basic | 1 (ref) | | | | | | |
| | Vocational | 0.82 (0.58–1.17) | | | | | | |
| | Higher | 0.89 (0.58–1.36) | | | | | | |
| | Unknown | 0.73 (0.39–1.36) | | | | | | |
| (5) | **Maternal** | | | | | | **SES index, tertiles** | |
| | Compulsory | 1 (ref) | | | | | Lower | 1 (ref) |
| | Secondary | 0.59 (0.39–0.90) | | | | | Medium | 0.70 (0.43–1.15) |
| | Tertiary | 0.52 (0.26–1.05) | | | | | Upper | 0.71 (0.44–1.15) |
| | **Paternal** | | | | | | | |
| | Compulsory | 1 (ref) | | | | | | |
| | Secondary | 0.62 (0.38–1.01) | | | | | | |
| | Tertiary | 0.48 (0.28–0.81) | | | | | | |
| (6) | **Parental** | | **Household, quartiles** | | | | | |
| | Postsecondary | 1 (ref) | 4th (highest) | 1 (ref) | | | | |
| | Upper secondary | 0.99 (0.77–1.26) | 3rd | 0.78 (0.57–1.07) | | | | |
| | Compulsory or less | 1.25 (0.90–1.73) | 2nd | 0.87 (0.64–1.19) | | | | |
| | | | 1st | 1.07 (0.79–1.43) | | | | |
| (7) | **Parental** | | **Combined parental, quartiles** | | **Maternal employment status** | | | |
| | Primary or less | 1 (ref) | 1st (lowest) | 1 (ref) | Employed | 1 (ref) | | |
| | Secondary | 0.75 (0.48–1.17) | 2nd | 0.62 (0.35–1.07) | Unemployed | 0.77 (0.45–1.32) | | |
| | Post-secondary | 0.69 (0.44–1.08) | 3rd | 0.92 (0.54–1.55) | Student | 1.47 (0.81–2.67) | | |
| | | | 4th | 0.69 (0.40–1.18) | Pensioner | 0.97 (0.31–3.06) | | |
| | | | Information missing | 1.16 (0.51–2.63) | Other non-working | 0.98 (0.67–1.43) | | |
| | | | Structural missing | 0.56 (0.25–1.28) | Information missing | 1.70 (0.54–5.38) | | |
| | | | | | **Paternal employment status** | | | |
| | | | | | Employed | 1 (ref) | | |
| | | | | | Unemployed | 1.01 (0.61–1.67) | | |
| | | | | | Student | 1.34 (0.59–3.04) | | |
| | | | | | Pensioner | 1.10 (0.48–2.52) | | |
| | | | | | Other non-working | 2.11 (0.86–5.16) | | |
| | | | | | Information missing | 1.38 (0.70–2.72) | | |
| (11) | | | | | | | **Education[b]** | |
| | | | | | | | | Univariate |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.30 (0.94–1.79) |
| | | | | | | | **Income[b]** | |
| | | | | | | | | Univariate |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.19 (0.87–1.65) |
| (22) | **Maternal** | | | | | | | |
| | Short | 0.91 (0.68–1.23) | | | | | | |
| | Medium | 1.10 (0.87–1.39) | | | | | | |
| | Higher | 1 (ref) | | | | | | |

*(Continued)*

**TABLE 2A |** Continued

| References | Education | | Income | | Employment/occupation | | Area-based SES indicator | |
|---|---|---|---|---|---|---|---|---|
| | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) | | HR[a] (95% CI) |
| (23) | | | | | | | **SES index, quartiles** | |
| | | | | | | | <25% | 1.13 (0.90–1.43) |
| | | | | | | | 25–50% | 1.17 (0.93–1.48) |
| | | | | | | | 51–75% | 0.97 (0.77–1.22) |
| | | | | | | | >75% | 1 (ref) |
| **OTHER TUMORS** | | | | | | | | |
| (9) | **Maternal** | | **Maternal, quartiles** | | | | | |
| | Basic | 1 (ref) | 1st (lowest) | 1 (ref) | | | | |
| | Vocational | 0.79 (0.56–1.11) | 2nd | 0.88 (0.65–1.20) | | | | |
| | Higher | 0.66 (0.44–0.99) | 3rd | 1.11 (0.80–1.55) | | | | |
| | Unknown | 0.88 (0.48–1.63) | 4th | 0.81 (0.53–1.24) | | | | |
| | **Paternal** | | | | | | | |
| | Basic | 1 (ref) | | | | | | |
| | Vocational | 0.81 (0.59–1.11) | | | | | | |
| | Higher | 0.97 (0.65–1.43) | | | | | | |
| | Unknown | 0.87 (0.45–1.54) | | | | | | |
| (11) | | | | | | | **Education[b]** | |
| | | | | | | | Univariate | |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.05 (0.73-1.49) |
| | | | | | | | **Income[b]** | |
| | | | | | | | Univariate | |
| | | | | | | | Advantaged | 1 (ref) |
| | | | | | | | Disadvantaged | 1.20 (0.84-1.71) |
| (24) | | | | | | | **SES index, quartiles** | |
| | | | | | | | <25% | 1.1 (0.9–1.3) |
| | | | | | | | 25–50% | 1.0 (0.8–1.2) |
| | | | | | | | 50–75% | 1.0 (0.8–1.2) |
| | | | | | | | >75% | 1 (ref) |
| (25) | | | | | | | **SES index, quartiles** | |
| | | | | | | | <=25% | 2.8 (0.8-9.6) |
| | | | | | | | 26–50% | 1.6 (0.4-6.3) |
| | | | | | | | 51–75% | 0.9 (0.3-3.6) |
| | | | | | | | >75% | 1 (ref) |
| (26) | | | | | **Paternal social class based on occupation** | | | |
| | | | | | Renal tumors (age 0–24), univariate | | | |
| | | | | | I/II (most affluent) | 1 (ref) | | |
| | | | | | IIIN/M | 1.18 (0.60–2.30) | | |
| | | | | | IV/V | 1.17 (0.53–2.62) | | |
| | | | | | Wilms' tumor (age 0-14), multivariate | | | |
| | | | | | I/II (most affluent) | 1 (ref) | | |
| | | | | | IIIN/M | 1.12 (0.48–2.59) | | |
| | | | | | IV/V | 1.47 (0.55–3.91) | | |

*(Continued)*

**TABLE 2A** | Continued

| References | Education | Income | Employment/occupation | Area-based SES indicator |
|---|---|---|---|---|
| | HR[a] (95% CI) | HR[a] (95% CI) | HR[a] (95% CI) | HR[a] (95% CI) |
| (27) | | | | **Median income and education, quartiles**<br>No estimates reported. Overall survival curves show no statistical significant differences between the groups. |
| (28) | | | | *5 year relative survival rates (%)*<br>**Percent low educated[b]**<br><=16.6: 97.0 (78.0–99.6)<br>>16.6: 87.8 (79.1–93.0) (*p*-value 0.156)<br>**Percent below poverty level[b]**<br><=8.85: 94.3 (85.0–97.9)<br>>8.85: 85.6 (73.7–92.3) (*p*-value 0.123) |
| (29) | | | | *5 year relative survival rates (%)*<br>**Poverty level[b]**<br>Low: 98.8<br>High: 96.4 (*p*-value 0.054)<br>**Education level[b]**<br>High: 98.5<br>Low: 96.8 (*p*-value 0.154)<br>**Socioeconomic index[b]**<br>Low: 98.9<br>High (more disadvantages counties): 96.5 (*p*-value 0.070) |

[a]*Adjusted results if not otherwise stated. RR instead of HR is presented in some studies.*

[b]*Several area-based indicators were reported in the study but only measures corresponding to education, income and SES index are included in this table*

*ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio; LBL, Lymphoblastic lymphoma; SEER, The Surveillance, Epidemiology, and End Results.*

However, only poverty was included in the final adjusted model and the risk estimate was not reported (11).

## Other Tumors

This section summarizes the findings for very diverse tumor types. Three studies investigated non-CNS solid tumors combined; a pattern of higher mortality among children of mothers with lower education was suggested (9), however, other indicators such as income and area-based SES-index did not show associations with mortality (9, 11, 24). Five of the studies were of small size or focused on cancer types with a very good survival which is reflected in the imprecise estimates and lack of statistical power (26–29). However, the point estimates in the majority of these studies were in the direction of lower survival among children of lower SES.

# DISCUSSION

Findings of the 24 reviewed studies are diverse; some studies found no associations between socioeconomic or sociodemographic factors and survival while several indicated a social gradient with higher mortality among children from families of lower SES. When comparing the association within different cancer types, there is no clear suggestion of a particularly vulnerable subgroup, but hematological malignancies were most frequently investigated. Different indicators of SES appeared to be of importance in the studies which may indicate underlying mechanisms that vary between cancer types and health-care contexts, but can also be a result of diverse methodology, bias or random variation.

It has been acknowledged previously that different measurements of SES should not be understood as proxies for each other but instead they might have associations with

**TABLE 2B |** Main results of the included studies regarding the associations between sociodemographic factors and survival.

| References | Siblings and birth order | | Place of residence | | Parental cohabitation/ marital status | | Other individual based indicators | |
|---|---|---|---|---|---|---|---|---|
| | HR* (95% CI) | | HR* (95% CI) | | HR* (95% CI) | | HR* (95% CI) | |
| **ALL DIAGNOSES COMBINED** | | | | | | | | |
| (9) | **Number of full siblings <19 years** | | | | **Cohabitation status** | | | |
| | 0 | 1 (ref) | | | Alone | 1 (ref) | | |
| | 1 | 1.12 (0.95–1.31) | | | Together | 0.82 (0.69–0.99) | | |
| | =>2 | 1.26 (1.03–1.53) | | | | | | |
| (5) | | | | | | | **Rooms per person** | |
| | | | | | | | <1 | 1 (ref) |
| | | | | | | | 1–1.25 | 0.76 (0.59–0.98) |
| | | | | | | | >1.25 | 0.80 (0.62–1.04) |
| | | | | | | | **Living space, tertiles** | |
| | | | | | | | Lower | 1 (ref) |
| | | | | | | | Medium | 0.78 (0.60–1.02) |
| | | | | | | | Upper | 0.78 (0.60–1.03) |
| **HEMATOLOGICAL CANCERS** | | | | | | | | |
| (9) | **Number of full siblings <19 years** | | | | **Cohabitation status** | | | |
| | 0 | 1 (ref) | | | Alone | 1 (ref) | | |
| | 1 | 1.08 (0.81–1.44) | | | Together | 0.92 (0.66–1.29) | | |
| | =>2 | 1.18 (0.83–1.69) | | | | | | |
| **LEUKEMIA** | | | | | | | | |
| (5) | | | | | | | **Rooms per person** | |
| | | | | | | | <1 | 1 (ref) |
| | | | | | | | 1–1.25 | 0.89 (0.55–1.43) |
| | | | | | | | >1.25 | 1.19 (0.76–1.87) |
| | | | | | | | **Living space, tertiles** | |
| | | | | | | | Lower | 1 (ref) |
| | | | | | | | Medium | 0.97 (0.59–1.58) |
| | | | | | | | Upper | 1.01 (0.62–1.63) |
| **ALL** | | | | | | | | |
| (12) | | | **Residential area** | | | | | |
| | | | Urban | 1 (ref) | | | | |
| | | | Mixed | 1.16 (0.71-1.91) | | | | |
| | | | Rural | 0.88 (0.50–1.55) | | | | |
| (13) | **Number of children** | | **Place of living** | | **Marital status** | | | |
| | Per increase of one child | 0.99 (0.80–1.25) | Rural | 1.08 (0.69–1.70) | Married | 0.47 (0.27–0.83) | | |
| | | | Semiurban | 1.16 (0.74–1.81) | Other | 1 (ref) | | |
| | | | Urban | 1 (ref) | | | | |
| | | | **Travel distance (km) to hospital** | | | | | |
| | | | <50 | 1 (ref) | | | | |
| | | | 50–249 | 1.29 (0.80–2.10) | | | | |
| | | | 250+ | 1.24 (0.82–1.87) | | | | |

*(Continued)*

**TABLE 2B |** Continued

| References | Siblings and birth order | | Place of residence | | Parental cohabitation/ marital status | | Other individual based indicators |
|---|---|---|---|---|---|---|---|
| | | HR* (95% CI) | | HR* (95% CI) | | HR* (95% CI) | HR* (95% CI) |
| (14) | **Birth order** | | **Place of residence** | | | | |
| | 1st | 1 (ref) | Urban | 1 (ref) | | | |
| | 2nd | 0.64 (0.37–1.10) | Mixed | 1.12 (0.69–1.84) | | | |
| | 3rd and later | 1.04 (0.55–1.95) | Rural | 0.85 (0.49–1.49) | | | |
| | **Number of siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 0.86 (0.48–1.52) | | | | | |
| | 2 | 0.83 (0.42–1.67) | | | | | |
| | =>3 | 1.58 (0.73–3.44) | | | | | |
| (15) | | | **Distance from tertiary center** | | | | |
| | | | | Univariate | | | |
| | | | Short | 1 (ref) | | | |
| | | | Long | 1.05 (0.79–1.38) | | | |
| | | | Rurality | | | | |
| | | | **Rurality** | | | | |
| | | | | Univariate | | | |
| | | | Urban | 1 (ref) | | | |
| | | | Rural | 1.15 (0.80–1.64) | | | |
| (20) | **Birth order** | | **Place of residence** | | | | |
| | 1st | 1 (ref) | Greater Copenhagen area | 1 (ref) | | | |
| | 2nd | 1.05 (0.78–1.42) | Provincial cities | 1.18 (0.88–1.59) | | | |
| | 3rd | 1.27 (0.85–1.89) | Rural areas | 1.24 (0.81–1.91) | | | |
| | 4th and later | 1.62 (0.85–3.09) | Peripheral rural areas | 1.15 (0.55–2.40) | | | |
| | **Full siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 1.05 (0.76–1.46) | | | | | |
| | 2 | 1.19 (0.80–1.77) | | | | | |
| | =>3 | 1.31 (0.83–2.08) | | | | | |
| | **Full and half siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 1.05 (0.71–1.55) | | | | | |
| | 2 | 1.28 (0.82–1.98) | | | | | |
| | =>3 | 1.25 (0.76–2.05) | | | | | |
| **AML** | | | | | | | |
| (13) | **Number of children** | | **Place of living** | | **Marital status** | | |
| | Per increase of one child | 1.07 (0.69–1.66) | Rural | 1.08 (0.48–2.46) | Married | 0.83 (0.23–2.94) | |
| | | | Semiurban | 0.52 (0.22–1.24) | Other | 1 (ref) | |
| | | | Urban | 1 (ref) | | | |
| | | | **Travel distance (km) to hospital** | | | | |
| | | | <50 | 1 (ref) | | | |
| | | | 50–249 | 0.84 (0.34–2.07) | | | |
| | | | 250+ | 1.06 (0.48–2.31) | | | |

*(Continued)*

**TABLE 2B |** Continued

| References | Siblings and birth order | | Place of residence | | Parental cohabitation/ marital status | Other individual based indicators | |
|---|---|---|---|---|---|---|---|
| | | HR* (95% CI) | | HR* (95% CI) | HR* (95% CI) | | HR* (95% CI) |
| (20) | **Birth order** | | **Place of residence** | | | | |
| | 1st | 1 (ref) | Greater Copenhagen area | 1 (ref) | | | |
| | 2nd | 1.62 (1.01–2.59) | Provincial cities: | 0.87 (0.54–1.40) | | | |
| | 3rd | 2.22 (1.13–4.34) | Rural areas | 0.83 (0.45–1.55) | | | |
| | 4th and later | 5.76 (2.01–16.51) | Peripheral rural areas | 0.54 (0.18–1.63) | | | |
| | **Full siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 1.11 (0.65–1.90) | | | | | |
| | 2 | 1.09 (0.59–2.00) | | | | | |
| | =>3 | 2.27 (0.92–5.58) | | | | | |
| | **Full and half siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 1.48 (0.79–2.75) | | | | | |
| | 2 | 1.34 (0.67–2.67) | | | | | |
| | =>3 | 2.69 (1.11–6.52) | | | | | |
| **LYMPHOMA** | | | | | | | |
| (5) | | | | | | **Rooms per person** | |
| | | | | | | <1 | 1 (ref) |
| | | | | | | 1–1.25 | 0.88 (0.35–2.23) |
| | | | | | | >1.25 | 0.35 (0.12–1.06) |
| | | | | | | **Living space, tertiles** | |
| | | | | | | Lower | 1 (ref) |
| | | | | | | Medium | 0.61 (0.22–1.70) |
| | | | | | | Upper | 0.31 (0.08–1.11) |
| (20) | **Birth order** | | **Place of residence** | | | | |
| | 1st | 1 (ref) | Greater Copenhagen area | 1 (ref) | | | |
| | 2nd | 0.97 (0.49–1.94) | Provincial cities | 0.82 (0.41–1.63) | | | |
| | 3rd | 1.18 (0.41–3.40) | Rural areas | 1.03 (0.38–2.78) | | | |
| | 4th and later | 1.00 (0.20–5.11) | Peripheral rural areas | 1.09 (0.23–5.17) | | | |
| | **Full siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 1.06 (0.44–2.59) | | | | | |
| | 2 | 2.26 (0.88–5.79) | | | | | |
| | =>3 | 0.91 (0.26–3.20) | | | | | |
| | **Full and half siblings** | | | | | | |
| | 0 | 1 (ref) | | | | | |
| | 1 | 2.51 (0.63–9.92) | | | | | |
| | 2 | 5.25 (1.40–19.70) | | | | | |
| | =>3 | 3.87 (0.92–16.31) | | | | | |

*(Continued)*

**TABLE 2B |** Continued

| References | Siblings and birth order | | Place of residence | | Parental cohabitation/ marital status | | Other individual based indicators | |
|---|---|---|---|---|---|---|---|---|
| | HR* (95% CI) | | HR* (95% CI) | | HR* (95% CI) | | HR* (95% CI) | |
| **CNS TUMORS/TUMORS OF THE NERVOUS SYSTEM** | | | | | | | | |
| (9) | **Number of full siblings <19 years** | | | | **Cohabitation status** | | | |
| | 0 | 1 (ref) | | | Alone | 1 | | |
| | 1 | 0.89 (0.67–1.18) | | | Together | 0.70 (0.51–0.97) | | |
| | =>2 | 1.03 (0.72–1.48) | | | | | | |
| (5) | | | | | | | **Rooms per person** | |
| | | | | | | | <1 | 1 (ref) |
| | | | | | | | 1–1.25 | 0.61 (0.39–0.97) |
| | | | | | | | >1.25 | 0.56 (0.34–0.92) |
| | | | | | | | **Living space, tertiles** | |
| | | | | | | | Lower | 1 (ref) |
| | | | | | | | Medium | 0.71 (0.43–1.17) |
| | | | | | | | Upper | 0.61 (0.37–1.01) |
| (22) | **Birth order** | | **Place of residence at diagnosis** | | **Cohabitation status** | | | |
| | 1st | 1.0 (ref) | Greater Copenhagen area | 1.0 (ref) | Living together | 1 (ref) | | |
| | 2nd | 0.97 (0.78–1.21) | Provincial cities | 1.23 (0.98–1.56) | Living not together | 1.07 (0.85–1.36) | | |
| | 3rd and later | 1.00 (0.75–1.32) | Rural areas | 1.38 (1.00–1.90) | | | | |
| | **Full siblings** | | Peripheral rural areas | 1.17 (0.63–2.18) | | | | |
| | 0 | 1.0 (Ref) | | | | | | |
| | 1 | 1.12 (0.88–1.42) | | | | | | |
| | 2 | 0.98 (0.73–1.31) | | | | | | |
| | =>3 | 0.87 (0.57–1.32) | | | | | | |
| | **Children living in the household** | | | | | | | |
| | 1 | 1.0 (Ref) | | | | | | |
| | 2 | 1.18 (0.91–1.52) | | | | | | |
| | =>3 | 1.07 (0.79–1.44) | | | | | | |
| (23) | | | **Driving distance to cancer center (miles)** | | | | | |
| | | | 0–25 | 1 (ref) | | | | |
| | | | 26–50 | 0.97 (0.78–1.20) | | | | |
| | | | >50 | 0.91 (0.76–1.11) | | | | |
| **OTHER TUMORS** | | | | | | | | |
| (9) | **Number of full siblings <19 years** | | | | **Cohabitation status** | | | |
| | 0 | 1 (ref) | | | Alone | 1 (ref) | | |
| | 1 | 1.45 (1.11–1.89) | | | Together | 0.80 (0.59–1.08) | | |
| | =>2 | 1.29 (0.93–1.79) | | | | | | |

*(Continued)*

**TABLE 2B** | Continued

| References | Siblings and birth order | Place of residence | Parental cohabitation/ marital status | Other individual based indicators |
|---|---|---|---|---|
| | HR* (95% CI) | HR* (95% CI) | HR* (95% CI) | HR* (95% CI) |
| (24) | | **Driving distance to cancer center (miles)** | | |
| | | <25 1 (ref) | | |
| | | 25–50 1.1 (1.0–1.3) | | |
| | | >50 1.1 (1.0–1.3) | | |
| (25) | | **Driving distance to cancer center (miles)** | | |
| | | Univariate | | |
| | | <25 1 (ref) | | |
| | | 25–49 0.6 (0.2–1.9) | | |
| | | >=50 0.7 (0.2–2.0) | | |

*Adjusted results if not otherwise stated. RR instead of HR is presented in some studies.
ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio.

health outcomes through different mechanisms (31). While income would indicate that economic resources of the family are of importance, education may reflect health literacy. However, our diverse findings do not clearly suggest a specific SES indicator of particular importance for childhood cancer survival. Parental education was more frequently investigated than income and also showed somewhat stronger associations; most often children of parents with lower education experienced higher mortality, however, there were also some findings pointing in the opposite direction but these were not statistically significant and not consistent. Only one study reported a statistically significant association between lower income and poorer survival (7), but point estimates in the other studies either pointed in the same direction, or were around the null value. These findings are very similar to the previous review by Gupta et al. (8).

## Potential Mechanisms

The finding of poorer survival among children with lower parental SES requires further attention. Understanding the underlying mechanisms is the basis for any strategy to reduce health inequalities, but is a challenge since they likely differ between health-care setting and also childhood cancer types. Most studies focused on leukemia, and especially ALL, which does not necessarily reflect a particularly strong hypothesis connecting parental SES to survival from this cancer type, but might be the result of difficulties with statistical power in studies including more rare diagnoses. In fact, one of the studies found the strongest association for CNS tumors (5). A reason for this might be that, compared to leukemia, a low proportion of children with CNS tumors are treated within international standardized protocols in Switzerland (5). With less standardized protocols, there might be more room for influence from parents from higher SES, for example for referrals or second opinions, although this hypothesis has not yet been examined (5).

Another suggested mechanism is related to differences in how parents manage treatment adherence. The treatment of childhood cancer differs substantially between diagnoses, and the treatment strongly influences if the child will stay in hospital or at home. For example, treatment of ALL is long and a substantial part takes place at home where parents are usually responsible for the oral administration of drugs, see Lightfoot et al. (4) for a visualization. The results from the study by Lightfoot et al. demonstrated that SES differences in survival emerged during this period (4), which suggests that treatment adherence may be involved. This hypothesis is supported by other studies suggesting that higher SES, measured by different indicators, are associated with better treatment compliance (32–34), and compliance is of importance for treatment results in children with ALL (34, 35). In addition, when only inpatient mortality during induction chemotherapy was compared between children with ALL of different area-based income levels, no differences were observed (18). If parental responsibility for adherence to treatment was the main explanation of SES differences in survival, one would not expect any differences in mortality during inpatient treatment. With this reasoning one would also expect survival differences in ALL to be more pronounced compared to survival differences in AML, since AML is mainly treated within hospitals; however, included studies provide insufficient data to evaluate this hypothesis.

Not only have socioeconomic differences in childhood cancer survival been observed after a period of time, but also within the first month (11), and during the first year (6) after diagnosis. Possibly, early SES differences reflect differences in disease severity at diagnosis. Some of the studies have adjusted for this, but an association between SES and survival was still found (5, 10). When a potential association between SES and stage, or disease severity, at diagnosis has been assessed, some studies found no or very weak associations (10, 21, 23, 24, 26), while others indicated that children of lower SES may be more likely to have advanced disease (25, 27, 29).

Another potential explanation for socioeconomic survival differences might be related to differences in incidence of

subtypes of cancers with different prognosis. Few of the studies have taken detailed subtype into account. However, Erdmann et al. (12) conducted a sensitivity analysis including only B-lineage ALL which resulted in similar conclusions as for all immunophenotypes of ALL combined, and Adam et al. (5) adjusted for histopathological group in their analysis of CNS tumors, which did not change their results.

## Methodology of Reviewed Studies

Several of the reviewed studies used register-based information which limits the risk of bias from non-participation and loss to follow-up. Most of the studies have identified their study population from cancer registers which also have been used by the International Agency for Research on Cancer for estimating cancer incidence (36, 37). Even if high registry coverage is even more important in incidence estimations, it is also important when assessing the association between social factors and survival. If the likelihood of being included in a study is associated with both SES and survival, biased results are obtained. However, such bias is not likely to have affected the conclusion of this review.

The source of information regarding social factors differed between studies, for example registers, birth certificates or questionnaires. One important aspect is, however, the temporality. Since a child's cancer diagnosis can affect some of the social factors, for example income, it is important that this information is collected before the diagnosis. All but one of the studies including individual measures of income assessed this before the child's cancer diagnosis. Income information in the study by Erdmann et al. (12) is based on interviews conducted within 2 years after a diagnosis, however, no association between family income and survival was found in this study. When area-based information is used, temporality is not that crucial since the child's diagnosis does not affect the income level in the neighborhood.

A general limitation with register-based studies is that they often are limited in terms of information on relevant confounders and mediators, such as severity of disease, treatment and adherence. As a result, several of the above discussed mechanisms are suggested but few are examined. Moreover, the choice of included SES indicators was seldom motivated in the reviewed studies.

Statistical power is weak in several of the studies, which reflects that the effect sizes are not very large, the overall prognosis is good and childhood cancer is rare. Different cancer types need to be considered separately due to diverse treatments and prognosis, however, this also decrease statistical power and studies on rare cancer types may not be able to detect potential socioeconomic differences. Of these reasons it is important to look at the direction and consistency of findings rather than only statistical significance. This is also important when interpreting the results of studies using area-based indicators of SES. As previously acknowledged, e.g., (10, 15), using area-based measures of SES as proxies for individual measurements can lead to ecological fallacy, a non-differential exposure misclassification which might dilute an association should one exist.

Time period of diagnosis differed greatly between studies. Studies focusing on recent periods have lower statistical power due to limited number of included children and increased survival rates. However, the association between parental SES and survival may have changed with calendar time; e.g., Njoku et al. (10) included children diagnosed 1968-2010 and showed a tendency of less SES differences during the latest years. However, focusing on more recent time periods, Tolkkinen et al. (7) found differences in survival according to parental education primarily in children diagnosed during 2000–2009, compared to in the 1990's.

Another time aspect is the differences in follow-up time between the included studies. While a few studies assessed mortality closely after the cancer diagnosis, most of the studies focused on mortality up to 5 or 10 years. Comparisons between these two types of studies should be done with caution since the mechanisms behind potential SES differences in mortality directly at time of diagnosis and several years after are probably very different.

## Strengths and Limitations

This review was based on an extensive literature search and includes studies of several indicators of SES and their associations with survival from different types of childhood cancer. The search strategy and study selection are described in detail to ensure reproducibility. Moreover, descriptions of included studies and relevant results are shown in detail to visualize the diversity. Since the choice of SES indicators, definition of study population, and adjustment variables differed to such extent between studies a comparison of effect estimates is hampered (8).

Some limitations with this review need to be acknowledged. Only one data source (PubMed) was used to identify studies; potential articles searchable only in databases other than PubMed are therefore not included. However, in the field of childhood cancer epidemiology we find it unlikely that significant articles are not identified in PubMed. Another limitation is that no formal bias assessment was performed. However, the methodology of included studies are described in **Table 1** for transparency, and commented in the above section. In addition, we cannot rule out that some publication bias may be present, i.e., that studies showing no associations are less likely to be published. In such case, the conclusions from our review may be too strong regarding the association of low SES and worse childhood cancer survival.

# CONCLUSION

This review has summarized the most recent publications on the association between parental SES and childhood cancer survival in high-income countries. Even though some of the reviewed studies found no differences in survival between children from diverse socioeconomic backgrounds, worse survival among children of lower SES were observed for several cancer types, contexts, and SES indicators. Studies that more carefully investigate specific underlying mechanisms for the socioeconomic differences in survival are lacking. Collaborative studies are needed to increase statistical power to enable

investigation of the association within homogenous cancer types which will increase the understanding of the mechanisms involved, and allow targeted interventions to reduce health inequalities.

## AUTHOR CONTRIBUTIONS

HM, KM, FE, GT, MH, and MF contributed to the design of the study. HM screened titles, abstracts and full-texts. HM drafted the manuscript. HM, KM, FE, GT, MH, and MF reviewed the manuscript and approved the final version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00485/full#supplementary-material

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