Socioeconomic Disparity in Endometrial and Head & Neck Cancer Survival in Germany

Thesis

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Abstract

Area-based socioeconomic deprivation has been established as an important indicator of health and a potential predictor of cancer survival. The aim of this thesis is to investigate the survival inequality experienced by endometrial (EC) and head and neck cancer (HNC) patients living in Germany.

This thesis is a cumulative doctoral project that consists of two studies based on German population-based cancer registry data. Area-based socioeconomic deprivation was defined according to the German Index of Socioeconomic Deprivation (GISD). The GISD is a composite index that was developed by the Robert Koch Institute and is based on three equally weighted socioeconomic dimensions: income, education and employment.

The analysis included 42,423 EC and HNC patients (21,602 and 20,821 patients, respectively). The observed five-year overall survival time dropped as deprivation levels increased in both groups of patients. Cox regression models showed that only stage I EC patients seemed to suffer from the socioeconomic disparity. Stage I patients living in the most deprived districts showed a higher hazard of overall mortality when compared to the cases living in the most affluent districts [Hazard ratio: 1.20; 95% Confidence interval (0.99–1.47)] after adjusting for patient and tumor characteristics, in addition to treatment information.

As for HNC patients, the performed mediation analysis showed that most of the effect of deprivation on survival was mediated through differential stage at diagnosis during the first six months after HNC diagnosis. As follow-up time increased, medical care, stage at diagnosis, and treatment played no role in mediating the measured effect of deprivation on survival.

Previous studies in Germany have shown that higher rates of obesity, smoking, and physical inactivity were linked to regions characterized by a high deprivation score. While acknowledging the data limitations of cancer registries, current efforts to reduce tobacco consumption and promote physical activity and healthier diets should be supported, in addition to continued socioeconomic reform.

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Referat

Die sozioökonomische Benachteiligung in einem bestimmten Gebiet ist ein wichtiger Gesundheitsindikator und ein potenzieller Prädiktor für die Überlebensrate bei Krebserkrankungen. Ziel dieser Arbeit ist es, die Ungleichheit bezüglich des Überlebens von Patient*innen mit Endometriumkarzinom (EC) und Kopf-Hals-Krebs (HNC) in Deutschland zu untersuchen.

Bei dieser Arbeit handelt es sich um ein kumulatives Promotionsprojekt, das aus zwei Studien besteht, die auf Daten des bevölkerungsbezogenen Krebsregisters in Deutschland basieren. Die sozioökonomische Benachteiligung in einem bestimmten Gebiet wurde anhand des Deutschen Index der sozioökonomischen Benachteiligung (GISD) definiert. Der GISD ist ein zusammengesetzter Index, der vom Robert-Koch-Institut entwickelt wurde und auf drei gleich gewichteten sozioökonomischen Dimensionen basiert: Einkommen, Bildung und Beschäftigung.

Die Analyse umfasste 42.423 EC und HNC-Patienten (21.602 bzw. 20.821 Patienten). Die beobachtete Fünf-Jahres-Gesamtüberlebenszeit sank mit zunehmendem Deprivationsniveau in beiden Patient*innengruppen. Cox-Regressionsmodelle zeigten, dass nur EC-Patient*innen im Stadium I unter der sozioökonomischen Ungleichheit zu leiden schienen. Patient*innen im Stadium I, die in den am stärksten benachteiligten Bezirken lebten, wiesen ein höheres Risiko für die Gesamtmortalität auf als Patient*innen, die in den wohlhabendsten Bezirken lebten [Hazard Ratio: 1,20; 95 % Konfidenzintervall (0,99-1,47)], nachdem neben der Behandlung auch die Patient*innen- und Tumormerkmale berücksichtigt wurden.

Bei den HNC-Patient*innen zeigte die durchgeführte Mediationsanalyse, dass der größte Teil des Effekts der Deprivation auf das Überleben durch das unterschiedliche Stadium bei der Diagnose in den ersten 6 Monaten nach der HNC-Diagnose vermittelt wurde. Mit zunehmender Nachbeobachtungszeit spielten die medizinische Versorgung, das Stadium bei der Diagnose und die Behandlung keine Rolle bei der Vermittlung des gemessenen Effekts von Deprivation auf das Überleben.

Frühere Studien in Deutschland haben gezeigt, dass höhere Raten von Fettleibigkeit, Rauchen und körperlicher Inaktivität mit Regionen verbunden waren, die durch einen hohen Deprivationswert gekennzeichnet waren. Unter Berücksichtigung der Beschränkungen von Krebsregisterdaten sollten die derzeitigen Bemühungen zur Verringerung des Tabakkonsums und zur Förderung von körperlicher Bewegung und gesünderer Ernährung zusätzlich zu den fortgesetzten sozioökonomischen Reformen unterstützt werden.

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1. Introduction

1.1 Area-based socioeconomic deprivation

1.1.1 Definition and history

In 1979, British Professor of Sociology, Peter Townsend, proposed a novel approach to better understand the impact of poverty on society. Townsend defined poverty as the lack of resources "to obtain the types of diet, participate in the activities and have the living conditions and amenities which are customary, or at least widely encouraged or approved in the societies to which they belong" [1]. He further argued that in order to objectively define and measure poverty consistently, it should only be viewed under the concept of 'relative deprivation'. This new understanding of poverty or deprivation, highlights both the financial/material aspect, as well as the social side, where an individual's social interactions within different communities can also be affected [2]. In that context, area-based socioeconomic deprivation refers to the potential compounded effect experienced by a group of deprived people living in nearby areas or the effect they may experience facing environmental disadvantages within the same neighborhood [3].

Using various material and social metrics, researchers developed numerous indices and scores to measure socioeconomic deprivation for different purposes. Most famously, the Townsend and the Carstairs scores, for example, were used to assess the socioeconomic impact on public health and to monitor trends over time within small areas in England and Scotland [4-7]. In 2000, the Index of Multiple Deprivation (IMD) was developed to measure relative deprivation in small areas across the United Kingdom (UK) [8]. The IMD was the first multi-dimensional nationwide deprivation index that combined seven dimensions (income, employment, education, health, crime, living situation and living environment) into a single overall deprivation measure [9]. The IMD laid the foundation for the development of similar indices in several countries such as Italy, Canada, France, Switzerland, and China [10-14].

In Germany, nationwide deprivation measures were only formulated rather recently with the introduction of the German Index of Multiple Deprivation (GIMD) and the German Index of Socioeconomic Deprivation (GISD) [15, 16].

1.1.2 The German Index of Socioeconomic Deprivation

The GISD was developed by the Robert Koch Institute (RKI) in 2017, in an effort to monitor and measure regional health inequalities in Germany. The index is based on three main socioeconomic dimensions: employment, income and education. The regional socioeconomic indicators, which the dimensions were based upon, were selected from the INKAR (Indicators and Maps on Spatial and Urban Development) database compiled by the German Federal Institute for Research on Building, Urban Affairs and Spatial Development (BBSR) [17]. The INKAR database contains around 600 indicators that provide information on the population, labor market, income and earnings, housing, education, social and medical care, transport and accessibility, land use and the environment, as well as public finances and budgets.

After a comprehensive literature analysis, the indicators selected for each dimension were as follows:

- Income = Mean net household income, Tax revenues, and Debtor quotas within a given district.
- Education = Proportions of employees in the district with (and without) a university degree, School dropouts without a degree, and School dropouts with the German "Abitur" or equivalent.
- Occupation = Local unemployment rates, Average gross wage of employees, and Employment rate.

Factor analysis was then performed to weight the indicators for the three dimensions. The three dimensions were eventually given equal weights in the resulting index, i.e. each contributing one third. The index ranges on a scale of zero to one, with zero representing the lowest level of socioeconomic deprivation (most affluent) and one representing the most socioeconomically deprived areas. In practice, the index is usually categorized into five quintiles [Quintile 1 (least deprived)-Quintile 5 (most deprived)].

The GISD has since been used in various studies to investigate health related social inequalities within Germany [18-24]. Most recently for example, in a nationwide SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) seroepidemiological study, Neuhauser et al. found that testing for SARS-CoV-2 was more common among more advantaged socioeconomic groups and that a higher rate of undetected cases were among residents in socioeconomically deprived districts, i.e. districts with a higher GISD score [25]. With regard to cancer research, Hoebel et al. found that for the majority of cancer sites, a higher incidence rate was associated with a higher level of deprivation [26].

Data from the RKI's German Health Update 2014/2015- European Health Interview Survey study (GEDA 2014/2015-EHIS) was used to measure associations between the GISD and several health indicators within the municipalities in which GEDA study participants lived in. The analysis revealed a link between a higher GISD score (more deprivation) and higher mortality rates within the included municipalities. Additionally, the population in regions characterized by high levels of deprivation were also found to have significantly higher rates of smokers, to be less physically active, and were more often obese [16]. These findings were in line with other studies published in Germany [27-30].

This inequality raises concern, since smoking and obesity, among other lifestyle-related factors, have not only been proven to be directly related to the increased risk of developing cancers such as endometrial and head and neck cancer, but they have also been found to negatively affect cancer survival.

1.2 Endometrial cancer

Endometrial cancer (EC) refers to malignant neoplasms arising from the endometrial lining of the uterus. EC is the most commonly diagnosed gynecological cancer in Europe and North America with an incidence that is estimated to be ten times higher than that in less developed countries [31]. According to the latest estimates, over 12,500 patients were diagnosed with EC and around 2,500 death cases were reported across Germany in 2020, causing EC to be the fifth most common cancer diagnosed in German women after breast cancer, colorectal and lung cancer, and skin melanoma [32]. This increased incidence could be related to the prevalence of obesity, physical inactivity, and metabolic syndromes like PCOS (polycystic ovaries syndrome) [33-36]. As the life expectancy continues to improve in Germany, the incidence of EC is expected to rise to 31.1 per 100,000 in 2030 [32].

In general, the main risk factor for developing EC is exposure to endogenous and exogenous unopposed estrogens [37]. Studies have shown that obesity and high dietary fat consumption could increase the concentration of circulating estrogens in postmenopausal women, and therefore, increase the risk of developing EC significantly [38, 39]. Other risk factors associated with EC include early age at menarche, high blood pressure, late-onset menopause, older age, and the use of tamoxifen, a selective estrogen receptor modulator used to prevent and treat breast cancer [40-43]. In contrast, physical activity and normal body weight maintenance, in addition to smoking and contraceptive pills, have been found to decrease the risk of developing EC through reducing the concentration of circulating estrogens [44-46].

EC is histologically classified into two main subtypes: endometrioid (type I) and non-endometrioid (type II) [47]. Type I is the most common subtype of endometrial cancer and is generally well differentiated, of low grade, and makes up around 80% of all EC cases. Type II, in contrast, is more aggressive. Type II variants such as clear cell and serous cell are high grade by definition and usually require extensive treatment since their prognosis is less favorable.

EC is symptomatic in its early stages, with patients often experiencing abnormal uterine bleeding as the first and most common symptom [48]. This leads EC to be diagnosed at earlier stages (stage I & II) in almost 75% of the cases [49]. At these early stages, the most important treatment is surgery. Total hysterectomy and removal of tubes and ovaries is regarded as standard treatment for stage I patients [50]. Considering that patients diagnosed at later advanced stages usually present with high-grade lesions or the more aggressive serous cell subtype, a more complex treatment plan is typically required and adjuvant chemotherapy is recommended [51, 52].

In Germany, the Robert Koch Institute estimates the five-year relative survival rates for endometrial cancer patients to be 93% for stage I, 77% for stage II, 53% for stage III, and 20% for stage IV [49]. These survival rates further highlight the importance of early diagnosis.

1.3 Head and neck cancer

Head and neck cancer (HNC) is a broad term that describes epithelial malignancies that arise in the oral cavity, pharynx, and the larynx [53]. HNC accounts for approximately 3% of all new malignancies in Germany, and is ranked the seventh most common cancer worldwide [54]. In 2018, there were approximately 18,246 new cases in Germany, and 8,227 deaths from HNC [32].

Tobacco and alcohol consumption have long been established as the main risk factors for developing HNC. Depending on the duration and extent of smoking, the risk for developing HNC could be ten times higher for smokers versus never-smokers [55]. The results of a pooled analysis of 17 European and American case-control studies from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) consortium confirmed the association between cigarette smoking, alcohol consumption, and developing HNC [56]. The study further estimated that approximately 72% of head and neck cancers could be attributed to tobacco use, alcohol consumption and a combination of both, noting the joint effect when consuming both at the same time.

Recently, an increase in oropharyngeal cancer has been noted. This increase has been linked to Human papilloma virus (HPV) type 16 infections [57]. Both molecular and epidemiological studies have shown that approximately 25% of all HNCs are HPV positive, with a general predilection to certain sites such as the oropharynx region [58, 59]. Patients diagnosed with HPV-positive HNC are more likely to be younger men, non-smokers, more sexually active and have a higher socioeconomic status (SES) when compared with HPV-negative HNC patients [60]. HPV-positivity could also be considered a favorable prognostic factor [61].

Unlike EC, only 30-40% of patients present with stage I/II [62]. Two-thirds of HNC patients are diagnosed at later stages, which are characterized by large tumors with marked local invasion, evidence of metastases to regional nodes or both. Decisions regarding therapy depend strongly on the size and anatomical site of the primary cancer, stage of disease, age of the patient, patient preferences, performance status, and comorbidities.

Surgery is the standard treatment for early-stage HNC patients [63]. This option is dependent however, on anatomical accessibility and the intention to achieve organ preservation. In which case, radiotherapy could be considered. For later stages, a multimodal approach has shown to improve survival rates [64]. The choice of initial therapy, sequencing, and administration of therapy should consider morbidity, toxicity, and preservation of function. In general, surgical resection followed by adjuvant radiotherapy or chemotherapy is the preferred mode of treatment. In cases where tumors are unresectable due to accessibility, chemoradiotherapy is the curative standard of care.

Due to the complex nature and different definitions of HNC, survival from the disease is difficult to report. In the United States, the five-year overall survival rate is estimated to be 65%, ranging from 32% for hypopharyngeal cancer to 90% for lip cancer [65]. This wide range highlights how survival could vary greatly according to stage, tumor site, patient history, and HPV status.

1.4 Deprivation and cancer survival in German literature

In 1991, Brenner et al. published the first study in Germany investigating area-based survival inequality among colorectal cancer patients living in Saarland, Germany [66]. Considering the lack of a standard index that measured socioeconomic deprivation at the time, Brenner et al. created two distinct indices using factor analysis. The factor analysis was based on six area-based socioeconomic variables, which included residential area per inhabitant, traffic area, proportion of Catholics, proportion of inhabitants with no more than 9 years of education, proportion of blue-collar workers among inhabitants, and mean number of persons per household. The index “Socioeconomic status” (SES) was mainly characterized by the education and employment variables, whereas the index “Urbanity” was characterized by the residential area and traffic density indicators. The indices were then categorized into three equal classes: high, medium, and low. Cases were allocated to these classes according to their community of residence at the time of diagnosis. Among 2,627 patients with colorectal cancer diagnosed from 1974 to 1983, the authors found patients from communities in the lowest SES class to have significantly lower survival rates than patients from other communities.

In the years to follow, several studies investigating other cancers would come to similar conclusions. Those studies, however, were limited to certain states and regions. Eberle et al. investigated socioeconomic inequalities in cancer incidence and survival within the city of Bremen [67]. The authors followed 27,500 cancer patients diagnosed 2000-2006 and used the Bremen Discrimination Index as a measure for area-based socioeconomic deprivation. The index was based on four main domains education, employment and earning capacity, identification, and de-mixing and conflict potential. The study found that for most cancer sites, a significant increase of cancer incidence and mortality was observed in men from a lower social class. Remarkably, for a few cancer sites such as breast and prostate cancer, a decrease in social status was associated with a decreased incidence rate.

In 2011, a similar study was performed in the southeastern state of Bavaria. Kuznetsov et al. investigated the association between deprivation and lung and colorectal cancer incidence and mortality, using the Bavarian Index for Multiple deprivation as their measure for deprivation [68]. Again, the results showed that the incidence and mortality for those two cancers were significantly higher in districts characterized by a high level of regional deprivation.

Jansen et al. published the first large-scale study that aimed to measure social inequalities among several cancer sites across Germany in 2013 [69]. The study was based on 200 districts representing almost 39% of the total German population. The German Index of Multiple Deprivation was used as a measure for socioeconomic deprivation at district level. The index includes seven domains of deprivation (income, employment, education, district revenue, social capital, environment and security). Using information collected from 983,601 cancer patients diagnosed between 1997-2006, the authors found that patients in the poorest district had a lower five-year survival rate than those in all other districts combined.

In 2018, Hoebel et al. published the first study to examine socioeconomic inequalities in cancer incidence at German national level [26]. The study was based on registries that covered nearly 59 million residents from 317 German districts, which is approximately 73 percent of the total resident population of Germany. The authors used the GISD as the measure for socioeconomic deprivation. Their results showed that for the majority of cancer sites, socioeconomic inequalities in cancer incidence do exist in both men and women. This inequality was most pronounced for cancers of the lung, oral and upper respiratory tract, stomach, kidney, and bladder. Similar to the findings of the Bremen study, some exceptions such as skin melanoma and breast cancer, showed a reverse socioeconomic gradient with the highest incidence in the least deprived districts.

In 2021, Finke et al and Jansen et al. published two studies exploring the effect of deprivation on cancer survival on the German municipality level [70, 71]. Jansen et al. estimated the number of potentially avoided excess deaths associated with deprivation using the GIMD as the measure of deprivation. The calculated five-year age-standardized relative survival in 2013–2017 for all cancer patients included in the study were found to decrease gradually with increasing deprivation. The authors estimated that if all regions in Germany had the same cancer survival rates and distribution of cancer types as the least deprived regions, it could have prevented 11,405 annual excess cancer deaths within five years of diagnosis (7.9% of all excess deaths). Patients suffering from colorectal, oral and pharynx, prostate, and bladder cancer contributed the most towards that estimate.

Finke et al. confirmed those results and also found that the majority of cancer patients living in the most deprived municipalities at the time of diagnosis had the lowest five-year survival compared to the least deprived patients even after adjusting for stage. The authors also performed a trend analysis for periods between 2003-2005 and 2012-2014. The analysis showed that even though an improvement in survival between the two periods was observed, significant differences in survival still persisted.

1.5 Objectives and aims

Cancer is the second most common cause of death in Germany and worldwide. With over 620,000 new cancer patients and 250,000 deaths being reported in 2020 alone, cancer remains to be a major public health concern in Germany [32]. According to the International Agency for Research on Cancer (IARC), almost 2.2 million Germans are currently living with a cancer that was diagnosed in the past five years. These figures, along with public health implications, are expected to continue rising as the population ages and grows in number.

To address the expected burden on health care systems, area-based socioeconomic deprivation, among other socioeconomic-based indicators, has recently moved into the focus of health services research and cancer epidemiology. The effect of the surrounding socioeconomic environment on cancer survival has been well documented in several countries and for several cancer sites. The literature has consistently showed that for the majority of cancer sites, patients living in affluent regions have better survival than those living in deprived regions, even within countries that offer universal health care, such as the UK, Canada, and Sweden.

While these disparities were also reported in several German studies, the exact nature and mechanism through which deprivation affects cancer survival is still poorly understood and explanations for these inequalities are yet to be thoroughly investigated.

This thesis focuses on the survival inequality experienced by endometrial and head and neck cancer patients living in Germany. By identifying potential risk factors, recommendations for improving secondary prevention policies are made in order to reduce the survival inequality among individuals with these types of cancer.

Therefore, the main aims of this thesis are as follows:

1) Measuring the differences in survival in EC and HNC patients according to level of area-based socioeconomic deprivation.

2) Identifying potential underlying explanatory factors, while acknowledging the different natures of both cancers.

2. Discussion

This doctoral thesis provides an in-depth overview of the regional socioeconomic-based inequality in survival experienced by EC and HNC patients in Germany. The dissertation is based on two publications that have addressed the research aims that were presented in the previous chapter (Introduction 1.5) [72, 73]. Both studies were based on German cancer registry data and used the GISD as the measure of area-based socioeconomic deprivation on the district level. The first publication examined a sample of 21,602 German endometrial cancer patients diagnosed during 2004-2014. The observed five-year overall survival (OS) time for patients living in the most affluent districts was slightly higher (78.6%) compared to patients living in the most deprived districts in Germany (74.7%). The ten-year OS time followed a similar pattern with patients in the deprived districts having a worse survival rate (60.2%) compared to patients in the least deprived districts (66.0%). The statistical analysis revealed a strong association between deprivation and EC survival among stage I patients only. Neither baseline patient characteristics, tumor characteristics, nor differences in the treatment received could explain the association of deprivation on survival.

The second publication investigated the effect of area-based socioeconomic deprivation on survival in a sample of 20,821 head and neck cancer patients diagnosed in 2009-2013. The observed five-year overall survival for patients living in the most socioeconomically affluent districts was found to be 53.2%. Similar to EC patients, the OS also decreased as the level of deprivation increased, reaching 47.9% in patients living in the most deprived districts. These findings were also reflected in the five-year age standardized relative survival analysis where patients in the most deprived districts were found to also have the worst five-year age-adjusted relative survival (50.8%) versus (56.7%) for those in the most affluent districts. The mediation analysis showed that most of the effect of deprivation on survival was mediated through differential stage at diagnosis during the first six months after HNC diagnosis. Differences in the treatment modalities received by the patients and the number of hospital beds available within a district played a minor role in the survival inequality.

In this chapter, we will discuss the main findings of our studies in relation to the current literature while providing possible explanations to the observed inequality. Furthermore, we will address the strengths and limitations concerning our results and we will provide recommendations for new policies and future research.

2.1 Survival disparity

2.1.1 Inequality in endometrial cancer survival

In Germany, only three large-scale studies investigated the effect of area-based socioeconomic inequality on cancer survival on a nationwide level [69-71]. In 2021, Jansen et al. reported the five-year age-standardized relative survival of patients diagnosed with Corpus Uteri cancer, among other cancer sites, during the period between 2013 and 2017. The study was based on 200 administrative German districts representing approximately 39% of the entire population. Similar to our results, the authors found no significant differences in terms of net survival between the most deprived (80.3%) and the most affluent patients (81.6%). These estimates were similar to the rates reported by Jansen et al. in 2014.

The relative excess risk (RER) estimates reported, showed the most deprived patients to have an increased RER of death [1.11; 95% Confidence Interval (CI) (0.99–1.25)] (adjusted for age) compared to the least deprived. These finding were similar to those reported by Finke et al., who also found the most deprived EC patients to have a slightly increased RER of death [1.08; 95% CI (0.91–1.30)] (adjusted for age and stage) compared to the least deprived.

Both studies used the GIMD as their measure for deprivation on the municipality level and both studies did not adjust for tumor characteristics (grade and type), nor did they adjust for treatment information.

Studies in neighboring European countries, where a similar universally accessible health care system exists, also investigated this survival inequality. A study recently published from France in 2019, found that the five-year age-standardized net survival of EC patients living in the most deprived areas to be 72.8% compared to 77.7% for EC patients living in the most affluent areas [74]. This study used the European Deprivation Index (EDI) as a measure for area-based deprivation. In another study, EC patients from lower socioeconomic groups in North West of England were found to have a 53% [adjusted Hazard Ratio = 1.53; 95% CI 0.77–3.04)] increase in cancer-specific mortality when compared with affluent patients while reporting no differences in overall survival between the two groups [75]. Another study conducted in Denmark during 1994–2003 concluded that increased excess mortality rates from endometrial cancer were associated with low educational level, mainly during the first year after diagnosis [76].

Possible causes

In our study, we found almost 80% of all cases to be diagnosed at stage I regardless of the level of deprivation. Among those patients, those living in the most deprived districts showed the highest hazard of overall mortality when compared to patients living in the most affluent districts [HR 1.20; 95% CI (0.99–1.47)].

This high proportion of stage I patients suggests that differential stage at diagnosis seemed to play a minor role in the survival inequality, possibly due to the early onset of observable symptoms, such as abnormal bleeding, that is usually present in that stage. In our analysis, we considered other explanations such as differences in age, gender, tumor characteristics, or the treatment received. These factors, however, did not explain the measured survival inequality among early-stage EC patients.

Since surgery is often the preferred treatment and most patients are diagnosed early, we think that socioeconomic deprivation and behavioral factors such as obesity and physical inactivity may be major contributing factors to the survival inequality. In a systematic review, Donkers et al. appeared to reach a similar conclusion [77]. The authors found that regardless of stage at diagnosis, socioeconomic deprivation seemed to affect survival in endometrial cancer patients through factors like body mass index (BMI), age, smoking and comorbidities.

In the latest version of the German Health Update (GEDA) 2019/2020-EHIS study, obesity, defined as (BMI ≥30 kg/m2), was found to be significantly more common in participants from a lower educational background. More than twice as many women in the low education group compared to the high education group were considered obese [78]. Linking the GISD to the municipalities in the which the GEDA responders lived in, low levels of leisure-time physical activity (<10 minutes of leisure-time physical activity per week) and obesity were found to be significantly more prevalent in municipalities with higher levels of socioeconomic deprivation than in those with lower levels of deprivation [16].

Morbidly obese women with endometrial cancer could be more likely to die of obesity-driven health problems such as type II diabetes and heart disease, or other cancers when compared to patients with lower BMI values [39, 79, 80]. Obesity-driven comorbidities could also significantly increase the risk for perioperative morbidity. Hence, a surgical procedure which minimizes duration under anesthesia and operative morbidity is usually recommended. The high prevalence of obesity and low physical activity among EC survivors is further supported by studies that have found that while EC survivors have a good cancer prognosis with the potential for long-term survival, most obese EC survivors do not adopt weight loss or healthier lifestyle modifications which puts them at risk for morbidity and mortality [81, 82].

2.1.2 Inequality in head and neck cancer survival

Referring to the two recent large-scale studies conducted in Germany, Jansen et al estimated the five-year age standardized relative survival of patients diagnosed with oral and pharynx cancer (ICD-10 (C00-C14)) during the period between 2013 and 2017, to be 49.9% for cases living in the most deprived districts versus 58.5% for the most affluent patients. Furthermore, the authors found the most deprived patients to show a significantly high RER of death [1.35; 95% CI (1.27–1.44)] compared to the least deprived. Supporting our results, Finke et al. also found the most deprived patients to show an increased RER of death [1.45 95% CI (1.39–1.52)] (adjusted for age and stage) compared to the least deprived cases.

In addition to the previously mentioned differences in methodology, it is also important to note that oral and pharynx cancer is a subset of HNC. In our study, we included ICD-10 (International Classification of Diseases, Tenth Revision codes) (C00-C14) which represented the following sites: the tonsils (C09), the base of the tongue (C01.9, C02.4), other oropharynx sites (C10), Waldeyer's ring (C14.2), the gum (C03), the floor of the mouth (C04), the palate (C05), other and unspecified parts of the mouth (C06), the pyriform sinus (C12), and the hypopharynx (C13). Cancers arising from the lip (C00), the nasopharynx (C11), the nasal cavity (C30), the sinuses (C31), and the salivary glands (C07-08) were not included in the analyses as they are linked to other etiological factors or to ill-defined sites (C14.0, C14.8).

In France, the five-year age standardized net survival measured for HNC patients living in the most deprived areas was 38.1% versus 49.7% for patients living in the most affluent regions [74]. Another study in France, estimated that for HNC patients living in the most deprived areas, the odds of dying was significantly higher [Odds Ratio = 1.98; 95% CI = 1.64–2.41)] compared with those living in the most affluent ones [83]. The authors also found that the influence of area-based socioeconomic status, measured by EDI, remained after controlling for individual socioeconomic characteristics.

Another study conducted in Belgium showed similar results. HNC mortality rates were found to be significantly higher for men living in deprived areas highlighting a significant regional disparity. Both individual and area-level deprivation were found to be important determinants of HNC mortality.

Possible causes

In comparison to EC, HNC varies greatly with respect to stage at diagnosis distribution. Almost 70% of the patients in our sample were diagnosed at later stages III-IV. This is mainly due to HNC's aggressive nature and the lack of symptoms in early stages. HNC also differs with regard to treatment. Treatment plans depend strongly on the size and anatomical site of the primary cancer, stage of disease, age of the patient, patient preferences, performance status, and coexisting conditions. Given the complex nature of HNC in contrast to EC, we decided to conduct a mediation analysis, where we were interested in measuring the effect of three potential mediators: medical care, stage at diagnosis, and treatment. Our study revealed that the total effect of deprivation seemed to be strongest during the first six months after diagnosis and that differential stage at diagnosis mediated most of that effect.

An early HNC diagnosis is especially critical considering the unfavorable prognosis and low survival rates that were demonstrated in our results and other studies. Considering the lack of an effective screening procedure to diagnose HNC lesions at the earliest stages, the role of oral health professionals in the early detection of oral cancer and management has been highlighted in recent years [84, 85]. Routine dental visits were found to be associated with a decreased risk of HNC [86-88]. Furthermore, oral hygiene and routine dental visits are strongly depended on socioeconomic factors [89, 90].

In Germany, studies have recorded significant inequalities in health care utilization [91, 92]. Patients from lower socioeconomic groups have been found to visit specialist practitioners less frequently, when compared with groups that are more affluent [93]. Furthermore, results from a systematic review by Klein et al., suggested that major inequalities result primarily from inadequate prevention strategies, such as cancer screening [94]. Additionally, German residents with a public health insurance option were estimated to wait three times longer for an appointment in comparison to residents with a private health insurance [95].

After the first six months, no effect was mediated by the three mediators, yet the survival disparity between the most deprived and most affluent remained substantial after five years. We believe this could be attributed to lifestyle-related factors such as smoking and alcohol consumption. Similar to obesity and physical inactivity, the proportion of current smokers was found to be higher in German municipalities that were more socioeconomically deprived [16, 96].

Studies have shown that persistent smoking may decrease the chances of survival among HNC patients through several pathways. Smoking was found to increase the risk of wound complications, general and pulmonary infections, neurologic complications, admission to an intensive care unit, and systemic perioperative complications within 30 days after a surgical intervention [97, 98]. Several studies have also reported that smoking before and/or during radiotherapy is associated with lower rates of response and survival [99-101]. Smoking also increases the risk of developing secondary primary tumors [102].

Other lifestyle factors such as diet, alcohol consumption, and body mass index have also been reported to be associated with survival in patients with head and neck cancer [103, 104]. Another possibility could be the HPV status of the diagnosed tumors. HPV-positive oropharyngeal carcinoma is associated with better response to treatment and better survival [105, 106]. Since our dataset was missing this information, we performed a sensitivity analysis based on HPV related-tumor sites, which we considered as a proxy for the missing HPV status. We found no significant differences in tumor-site proportions according to deprivation, nor did our results change when we included tumor site as an additional confounder.

2.2 Strengths and limitations

The main strength of this thesis is its attempt to thoroughly investigate the association between area-based socioeconomic deprivation and EC and HNC survival, while addressing the different natures of both cancers. To the best of our knowledge, both publications included in this dissertation, were the first to focus on those cancers in Germany. In the following sections, we present other strengths and limitations of the methods and statistical analysis used in the included studies.

2.2.1 Cancer registry data

Population-based cancer registries are crucial sources of information for cancer epidemiology and health services research. Following the enactment of the Federal Cancer Register Data Act (Bundeskrebsregisterdatengesetz, BKRG) in 2009, the German Center for Cancer Registry Data (Zentrum für Krebsregisterdaten, ZfKD) was set up at the Robert Koch-Institute to annually collect anonymized incidence and survival data from all the federal states' population-based cancer registries [107]. The data then undergoes quality checks before being pooled to be freely available for nationwide and regional analyses.

To further ensure data quality, we measured the overall proportion of death certificate only (DCO) cases to make sure that the proportion in the included registries did not exceed 13% as recommended by the European Cancer Registry-Based Study on Survival and Care of Cancer Patients (EUROCARE-5 study) [108].

The pooled dataset, on which our publications were based upon, represented a significant proportion of the German population from both former East and West German states. This adds to the importance of the thesis, since our findings could be considered nationally representative. Furthermore, the dataset included key information on demographics such as gender, month and year of birth, and area of residence; data about the tumor at time of diagnosis including date of diagnosis, tumor topography and morphology, and tumor grading and stage; and data on delivered treatments, death events, and cause of death for deceased cases.

Even though this rich source of information on cancer patients enabled us to measure the effect of several factors on survival, other important variables were missing. Missing details on the date and intent of treatment, the administered radiation doses, and the type of chemotherapy received by the patient were essential to be able to differentiate between treatment regiments. This limitation should be considered when interpreting our results. In addition, key information on comorbidities or lifestyle related risk factors such as smoking, alcohol consumption, diets, physical activity, and obesity that have been proven to be directly related to socioeconomic status as well as cancer survival in general, were also not available. We consider the lack of information on these important variables to be our main limitation.

2.2.2 Area-based socioeconomic index

In this thesis, we used the GISD as the measure for area-based socioeconomic deprivation. The German Index of Socioeconomic Deprivation has contributed to the existing literature that aims to explain regional health differences through investigating the links between social inequalities and health in Germany. While the index has been used extensively in previous research, some important points need to be discussed to facilitate the interpretation of our findings.

The index measures deprivation at different spatial levels. In this study, it was used at the district level because this was the smallest spatial level that could be analyzed using the pooled cancer registry data. This could be considered a limitation because of the relatively larger size of some districts, in comparison to municipalities. The potential lack of homogeneity within a certain district could increase the risk of false conclusions [109]. It should also be noted that socioeconomic indices should only be considered as a tool to identify socioeconomically deprived regions and that they do not provide insights on an individual's socioeconomic status [7, 110, 111]. Potential misclassification due to grouping individuals with a higher socioeconomic position into the most deprived socioeconomic quintile because they live in a district where the majority of its residents have a lower socioeconomic status is therefore unavoidable. Consequently, it should be understood from our results that it is not individuals of low or high socioeconomic status, but rather patients *living* in deprived or affluent districts, that have higher or lower chances of cancer survival.

As explained earlier, the GISD is based on three dimensions: education, income, and employment, which are widely considered as central defining factors for socioeconomic status and the core dimensions of social inequality [112, 113]. The included indicators, within each dimension, were weighted using factor analysis, which was the same approach used in creating indices in New Zealand, Canada, Spain, and Denmark [14, 114-116]. Being based only on those dimensions, also makes our results easier to interpret in comparison to indices of multiple deprivation that include indicators going beyond socioeconomic ones, such as social capital, the share of single-parent households, crime rates, the physical environment or morbidity [117, 118]. Using multiple deprivation indices may help to explain variations in healthcare needs among different regions, but they may not be very useful for epidemiological research because they do not clearly distinguish between the factors that influence health and the effects of diseases [119]. Another clear advantage of the GISD is that it is publicly available at the GitHub repository, which is not the case with the GIMD.

Due to the lack of access to individual data because of Germany's strict data protection regulations, the index should be seen as a complement to the data on individual socioeconomic status and therefore be used to reveal the extent of health inequalities while providing enough evidence to motivate the collection of individual data.

2.2.3 Statistical analysis

Our analysis included a large sample of 42,423 endometrial and head and neck cancer patients (21,602 and 20,821 patients, respectively) diagnosed over a relatively long time-period (2004-2014 and 2009-2013, for EC and HNC patients respectively). We were able to describe and visualize the overall survival for both groups of patients according to their level of deprivation using Kaplan-Meier curves. Kaplan-Meier (KM) survival analysis is a powerful method of measuring survival rates [120]. KM curves visually demonstrate the probability of survival of a group of people against follow-up time, while taking into account that the date of entry of each person in the study is different. The reported five and ten-year overall survival probabilities were based on the KM estimates.

To be able to identify the underlying reasons behind the potential disparity, we conducted a stratified Cox proportional hazard regression analysis. The Cox proportional hazards model is a semiparametric model that enables researchers to study the dependency of survival time on predictor variables [121]. In our study, we used different models to adjust for patient and tumor characteristics, in addition to treatment information, for each stage of diagnosis separately. We viewed this approach as necessary since 77% of our sample was diagnosed at stage I and fewer patients were diagnosed at later stages across the five quintiles.

HNC on the other hand, is a much more complex disease, with a more varied distribution of stage at diagnosis. A different analytical approach addressing the different nature of HNC was therefore required. We first measured the relative survival rates for HNC to acknowledge their shorter overall survival rates. Relative survival is defined as the excess mortality between the observed mortality of a group of people under investigation and the expected mortality of a disease-free group in the population with the same demographic characteristics as the study group [122]. Relative survival is useful when cause of death information is unknown and provides a more accurate representation of the mortality from a disease of interest by disentangling other causes of death. Expected survival was estimated according to the Ederer II estimator using population life tables stratified by age, sex, and calendar period [123]. The estimates reported were adjusted to the International Cancer Survival Standards [124].

Furthermore, we presented a Directed Acyclic Graph (DAG) to visually illustrate the causal relationship between deprivation and survival. The DAG also demonstrated the different pathways through which other variables could mediate the measured effect. A directed acyclic graph is composed of variables (nodes) and arrows between nodes (directed edges) such that it is not possible to start at any node, follow the directed edges in the arrowhead direction, and end up back at the same node. DAGs are currently being used extensively in epidemiologic research to help determine mediators and the confounding variables that are necessary to control for [125].

In our study, the DAG presented three potential mediators: medical care, stage at diagnosis, and treatment received. This warranted a mediation analysis based on the counterfactual framework [126]. The counterfactual approach, as described by Pearl, helped us separate the indirect effects that operate through each of the aforementioned mediators from the remaining direct effect and to quantify their respective contribution towards the overall total effect. In other words, "How would the survival of patients living in the most affluent districts be affected, had they moved to the deprived districts, while keeping their level of medical care, stage at diagnosis, and treatment received unchanged and adjusting for age, sex, and year of diagnosis?". We measured the indirect effect of our mediators, by changing the values of one mediator at a time to resemble that of our comparator group (patients living in the more deprived districts).

To be able to achieve this "four-way decomposition" (direct effect of deprivation + three indirect effects for each mediator), we conducted a flexible mediation analysis [127]. We first had to extend our dataset by replicating the observed dataset eight times. We then weighed our extended dataset, by the ratio of densities of the mediators whose corresponding models we believed were less prone to misspecification (medical care and treatment received). An extended version of the outcome model (natural effect model) was then fitted to the original data by regressing imputed nested counterfactuals using our pre-calculated weights. To obtain population-average analogs (rather than effects adjusted on the set of confounders), we updated the weights by inverse probability weighting. Inverse weighting enables transporting results to the entire target population. Finally, a total of 1,000 bootstrap samples were drawn to calculate 95% (standard normal) bootstrap confidence intervals. This procedure was repeated for each of the previously mentioned time points and only two quintiles were compared at a time.

We controlled for missing stage and treatment information, by including only complete cases in our main analyses. To assess the robustness of our results, we conducted several sensitivity analyses to measure the potential bias resulting from the missing variables. In both studies, we imputed missing stage information using multiple imputation-chained equations and repeated the statistical analysis. On the other hand, we were not able to impute missing treatment information. Treatment plans depend on many variables, such as comorbidities and patient preferences, that were not available in our dataset. However, we conducted a stepwise logistic regression to help identify variables, in our dataset, that were associated with the missing variable. Furthermore, we recoded patients with missing treatment information as patients that did not receive treatment to address the unstandardized process of recording treatment information across the included registries. Our main conclusions were largely unchanged.

All analyses were conducted in R statistical software version 3.2.3 [128].

2.3 Recommendations

2.3.1 Prevention of risk factors

Tobacco consumption

The association between smoking and head and neck cancer has long been documented in the literature [129]. While cessation does decrease the risk over time, it never reaches the level of a never-smoker, thus highlighting the importance of implementing effective prevention measures for tobacco consumption [55].

Since the early 2000s, several measures were introduced to decrease the burden of smoking on the German health care system that was estimated to reach 30 billion euros [130]. In addition to significantly increasing taxes on tobacco, Germany also introduced several smoking bans on both the federal and state level [131]. Despite the success of these measures in producing a general decline in adult smoking, inequalities in smoking rates based on factors such as income, education, and occupation have persisted and even increased, particularly among women [16, 96]. More alarming are the results from the recent COSMO (COVID-19 snapshot monitoring) study, which suggested that the spread and the frequency of the consumption of tobacco and electronic cigarettes has started to increase again during the Covid-19 (Coronavirus disease 2019) pandemic [132].

The high burden of smoking has led the German Cancer Research Centre (DKFZ), together with more than 50 health organizations, to present the ‘strategy for a tobacco-free Germany 2040’ [133]. The main goal of this strategy is to reduce the consumption of tobacco products and electronic cigarettes to less than five percent among adults and to less than two percent among adolescents, by 2040. These actions, along with smoking cessation programs, need to be supported with the aim to improve health and reduce inequalities in the general public.

Obesity and physical activity

As explained in the previous chapters, obesity is considered the main risk factor for developing EC. The prevalence of obesity in Germany is 23% among adults and 6% among children [78]. As rates of obesity among women continue to rise, the incidence of endometrial cancer is bound to increase [134]. Endometrial cancer survivors have a good cancer prognosis with the potential for long-term survival. However, not adopting a healthier lifestyle puts most endometrial cancer survivors at risk for morbidity and mortality [82].

In 2008, the direct health-related cost of excessive consumption of sugar, fat, and salt in Germany was estimated to be 17 billion euros [135]. In the same year, Germany launched the National Action Plan "IN FORM" to promote physical activity and healthy dietary options [136]. The main objective of the national plan was to reduce the burden of chronic diseases caused by unhealthy lifestyle behaviors. Further efforts to promote healthier diets on the population level included a National Reformulation and Innovation Strategy for Sugar, Salt and Fat in Processed Foods and the recent introduction of the Nutri-Score nutrition labelling system. In addition, the founding of a new national nutrition education and information center (Bundeszentrum für Ernährung, or BZfE) aimed to improve the quality of food served in schools and kindergartens through information and practice [137].

These nutrition policies and programs were assessed by von Philipsonborn in a study published in 2021 [138]. Their results showed that Germany still lags behind significantly in several key policy areas. Adopting international practices in areas such as the regulation of food advertising, unhealthy food taxation, and the promotion of a healthy food supply in retail could help to reduce the burden of diet-related chronic illnesses and health related inequalities in Germany.

Further efforts by academics and policy makers targeted at promoting physical activity and healthier dietary options are warranted.

2.3.2 Socioeconomic reform

After the German reunification in 1990, East Germany went through intense socioeconomic and political reform that has led to the convergence of the sizeable mortality gap previously observed between the two German states [139]. Investments in the health care sector, social welfare, and pension benefits are widely considered the main contributing factors for this convergence [140, 141]. While the east–west mortality rates among women have fully converged, a gap can still be observed among males. Other studies have also hinted that a developing north-south divide could alter future trends in regional cancer-related mortality in Germany [142].

The reasons behind these regional differences are still not fully understood. Recent studies provide some evidence that economic factors, as well as differences in lifestyle behavior, have been especially important contributors [143]. The role of economic factors is supported by the evident differences in the economic power between the Northeastern and Southwestern states. The Northeastern federal states of Berlin and Saxony-Anhalt for instance, recorded the highest unemployment rates in 2017 (7.9% and 7.5% respectively), whereas the Southern states of Bavaria and Baden Wuerttemberg reported the lowest employment rates in Germany.

Possible explanations for this economic divide include the absence of large industries and the lower population density in the Northeastern region [144]. As a result, younger, healthier, well- educated adults have migrated to the Southern states seeking better job opportunities.

Regions characterized by high levels of unemployment and lower levels of education have been linked to higher proportions of premature deaths, high smoking and alcohol consumptions levels, obesity, and low physical activity [16, 29].

Substantial investments in the labor market to limit the migration of highly educated young people across Germany could help narrow the economic gap and rebuild communities. German health policies should also promote better access to medical care in regions with a lower population density, while focusing on implementing policies aimed at controlling lifestyle risk factors.

2.3.3 Impact of COVID-19 on screening and treatment

The speed and scale of the global COVID-19 pandemic has resulted in an unprecedented pressure on the German health care system. Since the country went into lockdown, elective surgeries and non-urgent clinical visits were cancelled to direct the existing intensive care capacities to COVID-19 patients [145, 146]. Even though these measures proved to be effective in reducing the number of new infections, they may however, have affected the diagnosis of other major medical conditions. Several studies have indicated that the incidence of certain cancers, particularly those detected through screening programs, has decreased during the lockdown [147-149]. In Germany, the Bavarian Cancer Registry recorded a significant decrease in diagnoses and surgical procedures during the period between January and September 2020 exclusively in stage I cancer patients [150].

These findings are alarming since prompt screening and early diagnosis are crucial for better response to treatment and higher chances of survival. Considering the current lack of information, it is therefore vital that studies continue investigating the full impact of COVID-19 on cancer screening and treatment facilities.

2.3.4 Linkage of data

Linking the German cancer registry data to other databases that include more information regarding individual socioeconomic factors, prognostic factors, biomarkers, and comorbidities will help provide a clearer picture of the potential underlying causes of the survival disparity. In an attempt to extend the current scope of the current registries, the new amendment to the Act on Cancer Registry Data stipulated that extensive data on therapy and disease progression should be merged nationwide at the ZfKD by the end of 2022. Researchers would then be able to apply for the extended dataset, through the ZfKD, by 2023 [49].

Merging the extended dataset with other sources, such as health insurance data or information collected from the German National Cohort (NAKO) study could prove beneficial. The NAKO is a population-based cohort study that includes more than 200,000 participants with the aim to identify risk factors for chronic diseases such as cardiovascular diseases, diabetes, cancer, and neuropsychiatric, infectious, and musculoskeletal diseases [151]. The German cancer registries are already involved in the NAKO study, by providing information on the incidence of new cancers among participants who have consented to such data linkage.

Standardizing the data across the federal states and recording it in a manner that enables it to be linked to other external sources, would help improve cancer research in general.

2.4 Conclusion

This thesis has provided a comprehensive examination of socioeconomic inequalities in survival of people with endometrial and head and neck cancer. First, a broad summary of the history of area-based socioeconomic deprivation indices was provided, as well as an overview of the current literature where different indices were used to describe the cancer survival disparity in Germany. The publications included in this thesis, involved in-depth analyses using German cancer registry data and addressed the different characteristics of both cancers. It also attempted to highlight which groups are most affected and when were they most vulnerable to the influence of the survival disparity. Our results suggested that socioeconomic disparity and lifestyle factors could have contributed the most towards the survival inequality experienced by stage I EC patients. As for HNC patients, our study found that early detection in deprived districts could eliminate a large portion of the survival inequality experienced during the first six months after diagnosis. Based on our results, we presented a number of recommendations with regard to prevention measures and further socioeconomic reform. The findings of this dissertation indicate that future cancer research in Germany should consider individual socioeconomic information, prognostic factors, biomarkers, complete data on cancer treatment, comorbidities, and area-based indices in order to better understand and reduce survival disparities. Future studies should also take into account the unique characteristics of different cancer types in their analyses. Through this dissertation, we presented a framework for policy and future research to help improve outcomes for cancer patients and reduce inequalities in survival.

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4. Theses

(1) Area-based socioeconomic deprivation refers to the potential effect experienced by a group of people with similar socioeconomic circumstances living in nearby areas. In an effort to monitor and measure regional inequalities in Germany, the Robert Koch Institute developed the German Index of Socioeconomic Deprivation (GISD). The GISD is a composite index based on employment, income, and education indicators. Regions recording a higher level of deprivation, as measured by the GISD, have been linked to higher rates of mortality, smoking, obesity, physical inactivity, and cancer incidence.

(2) In a sample of 21,602 German endometrial cancer patients diagnosed during 2004-2014, only stage I patients were found to be affected by socioeconomic deprivation. Cox regression models showed stage I patients living in the most deprived districts to have a higher hazard of overall mortality when compared to the cases living in the most affluent districts [Hazard Ratio: 1.20; 95% Confidence interval (0.99–1.47)]. This association could not be explained by differences in age, sex, tumor characteristics, or treatment.

(3) In a sample of 20,821 head and cancer patients diagnosed in 2009–2013, patients in the most socioeconomically deprived districts were found to have the highest hazard of dying when compared to patients living in the most affluent districts [Hazard Ratio: 1.25; 95% Confidence interval (1.17–1.34)]. The mediation analysis performed showed that most of the effect of deprivation on survival was mediated through differential stage at diagnosis during the first 6 months after HNC diagnosis. As follow-up time increased, medical care, stage at diagnosis, and treatment played no role in mediating the effect of deprivation on survival

(4) While German cancer registries are a reliable source of high-quality data, it also lacks key information on treatment, individual socioeconomic factors, and comorbidities.

(5) Area-based socioeconomic deprivation indices should be seen as a complement to individual data and should motivate the collection of individual data.

(6) Efforts to reduce tobacco consumption and promote physical activity and healthier diets could help reduce the observed survival disparity. Furthermore, socioeconomic reform has been proven to effectively converge mortality rates across Germany.

Publications

Copyrights

List of included publications and posters presented at conferences

(1) **Bedir, A.,** Abera, S.F., Vordermark, D., Medenwald, D.. Socioeconomic disparities in endometrial cancer survival in Germany: a survival analysis using population-based cancer registry data. *Journal of Cancer Research and Clinical Oncology* 148, 1087–1095 (2022). https://doi.org/10.1007/s00432-021-03908-9

(2) **Bedir, A.,** Abera, S.F., Efremov, L, Hassan, L, Vordermark, D, Medenwald, D. Socioeconomic disparities in head and neck cancer survival in Germany: a causal mediation analysis using population-based cancer registry data. *Journal of Cancer Research and Clinical Oncology* 147, 1325–1334 (2021). https://doi.org/10.1007/s00432-021-03537-2

(3) **Bedir, A.,** Abera, S.F., Vordermark, D., Medenwald, D.. Socioeconomic disparities in endometrial cancer survival in Germany: a survival analysis using population-based cancer registry data. *Die Deutsche Gesellschaft für Radioonkologie (DEGRO) 2022.*

(4) **Bedir, A.,** Vordermark, D, Medenwald, D. Socioeconomic disparities in head and neck cancer survival in Germany: a causal mediation analysis using population-based cancer registry data. *Deutscher Krebs Kongress (DKK) 2020.*

Declaration of contribution as an Author

I have contributed to the conception and design of the work, formulation of the research questions, and the planning of the statistical analysis. I conducted all the statistical analysis and interpreted the results. I wrote both manuscripts myself as first author. Along with Daniel Medenwald and the co-authors, we revised the manuscript. I was responsible for the whole submission process until the manuscript was published.

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ORIGINAL ARTICLE – CANCER RESEARCH

Socioeconomic disparities in endometrial cancer survival in Germany: a survival analysis using population-based cancer registry data

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Abstract

Purpose Area-based socioeconomic deprivation has been established as an important indicator of health and a potential predictor of survival. In this study, we aimed to measure the effect of socioeconomic inequality on endometrial cancer survival.

Methods Population-based data on patients diagnosed with endometrial cancer between 2004 and 2014 were obtained from the German Centre for Cancer Registry Data. Socioeconomic inequality was defined by the German Index of Socioeconomic Deprivation. We investigated the association of deprivation and overall survival through Kaplan–Meier curves and Cox proportional regression models.

Results A total of 21,602 women, with a mean age of 67.8 years, were included in our analysis. The observed 5-year overall survival time for endometrial cancer patients living in the most affluent districts (first quintile) was 78.6%. The overall survival rate decreased as the level of deprivation increased (77.2%, 73.9%, 76.1%, 74.7%, for patients in the second, third, fourth, and fifth quintile (most deprived patients), respectively). Cox regression models showed stage I patients living in the most deprived districts to have a higher hazard of overall mortality when compared to the cases living in the most affluent districts [Hazard ratio: 1.20; 95% Confidence interval (0.99–1.47)] after adjusting for age, tumor characteristics, and treatment.

Conclusion Our results indicate differences in endometrial cancer survival according to socioeconomic deprivation among stage I patients. Considering data limitations, future studies with access to individual-level patient information should be conducted to examine the underlying causes for the observed disparity in cancer survival.

Keywords Endometrial cancer · Socioeconomic deprivation · Survival analysis

Introduction

Endometrial cancer (EC) is the most commonly diagnosed gynecological cancer in Germany, with 12,356 new cases and 2444 deaths being reported in 2020 alone (Sung et al. 2021). According to the International Agency for Research on Cancer, the incidence of EC is projected to rise up to 5% within the next 10 years (Ferlay et al. 2020). While the 5-year relative survival rate is estimated to be about 78%, few studies have investigated potential regional differences concerning EC survival within Germany (Robert-Koch-Institut 2019).

In a recent study by Finke et al., the majority of cancer patients living in the most socioeconomically deprived municipalities were found to have significantly lower survival compared to the most affluent patients in Germany (Finke et al. 2021). These findings confirm the survival disparity reported in previous studies (Brenner et al. 1991; Jansen et al. 2014, 2020, 2021). In regard to EC, social deprivation could affect clinical outcomes on several levels from early pathogenesis to stage at diagnosis and treatment. Important risk factors such as obesity, comorbidities, and smoking are especially prevalent in deprived populations (Amant et al. 2005; Arem and Irwin 2013; Bouwman et al. 2015; Donkers et al. 2020; Dragano et al. 2007). Moreover, the availability and access to care could prove to be crucial to women diagnosed at later stages when a more complex treatment plan is required (Network 2021).

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Table 1 Description of the cancer registries and administrative districts included in our analysis, 2004–2014

Cancer registry	Population (Million in 2017)	% DCO Cases	Cases[a]	Mean GISD of included districts (SD)	Number of included districts
Nordrhein-Westfalen	17.91	3.1%	5339	0.62 ± 0.13	53
Hessen[b]	6.29	8.3%	635	0.51 ± 0.16	26
Bayern	13.14	3.8%	2892	0.50 ± 0.12	84
Brandenburg	2.53	1.1%	2129	0.80 ± 0.11	18
Mecklenburg-Vorpommern	1.61	2.0%	1134	0.87 ± 0.05	8
Sachsen	4.06	0.7%	4859	0.75 ± 0.08	13
Sachsen-Anhalt	2.18	2.8%	2073	0.88 ± 0.06	14
Thüringen	2.12	2.2%	2547	0.76 ± 0.10	23
Total	49.84	3.2%	21,602	0.63 ± 0.18	239

DCO death certificate only, *GISD* German Index of Socioeconomic Deprivation, *SD* standard deviation

[a]Final number of cases diagnosed with endometrial cancer, 2004–2014, after excluding DCO and autopsy-only cases

[b]Patients diagnosed in Darmstadt, Hessen before 2007 were not available in the respective cancer registry data

Considering the impact of area-based socioeconomic deprivation and how it is considered today as an important indicator of health (Diez Roux 2016; Marmot et al. 1987; Pickett and Pearl 2001), it is therefore, our aim to explore survival inequalities related to EC. Using data from German population-based cancer registries, we measured the association between area-based socioeconomic deprivation and endometrial cancer survival on the district level. Furthermore, we examined whether this association depended on the age at diagnosis, tumor characteristics, or the cancer therapy received.

Materials and methods

Data source and study population

This retrospective study is based on population-based cancer registry data from 8 out of 16 German federal states (Nordrhein-Westfalen, Hessen,[1] Bayern, Brandenburg, Mecklenburg-Vorpommern, Sachsen, Sachsen-Anhalt, and Thüringen) covering a population of 49.9 million people (~ 59% of the total German population). The data was pooled and provided by the German Centre for Cancer Registry Data at the Robert Koch Institute (RKI) (https://doi.org/10.18444/5.03.01.0005.0015.0001) (Hiripi et al. 2012). The overall proportion of death certificate only (DCO) cases in the period 2004–2014 was calculated to ensure that the proportion in the included registries did not exceed the recommended 13% (Rossi et al. 2015) (Table 1).

Women at the age of 18 years or older with a primary diagnosis of endometrial cancer (International Classification of Diseases for Oncology topography codes C541) diagnosed during 2004–2014 were included in this analyses. Follow-up as recorded in the registries ended in December 2014. Cases notified by autopsy only or by death certificate only (DCO) were excluded. Only complete cases were included in our analysis.

Exposure and outcome

The exposure of interest was the socioeconomic deprivation level of the respective case, which was determined by the German Index of Socioeconomic Deprivation (GISD) (Kroll et al. 2017) allocated to the residential district of the case at the time of diagnosis.

The GISD is a composite index of three equally weighted socioeconomic domains: income, education and employment. The income dimension is based on the mean net household income, tax revenues, and debtor quotas within a given district. The educational component is defined by the proportions of employees in the district with (and without) a university degree, school dropouts without a degree, and school dropouts with the German "Abitur" or equivalent. Finally, the employment dimension is measured through the local unemployment rate, average gross wage of employees, and the labor force participation rate. The index ranges on a scale of zero to one, with zero representing the lowest level of socioeconomic deprivation (most affluent) and one representing the most socioeconomically deprived districts. The indices were then categorized into five quintiles [Q1 (least deprived)-Q5 (most deprived)].

[1] Information on cases from Darmstadt, a city in the state of Hessen with a population of 159,207 (2019), was not available in the Hessen cancer registry data prior to 2007.

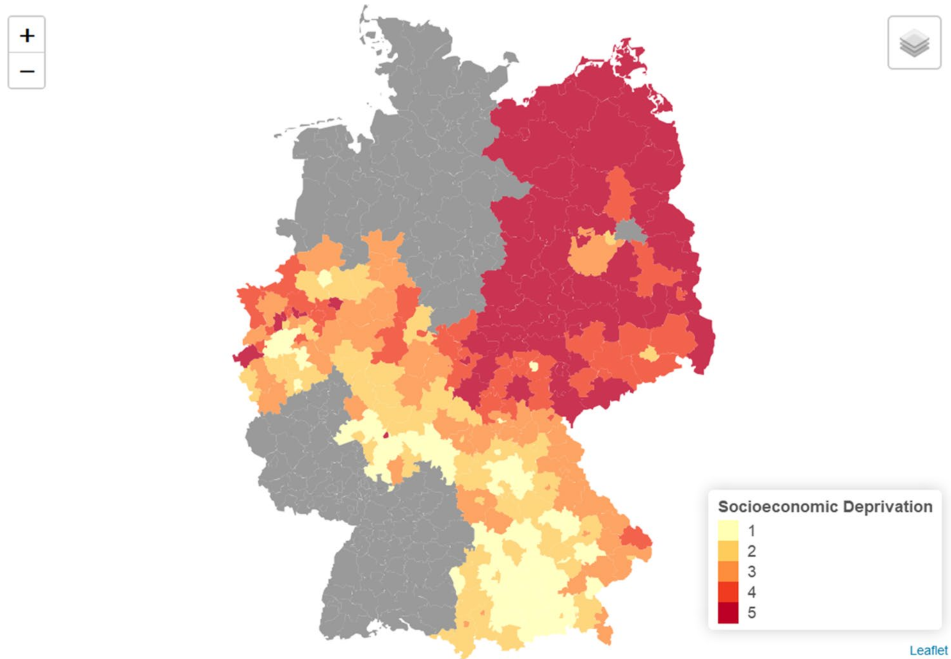

Fig. 1 Map of Germany with districts included in the analysis, colored according to their mean level of socioeconomic deprivation over the study period, 2004–2014. Quintiles are listed in ascending order according to deprivation (quintile five = most deprived)

In the end, 239 districts out of 401 German districts were included in our study after being linked with the pooled registry dataset (Fig. 1).

The primary outcome measured was overall survival (OS). Overall survival was computed from date of cancer diagnosis to date of death from any cause. Vital status was ascertained using death certificates and information from the registration offices. Patients lost to follow-up before death or still alive at the last vital status assessment were right-censored at the date of the last vital status assessment or at the censor date (December 2014), whichever came first.

Covariates

The pooled dataset contained information on grading and histology, TNM (tumor–node–metastasis) stage, cause and date of death, date of birth and date of diagnosis, and treatment. We categorized stage at diagnosis into four groups based on the TNM cancer staging system (Edge et al. 2010). We also classified endometrial carcinoma according to its two subtypes: I (low-grade) and II (high-grade). Type I included endometrioid adenocarcinoma and its variants: villoglandular, secretory, with ciliated cells, adenocarcinoma with squamous differentiation, and other unspecified adenocarinoma variants (histology codes 8380, 8382, 8383, 8480–8482, 8210, 8140, 8560, 8570). Type II histologies included serous, clear cell, mixed cell, small cell, and squamous cell adenocarcinomas (codes 8440, 8441, 8460, 8461, 8310, 8323, 8041, 8070, 8071, 8076) (Amant et al. 2005). Furthermore, we considered type I cases with grade 3 or worse, as type II cases.

Information on treatment was available as dichotomous variables (surgery yes/no, radiotherapy yes/no, chemotherapy yes/no). Details on administered radiation doses, specific chemotherapy treatment, or date of treatment were not available.

Statistical analysis

Demographic and clinical characteristics according to deprivation quintiles were described using common descriptive statistics. The observable 5- and 10-year overall survival rates (OS) for each quintile was calculated and visualized by the Kaplan–Meier estimates and curves. Multivariate analysis was performed using the Cox proportional hazards model to investigate the association between area-based deprivation and survival. The hazard ratio (HR) and 95% confidence interval (CI) were reported using the most affluent quintile (Q1) as the reference group. The potential impact contributed by our covariates to the survival disparity between the quintiles was assessed by entering these factors sequentially into our cox proportional hazards models. The base model included adjustment for age and year of diagnosis. We further adjusted for subtype and grading, tumor stage, and treatment in models 2, 3, and 4 respectively. In an additional fifth model, we adjusted for cancer registry. All analyses were conducted in R statistical software version 3.2.3 (Team 2013).

Table 2 Characteristics of patients diagnosed with endometrial cancer 2004–2014 according to socioeconomic deprivation quintiles

	All patients	Deprivation level				
		Least deprived	2	3	4	Most deprived
Number of patients	21,602	1685	3146	2908	5604	8259
Alive at end of follow-up (%)	14,985 (69.4)	1202 (71.3)	2213 (70.3)	1967 (67.6)	3915 (69.9)	5688 (68.9)
Mean age at diagnosis (SD)	67.8 (11.2)	66.7 (11.2)	67.0 (11.5)	66.9 (11.4)	68.2 (11.0)	68.3 (11.0)
Period of diagnosis (%)						
2004–2008	9315 (43.1)	675 (40.1)	1382 (43.9)	1108 (38.1)	2435 (43.5)	3715 (45.0)
2009–2013	12,287 (56.9)	1010 (59.9)	1764 (56.1)	1800 (61.9)	3169 (56.5)	4544 (55.0)
Type (%)						
Low grade	17,225 (79.7)	1288 (76.4)	2472 (78.6)	2245 (77.2)	4515 (80.6)	6705 (81.2)
High grade	4377 (20.3)	397 (23.6)	674 (21.4)	663 (22.8)	1089 (19.4)	1554 (18.8)
Grade (%)						
I	8248 (38.2)	552 (32.8)	1094 (34.8)	1047 (36.0)	2109 (37.6)	3446 (41.7)
II	9175 (42.5)	756 (44.9)	1403 (44.6)	1221 (42.0)	2465 (44.0)	3330 (40.3)
III	4179 (19.3)	377 (22.4)	649 (20.6)	640 (22.0)	1030 (18.4)	1483 (18.0)
Stage at diagnosis (%)						
I	11,699 (54.2)	852 (50.6)	1602 (50.9)	1330 (45.7)	3264 (58.2)	4651 (56.3)
II	1244 (5.8)	109 (6.5)	164 (5.2)	152 (5.2)	310 (5.5)	509 (6.2)
III	1564 (7.2)	154 (9.1)	270 (8.6)	204 (7.0)	375 (6.7)	561 (6.8)
IV	530 (2.5)	58 (3.4)	84 (2.7)	70 (2.4)	125 (2.2)	193 (2.7)
Missing	6565 (30.4)	512 (30.4)	1026 (32.6)	1152 (39.6)	1530 (27.3)	2345 (28.4)
Treatment (%)						
Radiotherapy	8832 (40.9)	691 (41.0)	1263 (40.1)	1096 (37.7)	2393 (42.7)	3389 (41.0)
Chemotherapy	1181 (5.5)	163 (9.7)	252 (8.0)	206 (7.1)	211 (3.8)	349 (4.2)
Surgery	20,438 (94.6)	1644 (97.6)	3055 (97.1)	2702 (92.9)	5393 (96.2)	7666 (92.8)

SD standard deviation

Sensitivity analysis

To assess the robustness of our findings, we explored potential bias arising from missing stage and treatment information. We assumed missing stage information to be missing at random (MAR). As a result, we used multiple imputation using chained equations (implemented in the R package "mice") to impute missing stage (van Buuren and Groothuis-Oudshoorn 2010). Our imputation model included all variables from our complete cases dataset. Based on five imputed datasets, we repeated our analysis to include previously excluded patients.

On the other hand, we found that the process of recording treatment information varied across the German cancer registries. The included registries from former West Germany (Nordrhein-Westfalen, Hessen, and Bayern) documented treatment as "received", "not received", or truly "unknown" (missing). Cases with missing treatment information within these registries were excluded from the main analysis. In the former East German states (Brandenburg, Mecklenburg-Vorpommern, Sachsen, Sachsen-Anhalt, and Thüringen) however, all patients are initially recorded as having received "no treatment" until the notifying institution provides information on the treatment procedure performed, whereupon the respective case's status changes from treatment "not received" to "received". Therefore, these registries did not include missing treatment information since there was no differentiation between a certain procedure being truly "not received" or if it was "missing" for that matter. In a sensitivity analysis, we recoded cases (from former West German registries) with missing treatment information as "not treated" and repeated our cox regression models.

Results

Descriptive

In total, 21,602 cases diagnosed with endometrial cancer between 2004 and 2014 were included in our analysis (Table 2). Of the patients living in the most deprived districts, 68.9% survived up to the end of follow-up compared to 71.3% of the patients living in the least deprived districts at the time of diagnosis. The mean age at diagnosis for all patients was 67.8 ± 11.2 years (range 24–104) with the patients living in the most deprived districts being the oldest

Table 3 Kaplan–Meier survival estimates according to deprivation levels of patients diagnosed with endometrial cancer in Germany, 2004–2014

Deprivation quintiles	Kaplan–Meier estimated overall survival (unadjusted) (95% CI)	
All stages	5-year	10-year[a]
Quintile 1	78.6 (76.3–80.9)	66.0 (62.3–69.9)
Quintile 2	77.2 (75.5–78.9)	65.8 (63.1–68.5)
Quintile 3	73.9 (72.1–76.0)	63.0 (60.0–66.1)
Quintile 4	76.1 (74.9–77.4)	62.2 (60.0–64.4)
Quintile 5	74.7 (73.6–75.8)	60.2 (58.5–61.9)

CI confidence interval

[a]Patients diagnosed in Darmstadt, Hessen before 2007 were not available in the respective cancer registry data, therefore were not included in the 10-year survival analysis

among the quintiles (68.3 ± 11.0). With regard to subtypes and tumor grading distribution, patients living in the more affluent districts were more likely to be diagnosed with the high-grade variant of EC. The vast majority of the cases were diagnosed at stage I across all the groups. The proportions of patients receiving treatment (radiotherapy, chemotherapy, or surgery) seemed to drop as the deprivation level of the district increased. The observed 5-year overall survival (OS) time was the highest for Q1 patients 78.6% (95% CI 76.3–80.9) and lowest for patients in Q3 (73.1%, 95% CI 72.1–76.0) and Q5 (74.7%, 95% CI 73.6–75.8) (Table 3, Fig. 2). The 10-year OS time followed a similar pattern with patients in Q5 showing the worst survival (60.2%, 95% CI 58.5–61.9) and Q1 having the best 10-year OS (66.0%, 95% CI 62.3–69.9).

Cox models

Our base cox regression model for the total population did not show an association between overall mortality and socioeconomic deprivation. Our stratified analysis on the other hand, consistently showed a higher hazard of overall mortality for the stage I patients living in the more deprived districts (especially Q3 and Q5). After including patient and tumor characteristics in addition to treatment received information to our model, Q5 showed the highest hazard of overall mortality when compared to our reference group (Q1) [HR 1.20, 95% CI (0.99–1.47)] (Table 4). Adjusting for registry did not alter our estimates. No association was seen in patients diagnosed at later stages.

Sensitivity analysis

Twenty eight percent of patients in the Q5 had missing stage information in comparison to 30.4% in Q1 (and 39.6% in Q3). After using the available information in our data to impute five complete datasets, slightly more patients in the deprived districts appeared to survive at the end of follow-up when compared to the affluent group. In contrast to the original data, a smaller proportion of patients in Q1 and Q2 were diagnosed during the later period of 2009–2013. The distribution of stage at diagnosis, tumor grading, treatment, and the patients' characteristics, did not change across the groups when compared to our original dataset (Online Appendix 1). After repeating the regression analysis, an association between deprivation and overall mortality was more evident in the total population even after adjusting

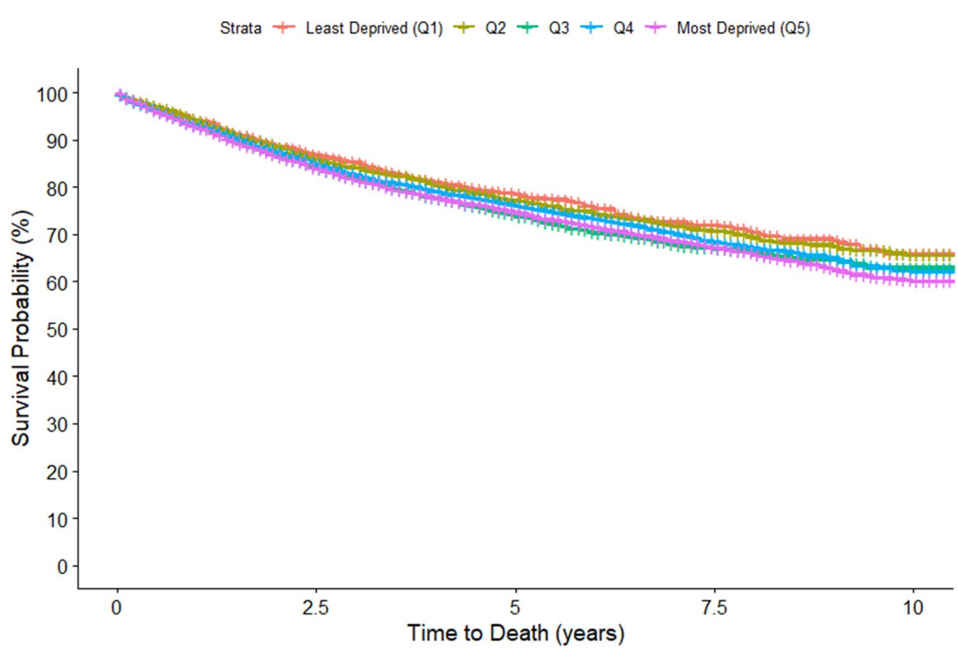

Fig. 2 Kaplan Meier Curves comparing 10 year overall survival of endometrial cancer patients diagnosed 2004–2014 according to deprivation quintiles

Table 4 Cox proportional hazards model survival estimates according to deprivation levels of patients diagnosed with endometrial cancer in Germany, 2004–2014

	N of Events	Hazard ratios (95% CI)				
		Model 1	Model 2	Model 3	Model 4	Model 5
All Stages	3038					
Q1		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2		0.91 (0.78–1.06)	0.89 (0.76–1.04)	0.92 (0.78–1.07)	0.90 (0.77–1.05)	0.90 (0.77–1.04)
Q3		1.03 (0.88–1.22)	1.00 (0.85–1.18)	1.03 (0.87–1.21)	1.00 (0.86–1.18)	1.02 (0.86–1.20)
Q4		0.85 (0.73–0.97)	0.87 (0.75–1.00)	0.95 (0.83–1.10)	0.94 (0.81–1.09)	0.92 (0.79–1.07)
Q5		0.94 (0.82–1.08)	0.98 (0.85–1.12)	1.02 (0.89–1.17)	1.01 (0.88–1.16)	0.98 (0.84–1.14)
Stage I	1701					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		1.01 (0.81–1.27)	0.99 (0.78–1.24)		0.98 (0.78–1.23)	0.98 (0.78–1.23)
Q3		1.27 (1.00–1.60)	1.22 (0.96–1.54)		1.19 (0.94–1.50)	1.18 (0.93–1.50)
Q4		1.06 (0.86–1.30)	1.05 (0.85–1.29)		1.05 (0.85–1.29)	1.06 (0.85–1.32)
Q5		1.19 (0.98–1.46)	1.20 (0.99–1.47)		1.20 (0.99–1.47)	1.21 (0.97–1.50)
Stage II	339					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.62 (0.37–1.01)	0.60 (0.37–1.00)		0.59 (0.36–0.99)	0.60 (0.36–0.98)
Q3		0.88 (0.55–1.41)	0.90 (0.56–1.44)		0.89 (0.55–1.43)	0.93 (0.58–1.51)
Q4		0.88 (0.58–1.35)	0.89 (0.59–1.36)		0.88 (0.58–1.34)	0.81 (0.51–1.26)
Q5		0.87 (0.58–1.30)	0.87 (0.58–1.30)		0.86 (0.57–1.28)	0.76 (0.48–1.19)
Stage III	659					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		1.01 (0.75–1.37)	1.05 (0.77–1.42)		1.00 (0.73–1.36)	1.01 (0.74–1.37)
Q3		0.93 (0.68–1.28)	1.03 (0.75–1.43)		0.97 (0.70–1.35)	1.00 (0.72–1.40)
Q4		0.99 (0.74–1.32)	1.07 (0.80–1.43)		1.01 (0.76–1.36)	0.97 (0.72–1.32)
Q5		0.94 (0.71–1.24)	1.00 (0.76–1.31)		0.97 (0.73–1.28)	0.91 (0.67–1.23)
Stage IV	339					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.83 (0.55–1.22)	0.80 (0.54–1.20)		0.78 (0.52–1.18)	0.79 (0.53–1.18)
Q3		0.81 (0.53–1.24)	0.76 (0.50–1.17)		0.71 (0.46–1.09)	0.73 (0.47–1.12)
Q4		0.64 (0.44–0.94)	0.61 (0.43–0.93)		0.54 (0.37–0.83)	0.51 (0.32–0.80)
Q5		0.75 (0.53–1.06)	0.73 (0.52–1.04)		0.67 (0.47–0.95)	0.61 (0.40–0.92)

Model 1: Adjusted for age and year of diagnosis. Model 2: Same as Model 1 plus Grade and Type. Model 3: Same as Model 2 plus stage Model 4: Same as Model 3 plus treatment. Stratified analysis: Same as Model 2 plus treatment, Model 5: Same as Model 4 plus registry. Stratified analysis: Same as Model 2 plus treatment and registry

Q quintiles, *CI* confidence intervals, *ref* reference group

for tumor characteristics and treatment received variables (Online Appendix 1). This association was replicated among stage I patients. Unlike the original analysis, the imputed dataset showed patients diagnosed at stage II and III, to have also been affected by the socioeconomic-based disparity in survival.

Reincluding cases with missing treatment information from the former West German cancer registries in our sensitivity analysis almost doubled the number of cases in Q1–3. This increase however, was also accompanied by an increase in the proportion of patients with missing stage at diagnosis. Overall the sensitivity analysis was conducted using 17,221 complete cases (1836 in Q1) compared to 15,037 patients used in the original analysis (1173 in Q1). The results from the cox regression models replicated the main results from the original analysis (Online Appendix 2).

Discussion

In this study, we found differences in endometrial cancer survival according to district-level socioeconomic deprivation. The regression models highlighted the association between deprivation level and overall survival in stage I endometrial cancer patients, with better survival for the patients living in the least deprived districts. This association remained after adjusting for patient and tumor characteristics and the treatment received. No effect was detected however, in patients diagnosed at later stages. This could be partly explained by the relatively small number of patients diagnosed at those stages across the five quintiles. Our sensitivity analysis, while confirming our main findings, revealed that missing stage information could have also played a role in influencing the results.

When comparing our findings to studies performed in other countries that offer a publicly accessible universal health care system, similar to the system present in Germany, we found the results to be somewhat comparable. Patients from lower socioeconomic groups in North West of England were found to have a 53% (adjusted HR = 1.53, 95% CI 0.77–3.04) increase in cancer-specific mortality when compared with affluent patients (Njoku et al. 2020). Another study conducted in Denmark during 1994–2003 concluded that increased excess mortality rates from endometrial cancer were associated with low educational level, mainly during the first year after diagnosis (Jensen et al. 2008).

In Germany however, as of the writing of this paper, we were unable to find studies that dealt with this topic. Jansen et al. (2021) measured the 5-year age standardized relative survival of women diagnosed with Corpus Uteri cancer, among other cancer sites, during the period between 2013 and 2017. The study was based on 200 administrative German districts representing approximately 39% of the entire population. The authors found no significant differences in terms of net survival between the most deprived (80.3%) and the most affluent patients (81.6%). The relative excess risk (RER) reported showed the most deprived patients to have an increased RER of death (adjusted for age at diagnosis RER: 1.11 95% CI (0.99–1.25)) compared to the least deprived (Jansen et al. 2021). These finding were similar to those reported by Finke et al. (2021). Finke et al. reported RERs adjusted for age and stage at diagnosis for patients diagnosed during the period of 2012–2014. The most deprived patients again showed an increased RER of death (1.08 95% CI (0.91–1.30) compared to the least deprived. These studies however, did not adjust for treatment information. It is also worth noting, that Corpus Uteri cancer (ICD-10 C54) encompasses tumors that arise in both the endometrium and myometrium, albeit 90% of uterine cancers originate from the endometrium.

The findings that cases are diagnosed at an early stage where treatment is less complex are especially prone to the effect of socioeconomic status might give reason to the argument that treatment is not the main contributor to these effects. Behavioral factors such as obesity affecting also non-cancer mortality might play the dominant role.

Strengths and limitations

The main strength of this study is its attempt to fill the current gap in literature concerning the association between socioeconomic deprivation and endometrial cancer survival. Despite the recent growing interest in the effect of deprivation on cancer survival in general, as evident in newly published studies (Bedir et al. 2021; Finke et al. 2020; Jansen et al. 2020; Kuznetsov et al. 2011), our study is the first to focus on endometrial cancer in Germany. Our findings could be considered nationally representative, since they are based on eight cancer registries representing almost 50 million people from 239 German districts (out of 401) from both former East and West German states. Another strength of this study is that our analysis included information on treatment, which was not the case in previous studies. Our data also included all stages and grouped all known histological variants of EC into the respective subtypes. By stratifying our analysis according to stage, we ruled out the probability that differential stage at diagnosis could have had an effect on survival. According to the literature and as supported by the baseline characteristics of our sample, the majority of the EC patients are usually diagnosed at stage I (Amant et al. 2005). Fewer cases were diagnosed at later stages in our dataset, thus producing no effect in the cox models. When we imputed missing stage information, the distribution of stage at diagnosis remained relatively the same as the original dataset, but with the increased number of cases, our cox models revealed a higher hazard of overall mortality in patients diagnosed at stages II and III and are living in the more deprived quintiles at the time of diagnosis.

In contrast to Jansen et al., we used the GISD, instead of the German Index of Multiple Deprivation (GIMD), as a measure of deprivation. As explained earlier, the GISD is based solely on three classical dimensions of socioeconomic inequality (education, income, and employment) and is publicly available. This helps make the analysis reproducible and the results easier to interpret.

Nevertheless, the GISD has its limitations. It is an area-based index and is not based on, for example, the individual's income or level of education. This could lead to the misclassification of patients by grouping individuals from a higher socioeconomic position into the most deprived socioeconomic quintile because they live in a district where the majority of its residents have a lower socioeconomic status. We were unable to measure the magnitude of this potential misclassification or its effect on our results, since individual-level information on socioeconomic position was not available in our dataset. However, since GISD covers a wide range of socioeconomic indicators, we believe it to be an accurate measurement for deprivation since it has been used in previous research (Hoebel et al. 2018; Moissl et al. 2020; Rommel et al. 2018).

Retrospective studies based on cancer registry data have several limitations. German registries do not systematically collect data on comorbidities or lifestyle-related EC risk factors such as smoking, unhealthy diets, physical activity, and obesity which have been proven to be directly related to socioeconomic status as well as cancer survival in general (Sarfati et al. 2016; Søgaard et al. 2013).

Another limitation of our study is the varied process of recording treatment information by different German cancer registries. The results of our sensitivity analysis did not differ from the main analysis; however, a standardized definition of "missing" across the cancer registries could help provide a more accurate insight on the effect of treatment on survival.

Furthermore, the registries do not contain data on the process of treatment decision, when was the treatment performed, or if the patient was publicly or privately insured. These unmeasured confounders could have led to the overestimation of the effect of socioeconomic deprivation.

Conclusion

Our results indicated differences in endometrial cancer survival according to socioeconomic deprivation among patients diagnosed at stage I. Future studies, with access to individual-level patient information, could take advantage of helpful tools like directed acyclic graphs (DAGs) in visualizing and explaining the underlying mechanism by which a complex factor, like area-based socioeconomic deprivation, would affect cancer survival.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-021-03908-9.

Author contributions AB and DM contributed to the conception or design of the work. DM and DV contributed to the data acquisition. AB, and DM contributed to the data analysis. AB and DM contributed to the interpretation of results. AB drafted the manuscript. AB, SFA, DV and DM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Availability of data and material This study was based on the German national cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). Data were provided by the Robert Koch Institute (RKI) (https://doi.org/10.18444/5.03.01.0005.0015.0001).

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

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Appendix 1: Missing Stage information: Sensitivity Analysis

Table 1. Characteristics of patients diagnosed with endometrial cancer 2004-2014 according to socioeconomic deprivation quintiles based on five imputed datasets .

		Deprivation Level				
	All patients	**Least Deprived**	**2**	**3**	**4**	**Most Deprived**
Number of patients	101002	7712	14246	12638	27025	39381
Alive at end of follow-up (%)	65388 (64.7)	4962 (64.3)	9024 (63.3)	7446 (58.9)	18120 (67.0)	25836 (65.6)
Mean age at diagnosis **(SD)**	68.1 (11.0)	67.1 (11.1)	67.6 (11.3)	67.4 (11.3)	68.4 (10.9)	68.5 (10.9)
Period of Diagnosis (%)						
2004-2008	43620 (43.2)	3435 (44.5)	6569 (46.1)	4915 (38.9)	11556 (42.8)	17145 (43.5)
2009-2013	57382 (56.8)	4277 (55.5)	7677 (53.9)	7723 (61.1)	15469 (57.2)	22236 (56.5)
Type (%)						
Low grade	78376 (77.6)	5660 (73.4)	10856 (76.2)	9314 (73.7)	21268 (78.7)	31278 (79.4)
High grade	22626 (22.4)	2052 (26.6)	3390 (23.8)	3324 (26.3)	5757 (21.3)	8103 (20.6)
Grade (%)						
I	35887 (35.5)	2280 (29.6)	4310 (30.3)	4149 (32.8)	9581 (35.5)	15567 (39.5)
II	43460 (43.0)	3473 (45.0)	6659 (46.7)	5262 (41.6)	11970 (44.3)	16096 (40.9)
III	21655 (21.4)	1959 (25.4)	3277 (23.0)	3227 (25.5)	5474 (20.3)	7718 (19.6)
Stage at Diagnosis (%)						
I	75848 (75.1)	5472 (70.8)	10438 (73.3)	9107 (72.1)	20962 (77.6)	29884 (75.9)
II	8741 (8.7)	747 (9.7)	1142 (8.0)	1151 (9.1)	2136 (7.9)	3565 (9.1)
III	12001 (11.9)	1076 (14.0)	1979 (13.9)	1736 (13.7)	2892 (10.7)	4318 (11.0)
IV	4412 (4.4)	432 (5.6)	687 (4.8)	644 (5.1)	1035 (3.8)	1614 (4.1)
Treatment (%)						
Radiotherapy	44202 (43.8)	3542 (45.9)	6305 (44.3)	5304 (42.0)	12087 (44.7)	16964 (43.1)
Chemotherapy	6091 (6.0)	833 (10.8)	1281 (9.0)	1054 (8.3)	1141 (4.2)	1782 (4.5)
Surgery	96218 (95.3)	7564 (98.1)	13923 (97.7)	12123 (95.9)	25715 (95.2)	36893 (93.7)

Abbreviations: SD= Standard Deviation

Table 2: Cox proportional hazards model survival estimates according to deprivation levels of patients diagnosed with endometrial cancer in Germany, 2004–2014 based on five imputed datasets.

	N of Events	Hazard Ratios (95%CI)				
		Model 1	Model 2	Model 3	Model 4	Model 5
All Stages	28148					
Q1		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2		1.00 (0.95-1.06)	1.01 (0.96-1.07)	1.05 (1.00-1.11)	1.04 (0.98-1.10)	1.04 (0.98-1.10)
Q3		1.26 (1.19-1.33)	1.25 (1.18-1.31)	1.27 (1.20-1.32)	1.25 (1.18-1.32)	1.22 (1.16-1.30)
Q4		1.00 (0.95-1.05)	1.04 (1.00-1.10)	1.14 (1.08-1.20)	1.11 (1.05-1.17)	1.14 (1.09-1.21)
Q5		1.10 (1.05-1.15)	1.15 (1.10-1.21)	1.20 (1.15-1.25)	1.15 (1.08-1.21)	1.20 (1.14-1.26)
Stage I	15368					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		1.09 (1.00-1.18)	1.08 (1.00-1.17)		1.08 (0.99-1.16)	1.08 (0.99-1.16)
Q3		1.49 (1.36-1.62)	1.44 (1.33-1.56)		1.40 (1.29-1.52)	1.37 (1.27-1.49)
Q4		1.19 (1.11-1.28)	1.20 (1.12-1.29)		1.18 (1.10-1.25)	1.25 (1.16-1.35)
Q5		1.31 (1.24-1.43)	1.34 (1.26-1.45)		1.31 (1.23-1.41)	1.39 (1.29-1.50)
Stage II	3246					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.80 (0.67-0.94)	0.81 (0.69-0.96)		0.80 (0.67-0.94)	0.80 (0.67-0.94)
Q3		1.11 (0.94-1.30)	1.13 (0.97-1.33)		1.14 (0.97-1.33)	1.13 (0.96-1.32)
Q4		1.02 (0.88-1.18)	1.05 (0.91-1.21)		1.04 (0.90-1.20)	1.06 (0.91-1.23)
Q5		1.04 (0.90-1.19)	1.06 (0.92-1.21)		1.01 (0.88-1.16)	1.03 (0.89-1.20)
Stage III	6343					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		1.11 (1.00-1.24)	1.16 (1.00-1.24)		1.10 (0.99-1.22)	1.10 (0.99-1.22)
Q3		1.15 (1.03-1.29)	1.25 (1.12-1.40)		1.16 (1.04-1.29)	1.18 (1.05-1.31)
Q4		1.16 (1.05-1.28)	1.25 (1.13-1.39)		1.13 (1.02-1.25)	1.11 (1.00-1.23)
Q5		1.15 (1.04-1.26)	1.22 (1.11-1.35)		1.09 (0.99-1.20)	1.05 (0.95-1.17)
Stage IV	3191					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.96 (0.83-1.10)	0.96 (0.84-1.11)		0.98 (0.85-1.12)	0.98 (0.85-1.13)
Q3		0.94 (0.81-1.08)	0.92 (0.79-1.06)		0.89 (0.77-1.02)	0.89 (0.77-1.03)
Q4		0.83 (0.72-0.95)	0.84 (0.73-0.96)		0.77 (0.67-0.88)	0.75 (0.65-0.87)
Q5		0.91 (0.80-1.03)	0.91 (0.80-1.02)		0.83 (0.74-0.94)	0.81 (0.70-0.93)

Model 1: Adjusted for age and year of diagnosis. **Model 2**: Same as Model 1 plus Grade and Type. **Model 3**: Same as Model 2 plus stage Model 4: Same as Model 3 plus treatment. Stratified analysis: Same as Model 2 plus treatment, Model 5: Same as Model 4 plus registry. Stratified analysis: Same as Model 2 plus treatment and registry

Abbreviations: Q= Quintiles, CI= Confidence Interval.

Appendix 2: Missing Treatment information: Sensitivity Analysis

Table 1. Characteristics of patients diagnosed with endometrial cancer 2004-2014 according to socioeconomic deprivation quintiles (missing treatment was considered as “not received”).

		Deprivation Level				
	All patients	**Least Deprived**	**2**	**3**	**4**	**Most Deprived**
Number of patients	31596	3971	6019	5544	7072	8990
Alive at end of follow-up (%)	22141 (70.1)	2870 (72.3)	4304 (71.5)	3846 (69.4)	4917 (69.5)	6204 (69.0)
Mean age at diagnosis **(SD)**	67.7 (11.3)	67.0 (11.4)	67.1 (11.5)	67.2 (11.6)	68.1 (11.2)	68.2 (11.1)
Period of Diagnosis (%)						
2004-2008	11943 (37.8)	1472 (37.1)	2066 (34.3)	1739 (31.4)	2752 (38.9)	3914 (43.5)
2009-2013	19653 (62.2)	2499 (62.9)	3953 (65.7)	3805 (68.6)	4320 (61.1)	5076 (56.5)
Type (%)						
Low grade	24982 (79.1)	3046 (76.7)	4668 (77.6)	4312 (77.8)	5689 (80.4)	7267 (80.8)
High grade	6614 (20.9)	925 (23.3)	1351 (22.4)	1232 (22.2)	1383 (19.6)	1723 (19.2)
Grade (%)						
I	11623 (36.8)	1234 (31.1)	1997 (33.2)	2021 (36.5)	2674 (37.8)	3697 (41.1)
II	13658 (43.2)	1855 (46.7)	2724 (45.3)	2331 (42.0)	3096 (43.8)	3652 (40.6)
III	6315 (20.0)	882 (22.2)	1298 (21.6)	1192 (21.5)	1302 (18.4)	1641 (18.3)
Stage at Diagnosis (%)						
I	13269 (42.0)	1338 (33.7)	2182 (36.3)	1668 (30.1)	3370 (47.7)	4711 (52.4)
II	1410 (4.5)	158 (4.0)	227 (3.8)	186 (3.4)	327 (4.6)	512 (5.7)
III	1816 (5.7)	231 (5.8)	366 (6.1)	254 (4.6)	394 (5.6)	571 (6.4)
IV	726 (2.3)	109 (2.7)	149 (2.5)	113 (2.0)	151 (2.1)	204 (2.3)
Missing	14375 (45.5)	2135 (53.8)	3095 (51.4)	3323 (59.9)	2830 (40.0)	2992 (33.3)
Treatment (%)						
Radiotherapy	9744 (30.8)	1010 (25.4)	1609 (26.7)	1242 (22.4)	2477 (35.0)	3406 (37.9)
Chemotherapy	1290 (4.1)	192 (4.8)	291 (4.8)	231 (4.2)	223 (3.2)	353 (3.9)
Surgery	23446 (74.2)	2518 (63.4)	4146 (68.9)	3492 (63.0)	5548 (78.5)	7742 (86.1)

Abbreviations: SD= Standard Deviation

Table 2: Cox proportional hazards model survival estimates according to deprivation levels of patients diagnosed with endometrial cancer in Germany, 2004–2014 (missing treatment was considered as "not received").

	N of Events	Hazard Ratios (95%CI)				
		Model 1	Model 2	Model 3	Model 4	Model 5
All Stages	3446					
Q1		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2		0.91 (0.80-1.04)	0.93 (0.82-1.06)	0.93 (0.82-1.06)	0.94 (0.82-1.06)	0.92 (0.80-1.04)
Q3		1.00 (0.87-1.15)	1.01 (0.88-1.16)	1.02 (0.89-1.17)	1.02 (0.89-1.17)	0.99 (0.85-1.15)
Q4		0.85 (0.75-0.96)	0.92 (0.81-1.04)	1.00 (0.89-1.13)	1.03 (0.91-1.16)	0.99 (0.84-1.17)
Q5		0.93 (0.83-1.04)	1.02 (0.91-1.14)	1.06 (0.95-1.19)	1.10 (0.98-1.23)	1.06 (0.89-1.25)
Stage I	1867					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.99 (0.82-1.20)	1.00 (0.83-1.22)		1.02 (0.84-1.22)	0.98 (0.80-1.19)
Q3		1.23 (1.00-1.51)	1.22 (0.99-1.49)		1.21 (0.99-1.48)	1.12 (0.90-1.40)
Q4		1.06 (0.89-1.26)	1.09 (0.92-1.30)		1.13 (0.95-1.35)	1.03 (0.82-1.30)
Q5		1.19 (1.01-1.41)	1.25 (1.05-1.48)		1.30 (1.09-1.53)	1.24 (0.98-1.57)
Stage II	373					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.67 (0.44-1.02)	0.67 (0.44-1.02)		0.68 (0.45-1.04)	0.65 (0.43-1.00)
Q3		0.90 (0.59-1.35)	0.93 (0.62-1.41)		0.93 (0.62-1.42)	1.00 (0.63-1.58)
Q4		0.89 (0.62-1.28)	0.93 (0.65-1.33)		0.97 (0.67-1.39)	0.87 (0.53-1.42)
Q5		0.88 (0.63-1.24)	0.92 (0.66-1.29)		0.97 (0.69-1.36)	0.88 (0.52-1.48)
Stage III	750					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		0.92 (0.71-1.18)	0.94 (0.73-1.21)		0.92 (0.72-1.19)	0.91 (0.70-1.18)
Q3		0.84 (0.63-1.11)	0.91 (0.69-1.21)		0.88 (0.66-1.17)	0.83 (0.61-1.13)
Q4		0.97 (0.76-1.24)	1.04 (0.81-1.33)		1.03 (0.80-1.32)	0.92 (0.66-1.28)
Q5		0.90 (0.71-1.14)	0.94 (0.74-1.19)		0.95 (0.75-1.21)	0.79 (0.55-1.12)
Stage IV	456					
Q1		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Q2		1.00 (0.74-1.35)	0.96 (0.71-1.30)		0.96 (0.71-1.31)	0.98 (0.72-1.34)
Q3		0.97 (0.70-1.34)	0.92 (0.66-1.28)		0.91 (0.66-1.28)	0.98 (0.68-1.40)
Q4		0.83 (0.60-1.14)	0.80 (0.58-1.11)		0.81 (0.58-1.12)	0.97 (0.64-1.49)
Q5		0.90 (0.68-1.20)	0.88 (0.66-1.17)		0.91 (0.68-1.22)	1.02 (0.67-1.57)

Model 1: Adjusted for age and year of diagnosis. **Model 2**: Same as Model 1 plus Grade and Type. **Model 3**: Same as Model 2 plus stage Model 4: Same as Model 3 plus treatment. Stratified analysis: Same as Model 2 plus treatment, Model 5: Same as Model 4 plus registry. Stratified analysis: Same as Model 2 plus treatment and registry

Abbreviations: Q= Quintiles, CI= Confidence Interval.

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ORIGINAL ARTICLE – CANCER RESEARCH

Socioeconomic disparities in head and neck cancer survival in Germany: a causal mediation analysis using population-based cancer registry data

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Abstract

Purpose Despite recent improvements in cancer treatment in Germany, a marked difference in cancer survival based on socioeconomic factors persists. We aim to quantify the effect of socioeconomic inequality on head and neck cancer (HNC) survival.

Methods Information on 20,821 HNC patients diagnosed in 2009–2013 was routinely collected by German population-based cancer registries. Socioeconomic inequality was defined by the German Index of Socioeconomic Deprivation. The Cox proportional regression and relative survival analysis measured the survival disparity according to level of socioeconomic deprivation with respective confidence intervals (CI). A causal mediation analysis was conducted to quantify the effect of socioeconomic deprivation mediated through medical care, stage at diagnosis, and treatment on HNC survival.

Results The most socioeconomically deprived patients were found to have the highest hazard of dying when compared to the most affluent (Hazard Ratio: 1.25, 95% CI 1.17–1.34). The most deprived patients also had the worst 5-year age-adjusted relative survival (50.8%, 95% CI 48.5–53.0). Our mediation analysis showed that most of the effect of deprivation on survival was mediated through differential stage at diagnosis during the first 6 months after HNC diagnosis. As follow-up time increased, medical care, stage at diagnosis, and treatment played no role in mediating the effect of deprivation on survival.

Conclusion This study confirms the survival disparity between affluent and deprived HNC patients in Germany. Considering data limitations, our results suggest that, within six months after HNC diagnosis, the elimination of differences in stage at diagnosis could reduce survival inequalities.

Keywords Head and neck cancer · Survival · Socioeconomic deprivation · Causality · Mediation analysis

Introduction

Head and neck cancer (HNC) accounts for approximately 3% of all new malignancies in Germany, and is ranked the seventh most common cancer worldwide (Global Burden of Disease Cancer et al. , 2017). While the effect of socioeconomic factors (SES) on HNC survival has been documented in past literature (Boing et al. 2011; Choi et al. 2016; Johnson et al. 2008), recent studies have started to investigate the effect of area-based socioeconomic deprivation on cancer survival in general (Chang et al. 2012; Rachet et al. 2010; Singh and Jemal 2017), and HNC in particular (Bryere et al. 2017; Chang et al. 2013; Hagedoorn et al. 2016; Megwalu 2017). In Germany, however, studies investigating socioeconomic disparity are scarce and are often limited to certain regions (Brenner et al. 1991; Eberle et al. 2010; Finke et al.

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2020; Jansen et al. 2020; Kuznetsov et al. 2011). Jansen et al. published the only large-scale study from Germany that aimed to measure social inequalities in cancer survival in 2014 (Jansen et al. 2014). This study found the 5-year age-standardized relative survival of the most deprived patients diagnosed with cancer of the mouth/pharynx to be 45.2% versus 49.3% for the most affluent patients. It is therefore essential to understand the mechanism by which social disparity affects cancer survival and to identify modifiable risk factors.

In this study, we aimed to (1) measure the survival gap according to socioeconomic deprivation level and (2) to decompose the total effect of deprivation on HNC survival into direct effect and indirect effect mediated through other possible factors. To this end, we used population-based and routinely collected data for patients diagnosed with HNC within Germany.

Materials and methods

Data source

This retrospective study is based on epidemiological cancer registry data (pooled data from federal registries) from the German Centre for Cancer Registry Data ('Zentrum für Krebsregisterdaten', ZfKD) at the Robert Koch Institute (RKI) (Hiripi et al. 2012). The ZfKD annually collects anonymized incidence and survival data from all federal states' population-based cancer registries. The data then undergo quality checks and are pooled for nationwide and regional analyses. In this analysis, data from the Niedersachsen cancer registry were excluded, as only aggregate socioeconomic data for the entire state (7.9 million inhabitants) were available. Data quality was assessed by proportion of death certificate only (DCO) and autopsy only cases among all registered malignant cancers. Cancer registries were included if the overall proportion of DCO cases in the period 2009–2013 was below 13% as recommended by the European Cancer Registry-Based Study on Survival and Care of Cancer Patients (EUROCARE-5 study) (Rossi et al. 2015). Therefore, the final dataset included data from 14 cancer registries covering a population of 69 million people (83% of the total German population).

The German Index of Socioeconomic Deprivation (GISD) was used as a measure for socioeconomic deprivation at the district level (Kroll et al. 2017). Developed by the RKI, the GISD is a composite index that is based on three equally weighted socioeconomic dimensions: income, education, and employment. The income dimension is based on the mean net household income, tax revenues, and debtor quotas within a given district. The educational component is defined by the district's proportions of employees with (and without) a university degree, school dropouts without a degree, and school dropouts with the German "Abitur" or equivalent. Finally, the employment dimension is measured through the district's unemployment rate, average gross wage of employees, and the labor force participation rate.

The second version of the index, available on GitHub, was used in this analysis (GISD-The German Index of Socioeconomic Deprivation 2020). In the end, 345 districts, out of Germany's 401 districts, were included in our study after being linked with the pooled registry dataset. We obtained the geo-data for the administrative German districts through the "Bundesamt für Kartographie und Geodäsie (BKG)" website (Bundesamt für Kartographie und Geodäsie (BKG) 2020). Figure 1 shows a map of Germany highlighting the included districts.

Study population

Our analysis included cases (aged 24–97) diagnosed with malignant squamous cell carcinoma (SCC) in the head and neck region during 2009–2013 and followed up until 31 December 2014. 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-0–3) (Fritz et al. 2000). Malignant SCC was determined through the morphology codes for squamous cell histology or morphologic variants of SCC (morphology codes: 8032, 8033, 8050–8052, 8070–8078, 8082–8084, 8094, 8123). The included anatomical sites, and their corresponding (ICD-0–3), were: tonsils (C09), base of the tongue (C01.9, C02.4), other oropharynx sites (C10), Waldeyer's ring (C14.2), areas of the oral cavity, gingiva (C03), floor of the mouth (C04), palate (C05), pyriform sinus (C12), and the hypopharynx (C13). Cases of head and neck cancer that could not be distinguished by specific sites were included and grouped as "not specified" (C06).

Carcinoma of unknown primary or recurrent metastasis in the head and neck region of other origin was excluded. In addition, we excluded cases notified by autopsy only or by death certificate only (DCO).

Exposure and outcome

The exposure under study was the patient's socioeconomic deprivation level. Each patient's socioeconomic deprivation level was determined according to the GISD allocated to the case's district of residence at the time of diagnosis. The indices were then categorized into five quintiles. Quintile one (Q1) represented the least socioeconomically deprived cases while quintile five (Q5) represented the most deprived.

The primary outcome was survival status after cancer diagnosis. For the descriptive analysis and overall survival

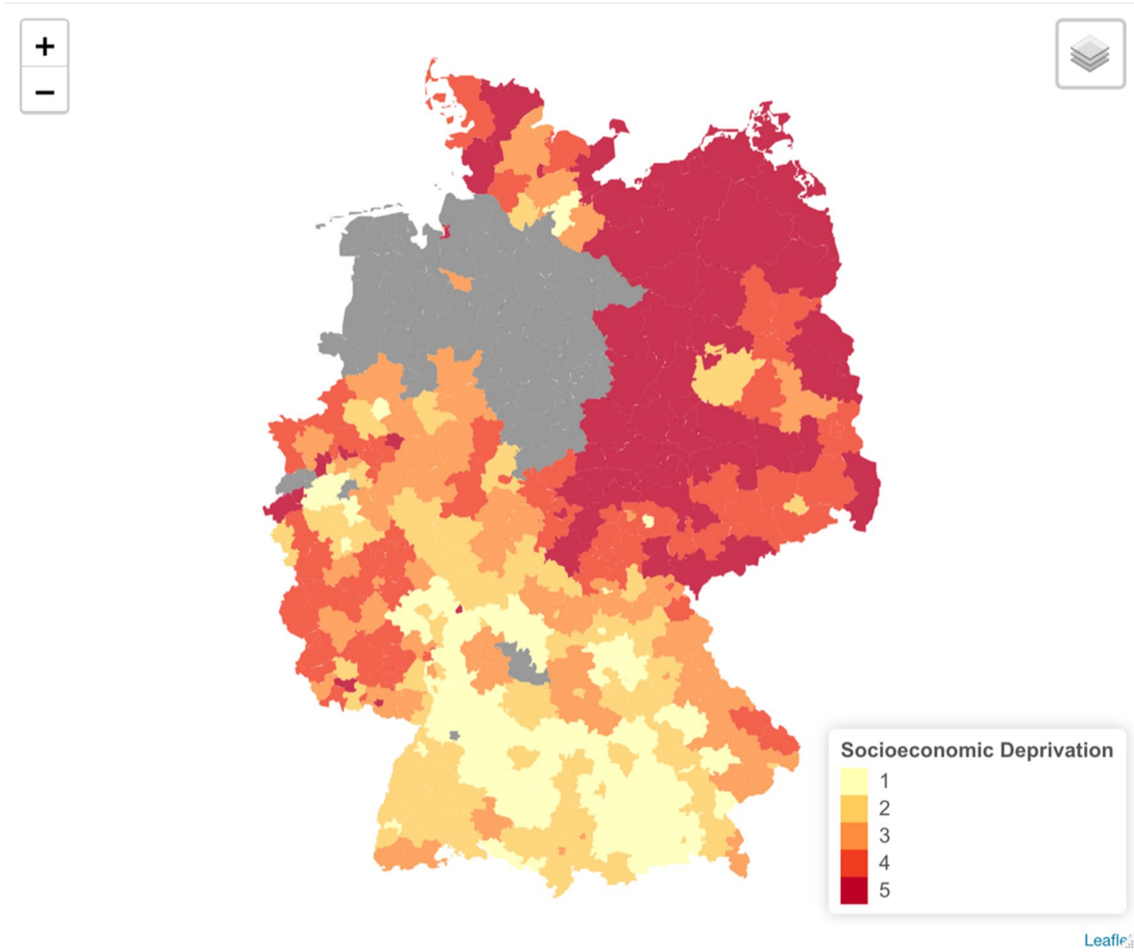

Fig. 1 Map of Germany with districts included in the analysis, colored according to their mean level of socioeconomic deprivation, 2009–2013. Quintiles are listed in ascending order according to deprivation (quintile five = most deprived)

calculation, survival was treated as a time to event outcome. For the mediation analysis, however, survival was dichotomized (dead vs. alive) and stratified according to time since diagnosis: at 6 months, 1 year conditional on 6-month survival, 2 years conditional on 1-year survival, and 5 years conditional on 2-year survival.

Covariates

To determine the covariates needed for our analysis and have a better visualization of the causal relationship between them, a directed acyclic graph (DAG) was prepared (Fig. 2). Based on previous research and literature evidence, we assumed that the level of socioeconomic deprivation the

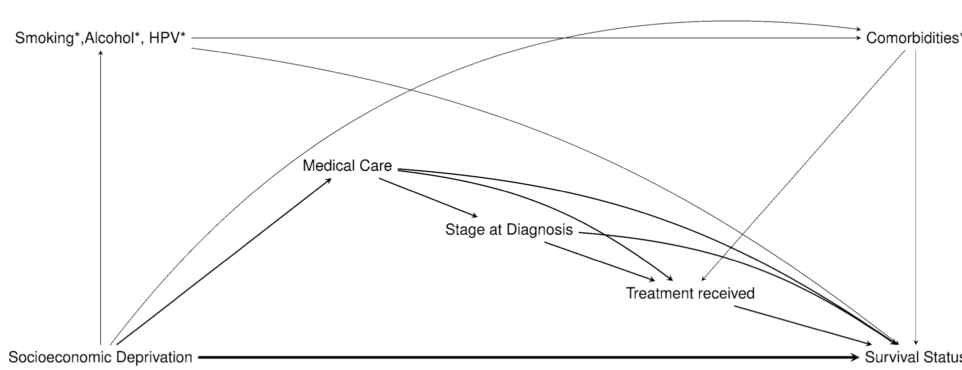

Fig. 2 Directed Acyclic Graph (DAG) depicting the causal relationships between deprivation and survival status in HNC patients. Age, sex, and year of diagnosis were considered as baseline confounders

patient could experience in his/her district at (the time of diagnosis) could influence the received medical care. In turn, socioeconomic deprivation could influence the patient's tumor stage at diagnosis and the applied treatment. Thus, while age, gender, and year of diagnosis, were considered as baseline confounders, medical care, stage at diagnosis, and treatment were considered three causally ordered mediators. Our DAG also shows another route that could mediate the effect of deprivation, through smoking, alcohol, and human papillomavirus (HPV) infection. These variables along with comorbidities were not available in our dataset, and therefore considered unmeasured variables.

Medical care was measured as the average number of hospital beds available (at the time of diagnosis) per person, within each district. The number of hospital beds was restricted to those in the oral and maxillofacial, ear-nose-throat (ENT), and radiotherapy departments. This information was available through the Federal Statistical Office (Destatis) registries that are updated annually (Statistisches Bundesamt: Deutsches Krankenhausverzeichnis 2015). Stage at diagnosis was categorized into four groups based on the tumor–node–metastasis (TNM) cancer staging system (Edge and Compton 2010). Information on treatment received was available as four binary variables (surgery yes/no, radiotherapy yes/no, chemotherapy yes/no, immunotherapy yes/no). Based on these variables, we dichotomized treatment into "advanced" and "minor" treatment modes based on what is recommended for each stage by the international guidelines (Network 2020). Only complete cases were included in our analysis.

Statistical analysis

The observable 5-year overall survival rates (OS) for each quintile were calculated by the Kaplan–Meier method. Multivariate analysis was performed using the Cox proportional hazards model to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for OS. The 5-year age-adjusted relative survival was calculated for each deprivation quintile, as the ratio of observed and expected survival with adjustment to the International Cancer Survival Standards (Corazziari et al. 2004). Expected survival was estimated according to the Ederer II estimator (implemented in the R package "relsurv") using population life tables stratified by age, sex, and calendar period (Perme and Pavlic 2018).

Mediation analysis, based on the counterfactual framework (Pearl 2013), was then conducted to separate the indirect effects that operate through each of the aforementioned mediators from the remaining direct effect and to quantify their respective contribution towards the overall total effect. We conducted our analysis according to the method proposed by Steen et al. (2017) due to the existence of mediator-outcome confounders that are affected by the exposure and the likely presence of many interactions (VanderWeele et al. 2014). Although this method allows flexible modeling, it still relies on the assumptions of no unaccounted confounding of the exposure–mediator, mediator–outcome or exposure–outcome relationship.

Mediator models were linear (medical care), ordered (stage at diagnosis), or logistic (treatment received) depending on the mediator. The outcome (survival status) was modeled using a logistic model. To obtain a four-way decomposition, we extended our dataset by replicating the observed dataset eight times. We then weighed our extended dataset, by the ratio of densities of the mediators whose corresponding models we believed were less prone to misspecification (medical care and treatment received). An extended version of the outcome model (natural effect model) was then fitted to the original data by regressing imputed nested counterfactuals using our pre-calculated weights. To obtain population-average analogs (rather than effects adjusted on the set of confounders), we updated the weights by inverse weighting. Inverse weighting enables transporting results to the entire target population. Finally, a total of 1,000 bootstrap samples were drawn to calculate 95% (standard normal) bootstrap confidence intervals. This procedure was repeated for each of the previously mentioned time points and only two quintiles were compared at a time. All analyses were conducted in R statistical software version 3.2.3 (Team 2013).

Sensitivity analysis

To assess the robustness of our findings, we performed different sensitivity analyses. We first explored potential confounding by HPV status. Since this information was not available, we classified HPV status according to tumor site (HPV-related sites vs HPV non-related). This classification was based on studies that found that HPV-positive HNC to be associated with 80% of oropharyngeal HNC and less than 20% of tumors at other anatomic sites of the head and neck (Mehanna et al. 2013). We repeated our Cox regression and mediation analysis while adjusting for this variable.

We also explored potential bias arising from missing treatment and stage information. To have a better understanding regarding variables associated with missing treatment information, we conducted a (forward/backward) stepwise logistic regression.

On the other hand, we assumed missing-stage information to be missing at random (MAR). As a result, we used multiple imputation using chained equations (implemented in the R package "mice") to impute missing stage (Buuren and Groothuis-Oudshoorn 2010). Our imputation model included all variables from our complete cases dataset. Based on five imputed datasets, we repeated our mediation analysis to include previously excluded patients.

Results

Descriptive analysis by deprivation quintiles.

Our analysis included 20,821 cases diagnosed with HNC between 2009 and 2013 from 345 districts in Germany (Table 1). Of the most deprived patients, 48.6% survived up to the end of follow-up, compared to 57.9% of the least deprived patients. Deprived patients were younger and diagnosed at a later stage. Compared to the most affluent (91%), only 79% of the most deprived patients received the advanced treatment according to our definition.

Overall and standardized survival (net survival)

The observed 5-year overall survival (OS) for the most affluent patients was 53.2% (95% CI 50.9–55.6). The OS decreased as the level of deprivation increased (51.2, 95% CI 49.0–53.6), (49.1, 95% CI 46.6–51.8), (51.0, 95% CI 49.3–52.8), (47.9, 95% CI 46.3–49.6), for patients in the second, third, fourth, and fifth quintile, respectively (Table 2, Fig. 3).

Table 1 Characteristics of patients diagnosed with head and neck cancer, 2009–2013

	Deprivation Level					
	All patients	Least Deprived	2	3	4	Most Deprived
Number of patients	20,821	3198	3148	3287	4916	6272
Alive at end of follow-up–no. (%)	10,959 (52.6)	1853 (57.9)	1731 (55.0)	1800 (54.8)	2528 (51.4)	3047 (48.6)
Mean age at diagnosis (SD)	60.9 (10.3)	61.7 (10.4)	61.4 (10.1)	61.7 (10.4)	60.8 (10.2)	59.8 (10.3)
Gender (%)						
Male	77.0	75.5	75.5	74.4	77.4	79.7
Female	23.0	24.5	24.5	25.6	22.6	20.3
Average number of beds[a,b] (SD)	20.3 (23.1)	23.6 (35.9)	19.1 (17.5)	15.9 (16.5)	21.0 (20.9)	21.1 (21.4)
Stage at Diagnosis (%)						
Stage I	14.5	15.4	14.7	13.3	14.5	14.3
Stage II	11.1	10.2	11.8	11.2	11.1	11.2
Stage III	15.2	14.4	16.4	15.8	14.8	15.0
Stage IV	54.6	53.6	51.3	54.4	55.5	57.6
Missing	4.6	6.2	5.9	5.2	4.0	1.9
Treatment (%)						
Minor	17.1	8.7	13.1	16.7	20.6	20.8
Advanced	82.9	91.3	86.9	83.3	79.4	79.2
Site (%)						
HPV-unrelated	58.2	55.8	58.5	57.0	58.2	60.0
HPV-related	41.8	44.2	41.5	43.0	41.8	40.0

SD Standard deviation, *HPV* Human papillomavirus

[a]The number of hospital beds was restricted to those in the oral and maxillofacial, Ear-Nose-Throat (ENT), and radiotherapy departments

[b]Per 100,000 population

Table 2 Kaplan–Meier, 5-year age-standardized relative survival, and Cox proportional hazards model survival estimates according to deprivation levels of patients diagnosed with head and neck cancer in Germany, 2009–2013

Deprivation quintiles	Kaplan–Meier estimated 5-year overall survival (unadjusted) (95% CI)	5-year age-standardized relative survival (95% CI)	Cox proportional hazards model* Hazard Ratio (95% CI)
Quintile 1	53.2 (50.9–55.6)	56.7 (53.2–59.9)	Reference
Quintile 2	51.2 (49.0–53.6)	56.0 (55.3–60.3)	1.09 (1.01–1.18)
Quintile 3	49.1 (46.6–51.8)	54.0 (50.6–57.3)	1.11 (1.03–1.21)
Quintile 4	51.0 (49.3–52.8)	55.3 (52.8–57.7)	1.13 (1.05–1.21)
Quintile 5	47.9 (46.3–49.6)	50.8 (48.5–53.0)	1.25 (1.17–1.34)

CI confidence interval

*Adjusted for age, sex, and year of diagnosis

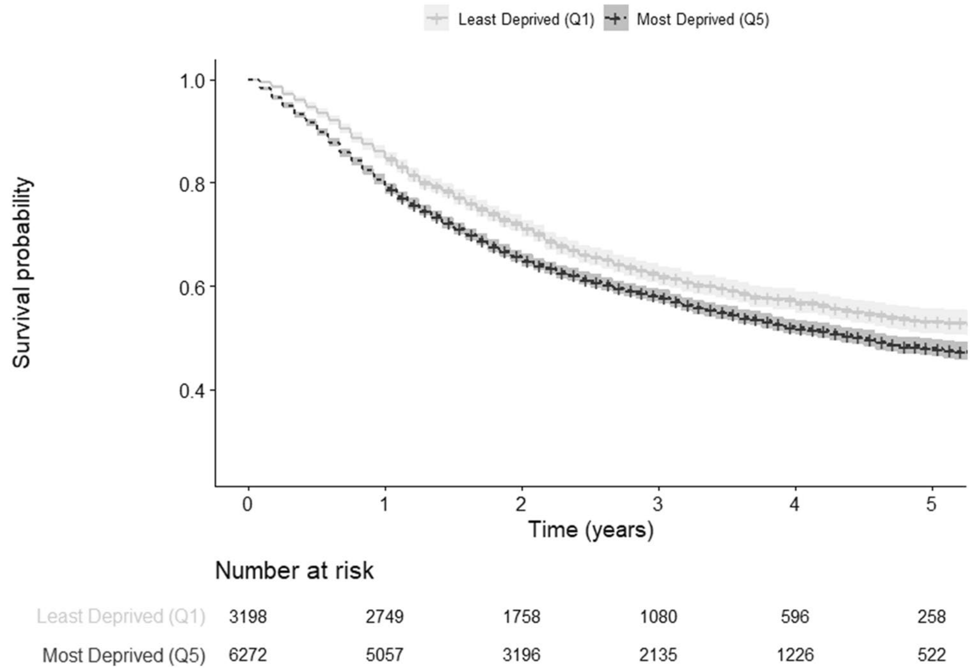

Fig. 3 Kaplan–Meier curves comparing survival between least and most socioeconomically deprived patients diagnosed with head and neck cancer in Germany, 2009–2013

The 5-year age-standardized survival (net survival) relative to the mortality rates of the general German population showed the first quintile to have the highest relative survival (56.7, 95% CI 53.2–59.9), followed by the second quintile (56.0, 95% CI 55.3–60.3). The fifth quintile still appeared to have the lowest relative survival (50.8, 95% CI 48.5–53.0) (Table 2).

Our Cox regression model, adjusted for age, sex, and year of diagnosis, showed the fifth quintile to have the highest hazard of overall mortality when compared to our reference group (quintile one) ([HR]1.25, 95% CI 1.17–1.34) (Table 2). In the same line, the hazard of overall mortality also increased as the level of deprivation rose. Adjusting for tumor site did not alter the results (Appendix 1).

Total effect

The total effect was defined as the joint effect of deprivation including the indirect effect of the three mediators. The odds of dying were highest during the first 6 months after diagnosis, across all quintiles when compared to the most affluent cases (Odds Ratio [OR] comparing quintile five to quintile one: 1.81, 95% CI 1.52–2.16). Five years after diagnosis (conditioning on 2-year survival), showed that the total effect remained fairly strong only when comparing the most deprived (quintile five) with the least deprived (quintile one) ([OR]: 1.26, 95% CI 1.12–1.47) (Table 3, Fig. 4).

Indirect effect: role of deprivation and mediators

During the first 6 months after diagnosis, stage at diagnosis seemed to mediate most of the effect of deprivation across the more deprived quintiles. Using a counterfactual reasoning, the odds of dying of the patients in the most affluent quintile would increase by 44% ([OR] 1.44, 95% CI 1.32–1.58) if they were to be diagnosed as patients in quintile five (while keeping their level of deprivation, medical care, and treatment received unchanged and adjusting for age, sex, and year of diagnosis).

One year after diagnosis, the mediated effect of differential stage at diagnosis is only apparent in the fourth and fifth quintile. As follow-up time increases, there was no evidence that the considered mediators could contribute to the effect of deprivation on survival. Medical care and differential treatment seem to play no relevant role in mediating the effect of deprivation on survival (Table 3, Fig. 4).

Including tumor site as a confounder or including imputed stage information did not alter our results (Appendix 1, 2).

Discussion

Patients living in the most deprived districts at the time of diagnosis, showed the lowest survival rates according to our analysis. The total effect of deprivation seemed to be

Table 3 Effect of Socioeconomic deprivation and mediators on odds of deaths at different times since head and neck diagnosis

	Deprivation level Odds ratio [a] (95%CI) (vs reference Q1)				
		Q2	Q3	Q4	Q5
	Direct Effect (SE Deprivation)[b]	1.18 (0.96–1.43)	1.14 (0.92–1.37)	1.32 (1.08–1.57)	1.37 (1.15–1.59)
	Mediator 1 (Medical Care)[c]	1.01 (0.99–1.04)	0.99 (0.97–1.00)	1.00 (0.97–1.04)	0.99 (0.98–1.00)
6 months	M2 (Stage at Diagnosis)[d]	1.08 (0.99–1.19)	1.14 (1.06–1.25)	1.32 (1.21–1.46)	1.44 (1.32–1.58)
	M3 (Treatment)[e]	0.97 (0.95–0.98)	0.97 (0.95–0.98)	0.93 (0.91–0.95)	0.93 (0.91–0.94)
	Total Effect (TE)	**1.25 (1.01–1.54)**	**1.23 (1.01–1.51)**	**1.63 (1.35–1.95)**	**1.81 (1.52–2.16)**
	DE (SE Deprivation)	1.19 (1.00–1.40)	1.14 (0.95–1.35)	1.13 (0.96–1.34)	1.35 (1.16–1.57)
	M1 (Medical Care)	0.99 (0.97–1.01)	1.00 (0.99–1.02)	1.01 (0.98–1.04)	1.00 (0.98–1.01)
1 year*	M2 (Stage at Diagnosis)	0.98 (0.93–1.05)	1.00 (0.93–1.06)	1.08 (1.02–1.15)	1.07 (1.01–1.14)
	M3 (Treatment)	0.98 (0.97–0.99)	0.97 (0.96–0.99)	0.96 (0.94–0.97)	0.95 (0.94–0.97)
	TE	**1.13 (0.96–1.34)**	**1.11 (0.92–1.30)**	**1.18 (1.01–1.38)**	**1.38 (1.20–1.60)**
	DE (SE Deprivation)	1.22 (0.97–1.30)	1.26 (1.08–1.45)	1.15 (1.00–1.31)	1.31 (1.15–1.49)
	M1 (Medical Care)	0.99 (0.97–1.01)	1.01 (0.99–1.02)	1.01 (0.98–1.03)	1.00 (0.99–1.02)
2 years*	M2 (Stage at Diagnosis)	0.95 (0.90–1.00)	0.99 (0.93–1.04)	1.00 (0.96–1.07)	1.01 (0.96–1.05)
	M3 (Treatment)	0.99 (0.98–0.99)	0.97 (0.96–0.98)	0.97 (0.96–0.98)	0.97 (0.96–0.98)
	TE	**1.12 (0.97–1.30)**	**1.21 (1.03–1.39)**	**1.13 (0.99–1.29)**	**1.29 (1.13–1.44)**
	DE (SE Deprivation)	1.01 (0.86–1.17)	1.14 (0.96–1.34)	1.09 (0.94–1.27)	1.33 (1.16–1.52)
	M1 (Medical Care)	1.00 (0.97–1.02)	0.98 (0.96–1.00)	1.02 (0.99–1.05)	1.00 (0.98–1.01)
5 years*	M2 (Stage at Diagnosis)	0.98 (0.89–1.04)	0.97 (0.88–1.04)	0.96 (0.90–1.03)	0.96 (0.92–1.04)
	M3 (Treatment)	1.00 (0.99–1.01)	1.02 (1.00–1.03)	0.98 (0.97–0.99)	0.99 (0.98–1.00)
	TE	**0.98 (0.82–1.13)**	**1.09 (0.91–1.28)**	**1.05 (0.90–1.22)**	**1.26 (1.12–1.47)**

Bold refers to the total effect

CI Confidence interval, *Q* Quintile. *SE* Socioeconomic deprivation

*Conditional on surviving previous time point

[a]Adjusted for age, sex, and year of diagnosis

[b]The natural direct effect odds ratio of exposure to socioeconomic deprivation levels in different quintiles on odds of death through neither medical care, stage at diagnosis, or treatment

[c]The natural indirect effect odds ratio mediated by exposure induced changes in medical care

[d]The partial indirect effect odds ratio mediated by exposure induced changes in stage at diagnosis

[e]The partial indirect effect odds ratio mediated by exposure induced changes in treatment received

strongest during the first six months after diagnosis. While the effect subsided considerably at later time points, the survival disparity between the most deprived and most affluent remained substantial after 5 years. Our mediation analysis showed that stage at diagnosis played a major role in mediating the effect of deprivation within the first 6 months after diagnosis. Its role diminishes, however, as follow-up time increases. In contrast, there was no evidence that treatment and medical care mediated any of the effect of deprivation on survival throughout the study period.

Given that our study is based on a large sample size drawn from the national cancer registry, our results confirmed the survival disparity between the deprived and affluent patients in Germany, which is in line with Jansen et al. (Jansen et al. 2014). This survival gap, however, is difficult to explain in light of the universal health care system present.

To our knowledge, this is the first study that employs a counterfactual causal inference approach to gain a comprehensive understanding of the direct and mediated effect of social disparity on HNC survival in Germany. Through our DAG, we presented a detailed framework to analyze causal relations and to identify potential factors that could help explain the effect of socioeconomic deprivation. By having a clear visualization of the causal relations among variables, we were able to avoid potential biases (such as indication bias or selection bias), which could arise, for example, from the medical care-comorbidities-treatment relationship.

Based on the current literature available, we presented three potential mediators: medical care, stage at diagnosis, and treatment. Medical care for instance, was included as a mediator in our analysis based on the inequalities in health

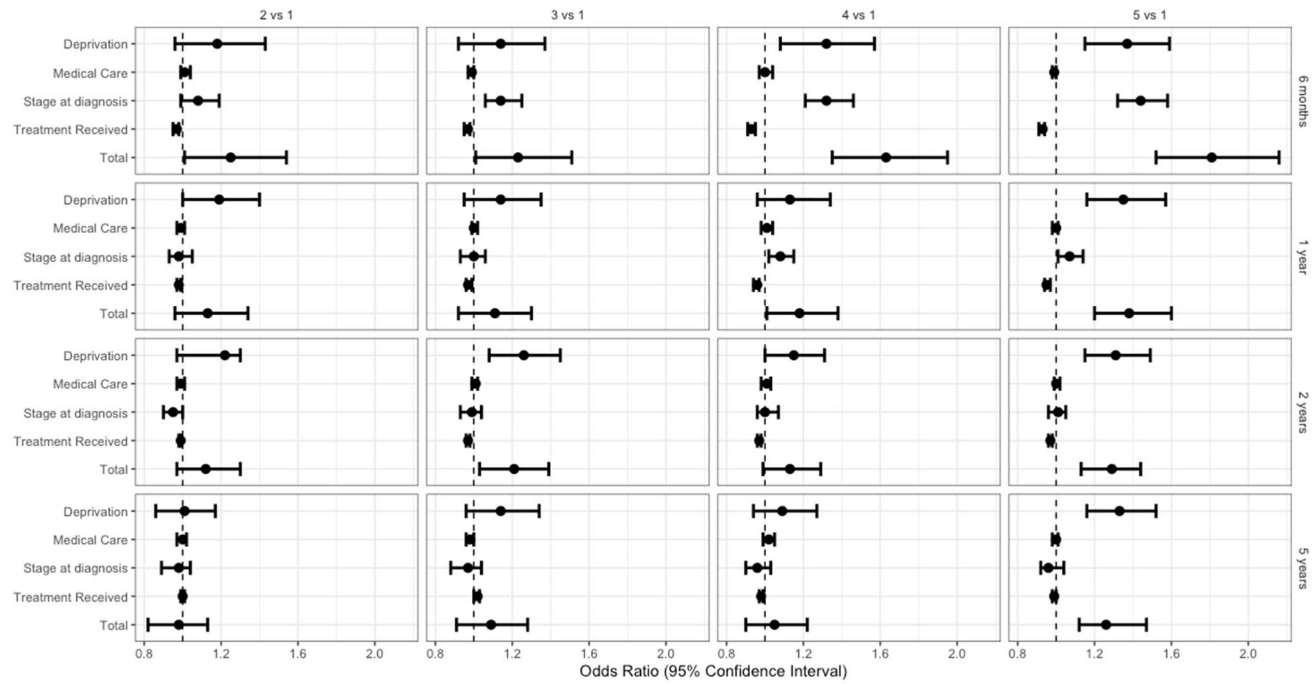

Fig. 4 Effect of deprivation and mediators on odds of deaths at different times since head and neck diagnosis

care utilization and availability experienced in Germany (Geyer 2008; Klein and von dem Knesebeck 2016). Patients from lower socioeconomic groups have been found to visit specialist practitioners less frequently, when compared with groups that are more affluent (Gruber 2010). Furthermore, results from a systematic review by Klein et al., suggested that major inequalities result primarily from prevention strategies, such as cancer screening (Klein et al. 2013).

Remarkably, in a study that investigated the effect of deprivation on breast cancer survival, Li et al. found that 35% (23–48%) of the higher mortality experienced by most deprived patients at six months after breast cancer diagnosis, was mediated by adverse stage distribution (Li et al. 2016). While stage at diagnosis is already recognized as a major prognostic factor in cancer survival, these results are interesting considering the wide availability of an advanced health care system in the UK, which is comparable to Germany.

Medical care along with minor vs. advanced treatment, on the other hand, revealed no evidence in mediating the effect of deprivation. Since the standardized "quality of health care" index is not available on a district level, we included the number of hospital beds (in the three previously mentioned departments) per districts' population as an indicator of health-care availability and access. Information, like health insurance coverage status (private vs public) or waiting times however, were not available in our measurement. In a study by Lungen et al., patients covered by the statutory health insurance (public option) were found to wait 3.08 times longer for an appointment than private health insurees in Germany (Lungen et al. 2008). Lacking this information could have led to the underestimation of the mediated effects of these factors. Moreover, missing-stage information could have also played a significant role in this regard. A large proportion of missing treatment information (49.3%) was linked to patients living in the most affluent districts (Appendix 2). This was confirmed by our stepwise logistic regression that revealed deprivation level, age, medical care, and stage as the most significantly associated variables to missing treatment information (Appendix 2). In contrast, only a small percentage of stage information was missing (4.6%).

From a clinical perspective, it seems surprising that treatment fails to mediate the mentioned effects. This could be explained by that treatment cannot compensate for the adverse survival prospect due to an advanced stage. However, in our analysis, we could not fully account for details of the treatment, such as the intent of treatment, administered radiation dose, the chemotherapy given, or the surgical procedure performed. Treatment in the form defined seems to be universally available and might follow the average health performance in a district that determines the received treatment.

Considering that the development of HNC is a multifactorial process associated with a variety of risk factors, we have also presented an alternate route in our DAG that could also explain the effect of deprivation on survival. Major risk factors that were missing in our dataset, such as tobacco, alcohol consumption, and comorbidities have already been established as prognostic variables that are directly influenced by socioeconomic factors. In addition, HPV infections have been recently linked to up to 25% of HNC cases (Kreimer et al. 2005). Patients diagnosed with HPV-positive HNC were more likely to be younger men, non-smokers, and have higher SES when compared with HPV-negative HNC patients (Gillison et al. 2008). HPV-positive oropharyngeal carcinoma is also associated with better response to treatment and better survival (Ang et al. 2010; O'Rorke et al. 2012). It was, therefore, necessary to address potential bias that might arise from the missing HPV status. The pathologic evaluation of HPV status is currently based on PCR-based strategies, type-specific in situ hybridization(ISH) techniques, and immune-histochemical detection of surrogate biomarkers (e.g. p16 protein) (Westra 2009). Tumors positive both for p16 immunochemistry and HPV ISH are usually classified as HPV-positive (Robinson et al. 2010). While acknowledging this as a limitation, we performed our sensitivity analysis based on tumor site, which we considered a proxy for the missing HPV status. We found no significant differences in tumor-site proportions according to deprivation, nor did our results change when we included tumor site as an additional confounder in our Cox regression and mediation analysis.

Conclusion

Our results confirmed the survival gap between deprived and affluent patients in Germany. We were able to quantify the direct effect of socioeconomic deprivation on survival and the effect mediated through medical care, stage at diagnosis, and treatment received. Considering data limitations, our results suggest that elimination of disparities in stage at diagnosis could contribute to a substantial reduction in survival disparities.

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Author contributions AB and DM contributed to the conception or design of the work. DM and DV contributed to the data acquisition. AB, LH, and DM contributed to the data analysis. AB and DM contributed to the interpretation of results. AB drafted the manuscript. AB, SFA, LE, LH, DV and DM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability This study was based on the German national cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, e. g, publications). Data were provided by the Robert Koch Institute (RKI).

Code availability Code is available in Appendix 3.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Appendix 1: Treating Tumor Site as a confounder: Sensitivity Analysis.

Table 1. Cox proportional hazards model analyses.

Deprivation Quintile *(vs Reference Quintile 1)*	**Hazard Ratio***	**95% CI**
Quintile 2	1.08	1.00-1.17
Quintile 3	1.11	1.03-1.20
Quintile 4	1.12	1.04-1.21
Quintile 5	1.24	1.16-1.33

*Adjusted for age, sex, year of diagnosis, and tumor site.

Abbreviations: CI=Confidence interval.

Table 2. Effect of Socioeconomic (SE) deprivation and mediators on odds of deaths at different times since head and neck diagnosis including tumor site as an additional confounder.

		Deprivation Level Odds Ratio [a] (95%CI) (vs reference Q1)			
		Q2	**Q3**	**Q4**	**Q5**
6 months	Direct Effect (SE Deprivation)[a]	1.17 (0.94-1.42)	1.14 (0.92-1.38)	1.32 (1.09-1.57)	1.37 (1.14-1.64)
	Mediator 1 (Medical Care)[b]	1.02 (0.99-1.04)	0.99 (0.97-1.00)	1.00 (0.97-1.04)	0.99 (0.98-1.00)
	M2 (Stage at Diagnosis)[c]	1.07 (0.98-1.19)	1.14 (1.04-1.26)	1.32 (1.22-1.45)	1.45 (1.33-1.58)
	M3 (Treatment)[d]	0.97 (0.95-0.98)	0.96 (0.95-0.98)	0.93 (0.91-0.95)	0.92 (0.90-0.94)
	Total Effect (TE)	**1.24 (0.99-1.53)**	**1.23 (1.00-1.51)**	**1.63 (1.35-1.95)**	**1.81 (1.51-2.16)**
1 year*	DE (SE Deprivation)	1.18 (0.99-1.39)	1.14 (0.96-1.34)	1.13 (0.96-1.32)	1.34 (1.17-1.56)
	M1 (Medical Care)	0.99 (0.97-1.01)	1.00 (0.99-1.02)	1.01 (0.98-1.04)	1.00 (0.98-1.01)
	M2 (Stage at Diagnosis)	0.98 (0.93-1.05)	0.99 (0.93-1.07)	1.08 (1.01-1.15)	1.08 (1.01-1.15)
	M3 (Treatment)	0.98 (0.97-0.99)	0.97 (0.96-0.99)	0.95 (0.94-0.97)	0.95 (0.94-0.96)
	TE	**1.12 (0.95-1.33)**	**1.10 (0.93-1.30)**	**1.17 (1.00-1.37)**	**1.37 (1.19-1.59)**
2 years*	DE (SE Deprivation)	1.21 (0.99-1.38)	1.25 (1.09-1.43)	1.14 (0.98-1.31)	1.30 (1.14-1.48)
	M1 (Medical Care)	0.99 (0.97-1.01)	1.01 (1.00-1.02)	1.01 (0.98-1.04)	1.00 (0.99-1.02)
	M2 (Stage at Diagnosis)	0.94 (0.88-0.99)	0.98 (0.92-1.05)	1.00 (0.95-1.07)	1.01 (0.95-1.05)
	M3 (Treatment)	0.98 (0.98-0.99)	0.97 (0.95-0.98)	0.97 (0.96-0.98)	0.96 (0.95-0.97)
	TE	**1.11 (0.95-1.27)**	**1.20 (1.04-1.37)**	**1.11 (0.96-1.28)**	**1.27 (1.10-1.43)**
5 years*	DE (SE Deprivation)	1.00 (0.85-1.17)	1.14 (0.98-1.33)	1.09 (0.94-1.26)	1.33 (1.15-1.51)
	M1 (Medical Care)	1.00 (0.97-1.02)	0.98 (0.96-1.00)	1.02 (0.99-1.05)	1.00 (0.98-1.01)
	M2 (Stage at Diagnosis)	0.97 (0.89-1.03)	0.96 (0.87-1.04)	0.96 (0.90-1.04)	0.96 (0.91-1.05)
	M3 (Treatment)	1.00 (0.99-1.01)	1.01 (1.00-1.03)	0.98 (0.97-0.99)	0.99 (0.98-1.00)
	TE	**0.97 (0.81-1.12)**	**1.09 (0.92-1.27)**	**1.05 (0.90-1.23)**	**1.26 (1.11-1.47)**

[a] Adjusted for age, sex, and year of diagnosis and tumor site.

[b] The natural direct effect odds ratio of exposure to socioeconomic deprivation levels in different quintiles on odds of death through neither medical care, stage at diagnosis, or treatment.

[c] The natural indirect effect odds ratio mediated by exposure induced changes in medical care.

[d] The partial indirect effect odds ratio mediated by exposure induced changes in stage at diagnosis.

[e] The partial indirect effect odds ratio mediated by exposure induced changes in treatment received.

* Conditional to surviving previous time point. Abbreviations: CI= Confidence interval, Q= Quintile. SE= Socioeconomic deprivation

Appendix 2: Missing Data: Sensitivity Analysis

Table 1. Proportion of missing information of stage at diagnosis and treatment received.

		Deprivation Level				
	All patients	Least Deprived	2	3	4	Most Deprived
Stage at Diagnosis (%)						
Stage I	14.5	15.4	14.7	13.3	14.5	14.3
Stage II	11.1	10.2	11.8	11.2	11.1	11.2
Stage III	15.2	14.4	16.4	15.8	14.8	15.0
Stage IV	54.6	53.6	51.3	54.4	55.5	57.6
Missing	4.6	6.2	5.9	5.2	4.0	1.9
Treatment (%)						
Minor	13.1	5.0	8.5	13.5	18.5	19.5
Advanced	58.1	45.7	49.4	58.4	63.4	71.8
Missing	28.8	49.3	42.1	28.1	18.2	8.6

Table 2. Logistic regression showing association of missing treatment information and age and deprivation quintile and their interactions.

Coefficients	**Odds Ratio**	**95% CI**	**P-value**
Age	1.01	1.00-1.02	<0.001
Quintile 1	Reference	---	----
Quintile 2	0.73	0.46-1.14	0.16
Quintile 3	0.74	0.45-1.21	0.24
Quintile 4	0.20	0.12-0.33	<0.001
Quintile 5	0.07	0.04-0.12	<0.001
Age*Quintile 2	1.00	0.99-1.01	0.88
Age*Quintile 3	0.99	0.98-1.00	0.02
Age*Quintile 4	1.00	0.99-1.01	0.51
Age*Quintile 5	1.00	1.00-1.01	0.13

[*] Interaction

Abbreviations: CI=Confidence interval.

Table 3. Stepwise logistic regression to determine variables that were associated the most with missing treatment information.

Coefficients	Odds Ratio	95% CI	P-value
Age	1.01	1.00-1.01	<0.001
Sex (male)	0.95	0.89-1.02	0.14
Quintile 1	Reference	---	---
Quintile 2	0.73	0.68-0.79	<0.001
Quintile 3	0.39	0.36-0.43	<0.001
Quintile 4	0.23	0.21-0.25	<0.001
Quintile5	0.10	0.09-0.11	<0.001
Stage I	Reference	---	---
Stage II	0.78	0.71-0.87	<0.001
Stage III	0.58	0.52-0.63	<0.001
Stage IV	0.54	0.50-0.59	<0.001
Medical care	0.99	0.98-1.00	<0.001

Abbreviations: CI=Confidence interval.

Table 4. Effect of Socioeconomic deprivation and mediators on odds of deaths at different times since head and neck diagnosis based on five imputed datasets.

		Deprivation Level Odds Ratio [a] (95%CI) (vs reference Q1)			
		Q2	**Q3**	**Q4**	**Q5**
6 months	DE (SE Deprivation)[a]	1.18 (1.10-1.28)	1.14 (1.05-1.22)	1.31 (1.23-1.40)	1.36 (1.28-1.44)
	M1 (Medical Care)[b]	1.02 (1.01-1.03)	0.99 (0.98-1.00)	1.00 (0.99-1.02)	0.99 (0.98-0.99)
	M2 (Stage at Diagnosis)[c]	1.09 (1.06-1.13)	1.14 (1.11-1.19)	1.32 (1.27-1.37)	1.42 (1.38-1.47)
	M3 (Treatment)[d]	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.93 (0.92-0.94)	0.93 (0.92-0.93)
	Total Effect (TE)	**1.28 (1.18-1.39)**	**1.24 (1.14-1.34)**	**1.60 (1.50-1.72)**	**1.76 (1.65-1.88)**
1 year*	DE (SE Deprivation)	1.21 (1.13-1.29)	1.14 (1.07-1.22)	1.14 (1.07-1.23)	1.36 (1.29-1.44)
	M1 (Medical Care)	0.99 (0.98-1.00)	1.00 (1.00-1.01)	1.01 (1.00-1.02)	1.00 (0.99-1.01)
	M2 (Stage at Diagnosis)	0.98 (0.96-1.00)	1.01 (0.99-1.04)	1.09 (1.06-1.12)	1.06 (1.04-1.09)
	M3 (Treatment)	0.98 (0.97-0.98)	0.97 (0.96-0.97)	0.95 (0.94-0.96)	0.96 (0.95-0.96)
	TE	**1.16 (1.08-1.23)**	**1.12 (1.05-1.20)**	**1.19 (1.13-1.28)**	**1.38 (1.31-1.46)**
2 years*	DE (SE Deprivation)	1.24 (1.17-1.31)	1.25 (1.18-1.33)	1.15 (1.08-1.21)	1.34 (1.29-1.41)
	M1 (Medical Care)	0.99 (0.98-1.00)	1.00 (1.00-1.01)	1.01 (1.00-1.02)	1.00 (1.00-1.01)
	M2 (Stage at Diagnosis)	0.95 (0.94-0.98)	0.99 (0.96-1.00)	0.99 (0.97-1.02)	1.01 (0.99-1.02)
	M3 (Treatment)	0.98 (0.98-0.99)	0.97 (0.96-0.97)	0.97 (0.96-0.97)	0.97 (0.96-0.97)
	TE	**1.15 (1.08-1.21)**	**1.20 (1.12-1.27)**	**1.12 (1.06-1.18)**	**1.32 (1.25-1.37)**
5 years*	DE (SE Deprivation)	1.01 (0.95-1.08)	1.10 (1.04-1.18)	1.07 (1.00-1.13)	1.30 (1.24-1.37)
	M1 (Medical Care)	1.00 (0.99-1.01)	0.98 (0.97-0.99)	1.02 (1.01-1.03)	1.00 (0.99-1.00)
	M2 (Stage at Diagnosis)	0.99 (0.96-1.02)	0.99 (0.96-1.02)	0.96 (0.93-0.99)	0.95 (0.93-0.98)
	M3 (Treatment)	1.00 (0.99-1.00)	1.01 (1.01-1.02)	0.98 (0.97-0.98)	0.99 (0.99-1.00)
	TE	**1.00 (0.94-1.07)**	**1.08 (1.02-1.16)**	**1.03 (0.96-1.09)**	**1.23 (1.17-1.29)**

[a] Adjusted for age, sex, and year of diagnosis.
[b] The natural direct effect odds ratio of exposure to socioeconomic deprivation levels in different quintiles on odds of death through neither medical care, stage at diagnosis, or treatment.
[c] The natural indirect effect odds ratio mediated by exposure induced changes in medical care.
[d] The partial indirect effect odds ratio mediated by exposure induced changes in stage at diagnosis.
[e] The partial indirect effect odds ratio mediated by exposure induced changes in treatment received.
* Conditional to surviving previous time point.
Abbreviations: CI= Confidence interval, Q= Quintile. SE= Socioeconomic deprivation

Declarations of Independence

(1) I declare that I have not completed or initiated a doctorate procedure at any other universities.

(2) I declare that all information given is accurate and complete. The thesis has not been used previously at this or any other university in order to achieve an academic degree.

(3) I declare under oath that this thesis is my own work entirely and has been written without any help from other people. I complied with all regulation of good scientific practice, and I used only the sources mentioned and included all the citations correctly both in word and content.

Halle (Saale), Ahmed Bedir

Declarations of Previous Dissertation Attempts

I declare that this work is the first attempt of writing a dissertation. Also, I declare that this work is exclusively submitted as a dissertation for the Medical Faculty of Martin Luther University Halle-Wittenberg.

Halle (Saale), Ahmed Bedir

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