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Social Environment and Cancer in Europe

Towards an Evidence-Based Public Health Policy

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Too many European citizens with cancer die prematurely every year because of inequalities in outcome between population groups—rich or poor, highly educated or not, living in urban or rural areas.

We dedicate this book to all Europeans who have been diagnosed with cancer, to their loved ones, and to those who may develop cancer in the future.

We hope that the wisdom of our co-authors will help European Union and national politicians to understand better these inequalities in cancer survival and to drive policy to reduce or eliminate them.

Foreword

The successes in health for each European Union (EU) citizen are sadly diminished by the absence of upfront awareness that we are not equal. Inequalities are numerous and their number and types may vary with time, geographic and socioeconomic characteristics, for example. Some are part of our societies' cultures and richness and need not be corrected, while others, unfortunately, are created by our societies themselves, which should be a source of concern. When health is concerned, efforts to eliminate disparities have always been, to some extent, in the mind of health stakeholders, including health policy-makers but most of all patients, their carers and even citizens. Nevertheless, it is clear that the number and extent of successes of breakthroughs in achieving equity do not correlate with those in health. The absence of synchronization creates further disparities and inequalities with time. Immediate measures are needed to stop widening the gap between health breakthroughs and health equity. One step forward would require that frameworks for the implementation of existing and future health guidelines and breakthroughs take into account disparities upfront and adapt accordingly. The greatest attention should be given to those characteristics that may engender disparities or inequalities.

In the cancer field, it is now acknowledged that cancer is not one but 200 diseases; that one given tumour is heterogeneous and consists of different types of cancer cells. Tumour development and response to treatment are exquisitely linked to surrounding normal cells such as the immune cells, and other features of the cancer patient such as the microbiome. A systems approach to understanding cancer is thus the gold standard, and the quest for a comprehensive personalized medicine approach has been advocated for decades. In the context of such a cultural transformation regarding cancer knowledge, it seems appropriate to underscore the need to integrate the heterogeneity of our society, to integrate socioeconomic inequalities and health determinants, with the heterogeneity of the tumour in its environment when the aim is to conquer cancer.

Conquering cancer, whatever the 'disparity', requires gaining knowledge of disparities at the same time as gaining knowledge of cancer, with similar enthusiasm, curiosity, motivation and scientific rigor. Numerous efforts have been made at national, EU and worldwide levels. The results are available albeit not specifically

dedicated to Europe, and documents to describe methodologies and future directions are lacking. A comprehensive analysis of what has been done and what should be done and how, may provide all stakeholders involved in conquering cancer with sufficient awareness to achieve, in a rapid and efficient manner, a major step for evidence-based public health policy.

This book is, to my knowledge, a unique document that fulfils this comprehensive analysis, bringing together in one volume not only the currently available data on social inequalities in cancer in Europe, reaching out to the description of contextual factors, but also highlighting the remaining questions to be answered. Although each chapter provides specific information and can be read individually, the order of the chapters as defined by the authors provides an effective training process for the reader to gain the necessary knowledge and find answers to questions. The chapters underscore the numerous national and EU networks that together have already provided much input, including a common measure for deprivation (European Deprivation Index), and move forward the necessary approaches towards an evidence-based European public health policy for tackling social inequalities in cancer.

This book, through its European authorship, sets the steps necessary to make a substantial difference in how conquering cancer in Europe will do so while reducing inequalities and guaranteeing equal access to all.

Christine Chomienne
Vice-Chair, Mission Board Cancer
at the European Commission
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About the Editors

Guy Launoy, MD has been a doctor of medicine since 1987 and a doctor of epidemiology and public health since 1997. He has worked as a researcher at the French Institute in Medical Research (INSERM) from 1993 to 2003 and as professor in epidemiology and public health at the University of Caen in France since 2004. Dr. Launoy was president of the French network of cancer registries (FRANCIM) during 2008–2012. He is director of Unit 1086 INSERM (Caen) since 2012 and president of the *Canceropole* of Northwest France since 2019. He has supervised approximately 20 PhD candidates in public health at the University of Caen. Dr. Launoy has published 300 articles on cancer, focusing on epidemiology, screening, and social and public health aspects. He is particularly interested in cancer registration at the national and European level, cancer screening organisation, and social epidemiology of cancer and its impact on public health policy. Dr. Launoy advocates for a concerted and evidence-based European policy for the measurement of social inequalities in health and for it to tackle social inequalities in health. He serves as an expert with the European Commission and several French institutions and agencies (INSERM, HCERES, INCa, HAS, ANSES).

Vesna Zadnik, MD, PhD has been a public health specialist and a doctor of science in the field of epidemiology since 2006. She is the head of the Epidemiology and Cancer Registry Sector at the Institute of Oncology Ljubljana in Slovenia since 2018. She directs and carries out detailed epidemiological analysis using data from the National Cancer Registry and the registries of cervical and breast cancer screening programmes in order to elucidate a certain condition, for example, cancer incidence, time series, spatial distribution, and survival of cancer patients.

Among other roles, Dr. Zadnik is currently serving as European representative on the board of directors of the International Association of Cancer Registries and as coordinator in the field of cancer burden surveillance in the Executive Council of the Slovene National Cancer Control Plan from 2017–2021.

Michel P. Coleman, MD, FFPH has been professor of epidemiology and vital statistics at the London School of Hygiene and Tropical Medicine (LSHTM) since

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Dr. Coleman has worked at the World Health Organization's (WHO) International Agency for Research on Cancer in Lyon, France (1987–1991), and was medical director of the Thames Cancer Registry in London, UK (1991–1995). He was head of the Cancer and Public Health Unit (LSHTM) during 1998–2003, deputy chief medical statistician at the Office for National Statistics (ONS) during 1995–2004, and head of the WHO UK Collaborating Centre on the Classification of Diseases at ONS during 1996–2004.

Dr. Coleman has published 500 articles on cancer and public health, and has taught epidemiology in many countries. His main interests are in the application of trends in cancer incidence, mortality, and survival to the public health control of cancer. He has been an advisor on cancer registration, cancer research, and cancer control to governments in several countries, and to the European Union.

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Part I
General Considerations and Methodologic Aspects

Chapter 1
Social Inequities in Cancer: Why Develop Scientific Research?

Guy Launoy, Vesna Zadnik, and Michel P. Coleman

Social inequities in health are defined as 'any relationship between health and the social category to which individuals belong' (Guichard and Potvin 2010) or as 'all the differences in mortality and morbidity between social groups that occupy hierarchical positions in terms of professions, income or access to knowledge' (Chauvel and Leist 2015). In fact, these mortality or morbidity gaps are the visible and measurable part of many complex processes by which an individual's social environment determines his or her health. Thus, according to the World Health Organization (WHO 2017), '*health inequities are differences in health status or in the distribution of health resources between different population groups, arising from the social conditions in which people are born, grow, live, work and age*'.

What characterises social inequities in health and distinguishes them from health inequities arising from biological diversity is that they are not 'natural' or 'innate' but are constructed by collective decisions pertaining to the organisation of care and the overall organisation of society, and as such are amendable. According to a principle of social justice—and, for the WHO, because they are constructed by collective decisions—these inequities are unjust since they may be avoided or amended by balanced public policies. In countries for which equality and equity are founding values, and beyond issues of individual freedom and philosophical, moral or ethical choices, the implementation of policies aiming to reduce social inequities in health is a necessary principle underpinning the functioning of the state. The reduction of these social inequities in health contributes to social cohesion.

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The implementation of an effective policy to reduce social inequities in health is not solely dependent on political will. Since the publication of the Black Report in the United Kingdom in 1980 (DHSS 1980), it has been acknowledged that poverty alone cannot account fully for health inequities because the latter do not disappear above a certain level of income. In fact, social inequities in health are not confined to the most disadvantaged categories of the population: they concern the entire population with a regular continuum of deterioration in health indicators from the most advantaged to the most disadvantaged, each social class having more deteriorated health indicators than the one immediately above. The distribution of health problems is thus socially stratified, with those in a higher social position being in better health than those just below them, and so on down to the most deprived. In Europe, this social gradient, highlighted by the pioneering work carried out in England and supported by charismatic opinion leaders, has been the mainstay of policy thinking in most European countries, including Sweden and Norway, where the extent of social inequities in income is moderated by proactive policies.

The social determination of health is an extremely complex phenomenon involving many factors of an individual, contextual, proximal or distal nature, all of which interact along different causal pathways. Broadly speaking, the most proximal determinants whose causality can be directly demonstrated concern individual behaviours and psychological processes, the intermediate determinants are those pertaining to access to the health system, family, friendship and professional networks, and the most distal ones concern macro-economic policies governing education, taxation, social insurance, culture and national solidarity. The latter can be considered as the ‘causes of the causes’, but their indirect implication can be demonstrated only by constructing models in which their effect is mediated by more proximal determinants.

As far as cancers are concerned, some schools of thought consider that they are socially determined only by individual behavioural factors such as tobacco and alcohol consumption, diet and lack of screening, thereby removing the dimension of social determination from the equation. These fatalistic theories (Rawls 1971; Dworking 2002) consider individuals to be totally responsible for the choices they make and that society should not bear the costs of those choices, nor that it should act upstream on their environment. Apart from the fact that this theory partly justifies the absence of even establishing any policy, it precludes the possibility of conceiving a satisfactory model for understanding the construction of these inequities and enacting an adequate health policy. In fact, the behaviour of individuals is highly dependent on their social entourage and networks, as well as on their environment and their living, working and educational conditions, and their access to resources, services and infrastructures. Finally, how this environment influences the behaviour of individuals depends on the overall socio-economic conditions of society: national wealth, the state of the labour market, the economy, cultural factors, etc., and how they are distributed in the population (Starfield et al. 2005; Warnecke et al. 2008; Marmot et al. 2012; Braveman and Williams 2011; Burgard and Lin 2013; Bélanger et al. 2016; Landrigan 2018).

The interactions between all factors involved in their construction make the study of the causes of social inequities complex, enthralling and eminently political. Indeed, while the variety of factors involved brings together many academic disciplines and many professions, making interdisciplinarity compulsory, the emphasis on one causal factor or another brings into play different philosophical choices or models of society. Thinkers who point the finger at social determinism and emphasise the behaviour of individuals regarding tobacco, alcohol, food, lack of screening, etc., insist on the responsibility of the individual and their choices for their future. Others who accord prime importance to the effects of context, such as the place of abode, stress the importance of urban planning. Those who highlight occupational exposures point to the importance of protecting employees in the workplace. The issue of proportionate universalism that will be discussed in this book also has major political implications. The now well-documented hypothesis of the 'life course perspective' (De Kok et al. 2008), according to which inequities begin even before birth and accumulate throughout life, posits the need for lifelong interventions. Still other thinkers underline the role of macroeconomic determinants, that is, the causes of the causes, and argue for the need for intersectoral policy programmes that are not limited to the organisation of care and prevention, but which aim to embed the objective of reducing social inequities in health into industrial and employment policies and in economic and fiscal measures. There are also European initiatives (DETERMINE programme in 2007) that have sought to develop an economic approach to reducing social inequities in health. Some economists even consider that the extent of income distribution is inversely associated with a country's overall health indicators (Wilkinson and Pickett 2009).

Because of their frequency and seriousness, social inequities in the field of cancer account for a major part of social inequities in health in Europe, and reducing them can be a major political issue at national and community levels, a priority established by several countries, the European Commission and the WHO in recent years (WHO 2019). Just as individual clinical care and the treatment of cancer patients must be based on scientifically grounded evidence, any community health policy aimed at reducing social inequities in cancer must be based on the measurement of observable facts, with detailed knowledge of the mechanisms and duly conducted experiments demonstrating the effectiveness and safety of the proposed measures in real-life conditions. As the chapters of this book demonstrate, we now have tools, databases and a body of knowledge that make it possible to quantify social inequities in cancer in Europe and to assess their importance on a site-by-site basis. Research teams are now unravelling the different mechanisms by which social inequities in incidence and survival are constructed. In addition to this knowledge which constitutes the scientific underpinnings for policy-making, interventional research conducted in the general population is giving rise to experimental action that is extremely useful for designing evidence-based policies for reducing social inequities in health.

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Chapter 2
Population-Based Cancer Registries: A Data Stream to Help Build an Evidence-Based Cancer Policy for Europe and for European Countries

Pascale Grosclaude and Vesna Zadnik

Modern cancer registration started in Europe in the 1930s and 1940s. It gradually developed over the following decades, and population-based cancer registries (PBCR) have now become the best tools for measuring the burden of cancer in the community. Historically, cancer registry data complemented mortality data and were used to estimate cancer incidence and trends over time. They are considered by the WHO as a core component of national cancer control strategies and serve as an example for surveillance of other important diseases (WHO 2000, 2011, 2017). For the European Union, population-based cancer registries play a key role in cancer control (Gouveia et al. 2008). Nowadays, the global cancer registration community consists of almost 500 population-based cancer registries in 65 countries. They collect data on all new cancer cases and provide information on individual records at various geographical scales, ranging from national to regional or more local areas (ECIS 2019).

According to the International Agency of Research of Cancer reports, there are currently 24 European countries out of 40 with complete population coverage, partial registration has been introduced in 10 countries, and only 6 countries have no registries (Ferlay 2019). At the end of 2015, 60% of the European population was covered by population-based cancer registration. In 1990, the European Network of Cancer Registries (ENCR; www.encr.eu) was established within the framework of the Europe Against Cancer Programme of the European Commission. For several years now, ENCR activities have been supported by the European Commission's Joint Research Centre. The ENCR currently has more than 150 members. Its main role is to promote collaboration between cancer registries, define data collection

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standards, provide training for cancer registry personnel and regularly disseminate information on incidence and mortality from cancer in Europe. Thus, the ENCR has set the following objectives: (1) to improve the quality, comparability and availability of cancer incidence data; (2) to create a basis for monitoring cancer incidence and mortality in the European Union; (3) to provide regular information on the burden of cancer in Europe and (4) to promote the use of cancer registries in cancer control, healthcare planning and research.

A population-based cancer registry (PBCR) is an ongoing surveillance system to collect, store, manage, analyse and disseminate information on the occurrence of cancer in a defined population. PBCRs collect information on all new cases of cancer that occur in a well-defined population, corresponding to a specific geographical region. Cancer registries in Europe, as in many other high-income countries, are now going beyond their original role of estimating cancer incidence rates and comparing cancer profiles in different populations. They are expanding their range of activities to include studies on the causes of cancer and its prevention. They are playing an important role in guiding the implementation of evidence-based interventions and in measuring changes in the population after the implementation of these interventions, particularly in the case of organised screening. They also conduct studies that provide information on the effectiveness of care, both by providing information on survival and by describing cancer management in the population (Coebergh et al. 2015; Siesling et al. 2015). PBCRs nowadays are considered critically important for planning and evaluation of National Cancer Control Plans, in the field of primary and secondary prevention, diagnostics, treatment and rehabilitation, so too when it comes to planning for facilities and funding needed for cancer control (personnel, equipment and hospital capacities) as well as for clinical and epidemiological research, including regional and international multi-centric studies. Piñeros et al. (2017) propose a general framework for cancer surveillance that permits monitoring of the core components of cancer control. PBCRs play a central role during early detection and treatment/care phases by providing indicators of population-based incidence and survival.

Data collection in cancer registries is carried out systematically from several sources, which may vary according to the organisation of the health system of the country. These sources generally include public or private hospitals, laboratories (including pathology laboratories), data from health insurance claims and death certificates. Despite rapid advances in computerised health information systems, most registries use a mixture of ‘passive’ collection of data (relying on health workers to complete notification forms and forward them to the registry) and ‘active‘ methods, whereby staff of the cancer registry visit the various sources to identify and abstract the relevant information.

Cancer registries should collect data that are adequate and relevant but not excessive. The number of data items should thus be limited for two reasons—quality (the fewer data items, the greater the likelihood that these will be recorded correctly) and confidentiality (the more data items, the more chance of an unintended breach of confidentiality when releasing data). There is a minimum dataset of 10–11 variables that no cancer registry could function without; however, a slightly broader list of

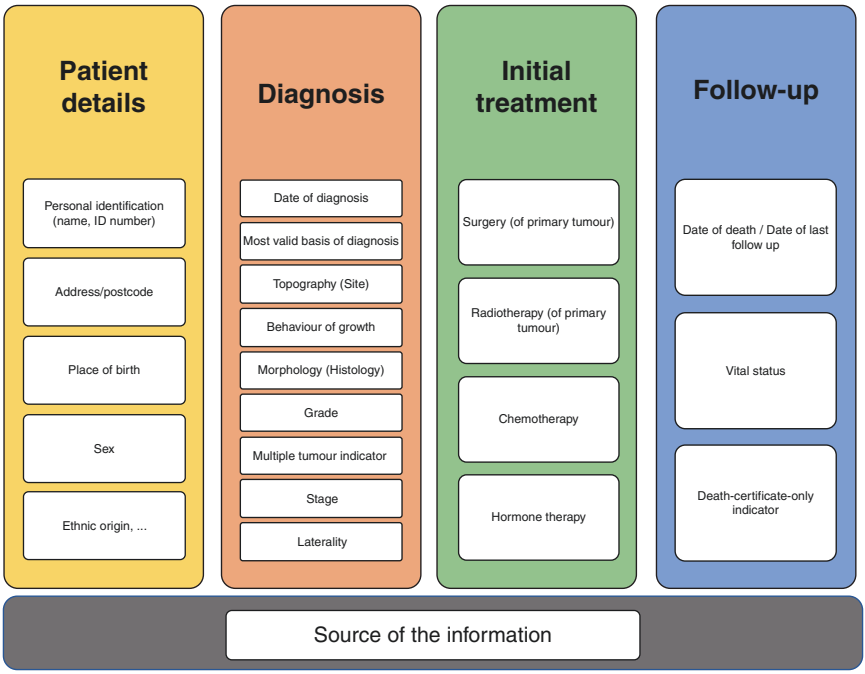

Fig. 2.1 Essential variables to be collected by population-based cancer registries—European Network of Cancer Registries recommendation (ENCR 2019)

essential variables is proposed by ENCR (ENCR 2019). They are presented in Fig. 2.1 divided into the following categories: patient's details, diagnosis data, initial treatment information and follow-up. In addition to information on cancer, patients demographic data from the background population should be available to the cancer registry to serve as the denominator for calculating rates or proportions.

As already stressed, cancer registration is not only an ongoing process of data collection and storage but also entails systematic analysis, interpretation and communication of data on the occurrence and characteristics of cancer. All these activities depend on the quality of the data in the registry; they must be comparable, complete and valid. The growing number of registries in Europe and the evolution of the data collected present challenges to maintain and improve the three decisive elements in the European registries to allow their use in comparative studies across Europe as well as with the rest of the world. Data comparability between registries has always been an important issue, and harmonisation of registries procedures is one of the main objectives of the cancer registries community. To enable global comparisons, registries code data using international classifications (ICD-O (Fritz et al. 2000), TNM (Brierley 2017), Toronto Guidelines (Bhakta and Rodriguez-Galindo 2018), and comply with the standards and guidelines prepared by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer IARC (Jensen 1991). These rules have been adapted by the

ENCR to also take into account the specificities of European registries (Tyczynski 2003). In order to follow the evolution of diagnostic and care practices while also reflecting the capacities for cancer registration, these standards and recommendations in relation to different aspects of cancer registry practice in Europe are updated by ENCR working groups. These guidelines deal with technical aspects of data collection, others with problems of confidentiality and privacy protection within the process of cancer registration (ENCR 2019).

It is also crucial to ensure that the registration does not leave out a part of the population, especially if it is the most disadvantaged. Studies using hospital registries data are likely to be subject to recruitment bias. The same risk of bias exists when using data from private or public health insurance groups. Population-based registries—by definition, capture all cases regardless of diagnostic modalities, nature or place of treatment by cross-referencing multiple sources of information—avoid this bias and correspond to the highest level of evidence when measuring the frequency of a problem (OCEBM Levels of Evidence Working Group 2019). However, even for a population-based registry, some populations are difficult to identify; this is what can happen to immigrants or homeless people. Completeness of registration in the PBCRs is traditionally monitored through semi-quantitative indicators such as the mortality-to-incidence ratio, stability of incidence over time, comparison of incidence rates with other (similar) populations, the proportion of cases microscopically verified and death certificate methods.

To conclude, the importance of population-based cancer registries cannot be overemphasised. The data provided by the PBCRs serve as a starting point for all coherent planning, evaluation and implementation of cancer control measures. In European countries, we already run numerous national or regional PBCRs of high quality which capture standardised, detailed information on all cancer cases occurring in the population. Nevertheless, further challenges remain for the European cancer registration community. Among the most complex are to ensure the legal basis for the operation of the registers in the context of GDPR, improvement of the coherence of European cancer registry data and further promotion of data from cancer registers among clinicians and stakeholders.

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Chapter 3
The European Deprivation Index: A Tool to Help Build an Evidence-Based Cancer Policy for Europe

Guy Launoy, Ludivine Launay, Joséphine Bryère, Olivier Dejardin, and Elodie Guillaume

Ever since the pioneering work highlighting social and geographical inequalities in health by Engels for the United Kingdom and Villermé for France in the nineteenth century, the relevance of tools for assessing the social environment and social status has been a burning issue. Furthermore, with the ever-increasing number of approaches for making such an assessment, the question of how these approaches can be compared across countries has become primordial. Since Marmot's work and the first reports on social inequalities in Europe (Marmot and Bobak 2000; Marmot 2013), the desire to implement European policies capable of reducing such inequalities has encountered the difficulty of measuring policies and comparing their effects in an equitable manner. Taking the example of cancer, the question of its social determinants at both proximal and distal levels is particularly important in types of cancer for which incidence and mortality data are available and comparable between European countries.

For several years, there has been a wide consensus that socioeconomic status cannot be summed up by a single marker (Braveman et al. 2005; Galobardes et al. 2006). At an individual level, socioeconomic status is usually explored in three fields: income, education and/or socio-professional category. The collection of individual socioeconomic data consistently comes up against the problem of their absence from medical files or from medico-administrative databases, together with the issue of legal protection. Data allowing the individual assessment of socioeconomic status is therefore rarely available. When they are available, for instance, in cohorts, they may be exposed to a non-response bias in questionnaire surveys. In addition, assessment at the individual level cannot account for contextual elements related to factors such as the place of residence (green spaces, criminality,

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equipment for physical activity, supply of consumer goods). Aggregated composite indices have been constructed to allow the measurement of the social environment in large, unbiased samples. Using a weighted combination of census data, they make it possible to integrate contextual elements and to assess the socioeconomic environment at different area levels (Krieger 1992). These kinds of aggregated socioeconomic index, which were originally developed in the early 1980s in the United Kingdom (Morris and Carstairs 1991; Jarman 1983), are now widely used. Most of them have been designed for their relevance in a given area or a given country, and their methodology of construction varies considerably, some having any theoretical basis. The absence of a shared definition of poverty or deprivation and the lack of a comparable methodology for assessing them drastically limits the scope for comparing results between countries, thereby hampering the transmission of a clear message to public health decision-makers for tackling socioeconomic inequalities at a national or international level.

At the European level, countries do not share the same culture, educational system, social structures, healthcare systems or macroeconomic environment, and thus it is inconceivable that any single index used identically in every country is able to account fully for the deprivation in every country in Europe. On the other hand, relevant national indexes could be designed with the same basic concepts, same method of construction, and with a common survey owing to administrative procedures accepted Europe-wide. The common concept is that of relative poverty, first proposed by the sociologist Peter Townsend:

> 'individuals, families and groups in the population can be said to be in poverty when they lack the resources to obtain the type of diet, participate in the activities and have the living conditions and the amenities which are customary, or at least widely encouraged or approved in the societies to which they belong. Their resources are so seriously below those commanded by the average family that they are in effect excluded from the ordinary living patterns, customs, and activities' (Townsend 1987).

Whatever the country, therefore, individuals may be considered as deprived when they lack the resources to obtain these fundamental needs, diet, type of living conditions, amenities or services which are commonly obtained by the majority of people in the societies to which they belong. This conceptual definition of deprivation, partly based on the population's own perception, was the basis for the construction methodology of the British indices (Gordon et al. 2000; Dorling et al. 2007). It involves the use of surveys specifically designed to study deprivation at the individual level. In order to propose a measure of relative poverty that should be as comparable as possible between European countries, these basic needs defined specifically in each country have to be identified using the same European survey.

The EU-SILC project was set up in 2003 to obtain data on structural indicators of social cohesion to ensure coordination in the field of social inclusion and pensions. These statistics on income and living conditions are an instrument intended to collect multidimensional, cross-sectional and longitudinal microdata, current and comparable, on objective poverty (income), subjective poverty, social exclusion and living conditions. The survey includes a European standardised questionnaire specifically designed to study deprivation, consisting of nine questions common to European Union members and evaluating needs that directly or indirectly induce

financial inability. For each European Union member, the sum of weights for the sample design and the response rate to the national questionnaire are tailored on the basis of the national population size (Gordon 1995). All analyses are weighted for non-response and adjusted for sample design to ensure the representativeness of the results for each member. This sample, which is regularly updated, constitutes a very precious tool to identify the fundamental needs in each European country and to build a deprivation indicator in the most comparable way possible between the different European countries (Fig. 3.1 – Step 1). Once the status relative to deprivation has been defined for each individual in the EU-SILC sample, the construction of the aggregated index is based on a logistic regression, making it possible to select the combination of variables associated with this status from the common variables between the EU-SILC database and the national census. The analysis is carried out separately for each country concerned (Fig. 3.1 – Step 2).

The global methodology for the national versions of the European Deprivation Index (EDI) has already been detailed extensively (Pornet et al. 2012; Guillaume et al. 2016). The EDI is built in three steps (Fig. 3.1).

Step 1: The first step consists in constructing an individual indicator of deprivation based on the identification of fundamental needs in EU-SILC data. To be considered as a potential fundamental need, a good or service has first to be possessed by at least 50% of households. Among these preselected needs, the goods/services that fewer than 50% of households did not have because they could not afford them (questions formulated with the wording 'ability to' or 'capacity to') are considered as potential fundamental needs. Fundamental needs are those associated with both

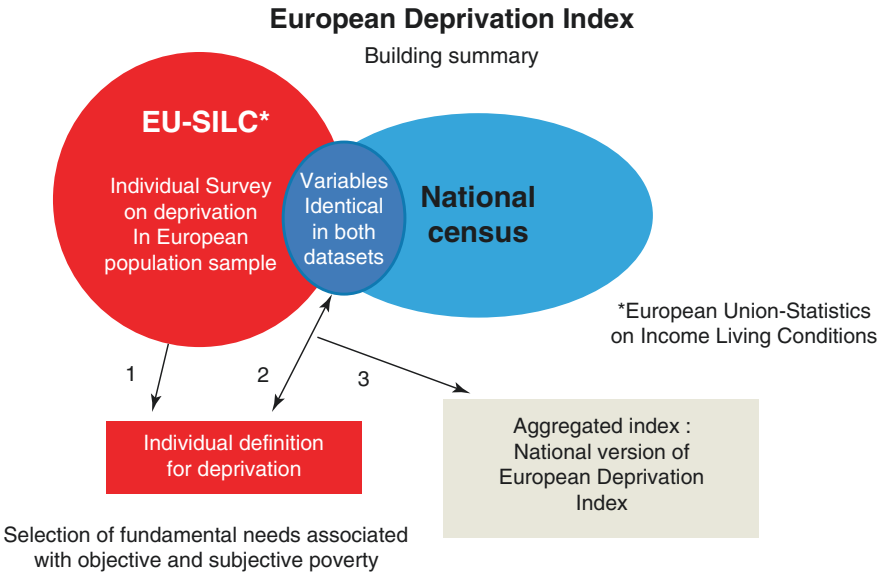

Fig. 3.1 European Deprivation Index

objective poverty (income) and subjective poverty (identified by the question 'Ability to make ends meet'). People lacking the minimal number (defined statistically in each country according to the principle of parsimony) of fundamental needs owing to their financial incapacity are thus considered as deprived.

Step 2: After identifying the variables available both in the EU-SILC database and the national census, a multivariable logistic regression conducted with EU-SILC data establishes the set of variables significantly and independently associated with the individual deprivation status defined in Step 1.

Step 3: The corresponding variables in the census thus constitute the components of the aggregated deprivation index, with the coefficients of the final regression model being used as the weights assigned to the corresponding variables.

Table 3.1 shows selected census variables and corresponding coefficients for national versions of the EDI for the first five European countries for which the EDI was available. Even if each national score is built independently using its own EU-SILC sample data, census data and principle of EDI construction, several variables are used in all national scores. Education, homeowner status, promiscuity and occupation are also selected components of the Slovenian version of the EDI, which is more recent than the other five (Zadnik et al. 2018).

Thanks to the methodology on which it is based, the EDI can be applied to all European countries. It can be regularly updated thanks to the renewal of EU-SILC data and national census data. Because it is built with census data, the deprivation score can be calculated for each area level for which census data are available.

As all aggregated indexes using census variables, the EDI assesses the social environment area from its sociodemographic composition (rate of unemployed

Table 3.1 Weighted components of 5 national versions of the European Deprivation Index

Census variable	Italy	Portugal	Spain	France	England
No high education level	+1.07	+1.29	+1.30	+1.17	+0.31
No bath or shower	+ 2.08	+0.06	+1.33	+0.71	------
Non-owner	+1.07	+1.19	+0.73	+1.02	+1.46
No indoor flushing toilet	+ 0.56	+1.46	------	------	------
Not married	+0.15	------	+0.37	------	+0.45
Women aged > 65 years	+ 0.33	+0.25	------	------	------
Promiscuity	0.83	0.40	0.99	0.21	0.95
Low-income occupations	+0.19	+0.01	+0.62	+0.57	+0.39
Unemployed	+1.18	+0.74	------	+0.94	------
Foreign nationality	------	------	------	+0.41	------
Household with ≥ 6 persons	------	------	------	+0.97	------
Crime/vandalism	------	------	+0.49	------	------
No employer with employees	------	------	+0.95	------	------
No car	------	------	+1.74	+0.71	+0.83
Single-parent household	------	------	------	+1.00	+1.35
Not a detached house	------	------	------	------	+0.85
Permanently disabled	------	------	------	------	+0.98

people, rate of low-income occupations, etc.). However, differences in health observed between these areas are not only due to these differences in composition but also to certain contextual elements that differ between these areas and do not fit into the components of the EDI but are associated with them. For instance, while the supply of care is not explicitly measured by the EDI, health supply in the vast majority of countries is greater in neighbourhoods made up of principally wealthy people than in those made up of mainly poor people. Likewise, Hofiman et al. (2017) have shown that proximity to a green space can affect health and is associated with the value of the EDI. Thus, as established by 'neighbourhood analysis' (Diez-Roux 2004), for an equal individual socioeconomic level, the social environment in which an individual evolves can have an influence on their health indicators. In other words, a deprived person living in a deprived area has poorer health than one living in an affluent area. This effect of the context is clearly highlighted in studies with individual and aggregated measures of social characteristics, and in which it is possible to conduct multilevel analysis (Bryère et al. 2017a) to distinguish between compositional (individual sociodemographic characteristics) and contextual effects on health.

Similar to all aggregated indexes, the EDI is exposed to ecological bias when it is used to approximate individual socioeconomic status. Ecological bias can lead to an error in estimating the degree of association between exposure and effect. One way to minimise ecological bias is to use the smallest geographical unit for which the index can be built according to the availability of census data. The ecological measure developed should thus concern the smallest geographical areas possible in order to improve its accuracy by decreasing the misclassification of individuals in deprived areas (Woods et al. 2005). The average population of such geographical units varies greatly from a few hundred to a few thousand across Europe. However, even with very small units, an ecological bias is unavoidable even if the EDI, similar to the Townsend Index, seems to limit it (Bryère et al. 2017b). Table 3.2 shows the characteristics of the smallest geographical unit for the first five European countries for which EDI is available. Ecological data are from the national population census conducted in 2001 for Italy, Portugal, Spain and England-Wales, and in 1999 for France.

Table 3.2 Census population and smallest geographical units for five European countries

	Total population	Year of census population	Smallest geographical units	Average population/ smallest unit	Number of smallest units/ country
France	66,000,000	1999	IRIS	2000	50,000
Italy	57,000,000	2001	Census tracts	200	350,000
Portugal	10,500,000	2001	Statistical sections	640	16,090
Spain	40,850,000	2001	Census tracts	1000	34,300
England-Wales	62,700,000	2001	LSOA	1500	34,400

Abbreviations: *IRIS* regrouped statistical information blocks, *LSOA* Lower Super Output Areas

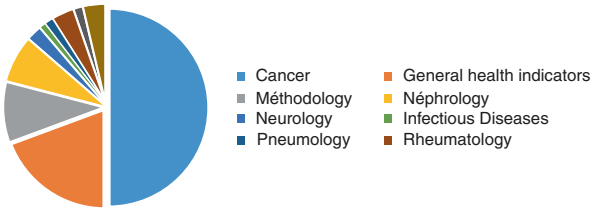

Fig. 3.2 Category of medical research using European Deprivation Index

Since its publication, the EDI has been used in several fields of application and has demonstrated the role played by social factors in global health and their involvement in the occurrence and prognosis of several pathologies in rheumatology, neurology and nephrology. As shown in Fig. 3.2, approximately half of the 100 publications on it concern cancer, where the focus has been incidence, screening attendance, management and patient survival. Their main findings are found in the different chapters of this book. The EDI is not currently available in all European countries, and the results to date have concerned France, Portugal, Italy and Slovenia. It is also being used in several ongoing international studies (Ribeiro et al. 2019), and other national versions of it are currently being developed (Ireland, Lithuania, Poland).

The use of international classifications and the standardisation of cancer registration methods in Europe promoted by the European Cancer Network and the GRELL are leading to consistent progress in the knowledge of cancer epidemiology and risk factors owing to valid comparisons between countries. Furthermore, much more is known about patient survival and we can validly compare patient management and healthcare systems between countries (EUROCARE, CONCORD). If the method for assessing the socioeconomic environment were to be similar in all European countries, then the influence of social determinants in cancer incidence and mortality, screening attendance and patient survival could truly be understood from a pan-European perspective. There are no longer any technical obstacles to the routine systematic integration of social deprivation level established with the EDI by using the patient's address in all the databases of the European registries. Such a step forward would allow very powerful comparative studies between different European countries regarding the influence of the social environment on the occurrence and outcome of cancer.

Beyond descriptive and analytic approaches, the availability of an aggregated deprivation index makes it possible to identify potential target populations for public health interventions and to easily conduct cluster randomisation stratified on deprivation (Guillaume et al. 2017). Moreover, a deprivation index of this type is precious for implementing interventions based on the principle of proportional universalism.

Even if national policies are capable to some extent of curbing the rise in inequality, we think that health inequalities should be analysed and tackled at the European level. The continued rollout of a transcultural deprivation index in a growing number of European countries and its use in cancer registry databases could help in achieving this overarching goal for Europe.

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Chapter 4
Social Disparities in Cancer Incidence: Methodological Considerations

Marc Colonna, Edouard Chatignoux, Joséphine Bryère, and Vesna Zadnik

Introduction

The description of spatial variations in the frequency of a disease belongs to the arsenal of epidemiological surveillance. A classic example is the study conducted by John Snow in the mid-nineteenth century on the link between water supply and the distribution of cholera cases in London, which is regularly cited (Järup 2000). The data from cancer registries that exhaustively list all the cases in a region, and the fineness of the division of the spatial units that make up the area covered, make it possible to produce atlases of cancer occurrence. The aims of these atlases are to inform on the spatial distribution of new cases of the disease, and especially to find out if this distribution has a particular structure, not linked to chance. This type of analysis is a preliminary descriptive step that can be supplemented by more targeted analyses, in an etiological sense (Elliott et al. 2000), such as studying the link between the incidence of certain cancers and the proximity of structures likely to induce exposure of neighbouring populations to toxic agents that are suspected of promoting the occurrence of disease cases (e.g. the incidence of leukaemia in children near nuclear installations (Evrard et al. 2006)). More generally, this type of

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study makes it possible to assess the influence of a particular element affecting all persons residing in the zone covered by the registry (e.g. incidence according to the level of socioeconomic hardship (deprivation); information available indirectly via the place of residence (Bryère et al. 2018)).

In this chapter, we present statistical approaches aimed at studying the structure of the spatial distribution of the frequency of a given type of cancer. Then we present methods for analysing the link between information (e.g. socioeconomic level) and the spatial distribution of cancer incidence. Next, we specify the elements that make it possible to highlight the impact of socioeconomic factors in the form of statistical indicators and maps of these indicators. Data on lung cancer in men and skin melanoma in women from the cancer registry of the Isère 'département' (equivalent to a county in the United Kingdom or United States) in France will serve to give illustrative examples.

General Context

The comparison of incidence indicators such as raw incidence rates between different geographical areas is generally rather uninformative, as it reveals mainly differences in incidence related to differences in the structure (in particular, age) of the populations. It is preferable to use standardised measures in this context, which make populations within geographical/spatial units 'comparable' in terms of the factors used for standardization, and thus better describe the risk. Among the standardisation methods, the standardised incidence ratio (SIR), derived from indirect standardisation, is usually used in spatial analyses to highlight differences in incidence (Elliott et al. 2000). The SIR compares the number O of cases observed in a geographical unit and the number E of cases expected if this spatial unit was subjected to the incidence in a reference group, where the SIR is the ratio O/E (Estève et al. 1994). More precisely, assuming an observed number of cases resulting from a Poisson distribution of mean $E\times\theta$, where θ is the relative risk in the geographical unit compared to the reference group, the estimator of the maximum likelihood of θ corresponds to the SIR (O/E). Clayton et al. (Clayton and Kaldor 1987), in particular, have shown that mapping the SIRs does not lead to the best estimate of the relative risks (in terms of total error): the variance of the SIRs, which is inversely proportional to the square of the number of expected cases, may be high and very different in different spatial units because of demographic differences. Thus, by the simple fact of the chance of the occurrence of statistically rare events, mapping the SIRs can create a strong impression of disparity between geographical units (even neighbours) and all the more so when the spatial scale is fine. Data smoothing, that is, the use of a method for estimating SIRs taking into account the (complementary) information provided by the SIR for all spatial units in the study area and/or by the

SIRs of neighbouring units, is a means of overcoming these difficulties. To do this, smoothing methods, which are part of Bayesian parameter estimation methods, have been widely used for many years (Lawson et al. 2000).

An analysis of the geographical variations in SIRs can lead to two situations. In the first case, the number of cases observed in the geographical units does not differ significantly from the number of cases expected under the assumption of a Poisson distribution: there is, in this case, no difference in the characterised risk between geographical units ($\theta = 1+$). In the second case, the variation in the number of cases observed in the geographical units is greater than that expected if one assumes a Poisson distribution of cases: in this case, the relative risks are not homogeneously distributed throughout the territory. The existence of spatial heterogeneity in risk naturally leads to an attempt to provide explanatory factors whose influence can be assessed using regression models. However, it is rare to be able to completely explain all the spatial heterogeneity by the available explanatory factors. On the one hand, it is often impossible to explain all the causes of variability (relevant explanatory variables not taken into account), and even when they are available, the existence of intra-spatial unit heterogeneity (e.g. units that may be composed of heterogeneous populations from a socioeconomic point of view) can lead to different levels of risk in two spatial units having the same mean levels for these factors. On the other hand, it is sometimes difficult to specify models (lack of linearity, the existence of an interaction between explanatory variables, etc.), and even after adjustment, there usually remains some residual variability in the relative risks that can be accounted for in the models using latent variables (random effects). This then leads to modelling a residual (latent) spatial process integrating prior knowledge (heterogeneity, autocorrelation), which can be achieved using a Bayesian approach.

Methodological Points

Context of Spatial Analysis

The analysis of the pattern of distribution of SIRs at a fine level of geographical division, which reduces the risk of 'ecological fallacy' (i.e. error made when interpreting observed associations between aggregated data as being valid associations for individuals) when considering the most homogeneous populations possible, can reveal two phenomena that can occur simultaneously or not (Wakefield 2000a): (i) heterogeneity of the SIRs, which are not identical throughout the region but of different values and randomly distributed across the area; (ii) spatial autocorrelation, which results in the fact that two adjoining spatial units (i.e. sharing a common border) have SIRs that are closer than two randomly selected units.

Bayesian Model for Smoothing Relative Risks

There are two distinct models of Bayesian smoothing. The distinction is due to the nature of the parameter to which an SIR tends and thus to a hypothesis made a priori (Wakefield 2000b). The analytical formulation of the two scenarios concerns the modelling of the logarithm of the mathematical expectation of the relative risk θi. This formulation allows, at a later stage, the integration of explanatory factor(s) (Wakefield 2000b; Lawson 2003a).

A first hypothesis (1) is based a priori only on the heterogeneity of the SIRs. If the SIRs were homogeneous, they would be equal with the same value, μ, but because of their heterogeneity, around this value, each SIR has its own source of variability, V, modelled by an a priori law that is normal. These normal laws, with a mean of zero, have the same variance. The first model can be written analytically as:

$$\log\left(\theta_i\right) = \mu + V_i \qquad V_i \underset{idd}{\sim} \mathcal{N}\left(0, \sigma_v^2\right) \tag{1}$$

The second hypothesis (2) is based on the addition of autocorrelation of the SIRs as well as the heterogeneity component. The a priori autocorrelation hypothesis is based on the idea that the SIR values of spatial units tend to be more similar if the units are geographically close than if they are distant (which occurs when a risk factor, for example, environmental, is distributed geographically). The principle consists in inducing a modification to the risk estimate, in addition to that related to the heterogeneity that is all the stronger when the similarity in the SIRS among neighbouring spatial units is close. Around the overall mean μ and the component V of each unit is added its source of variability U (a negative or positive value), which follows an a priori normal distribution, whose expectation is the mean of the values in the nearby geographical units and whose variance is inversely proportional to the number of these units that are considered to be close. This assumes the building of a proximity matrix to determine which units are close to each other. Most often, two units that share a common border are considered as being close. In this case, it is called an adjacency matrix. The model is written as:

$$\log\left(\theta_i\right) = \mu + U_i + V_i \qquad V_i \underset{idd}{\sim} \mathcal{N}\left(0, \sigma_v^2\right) \qquad U_i \left| U_j \;\; i \neq j \sim \mathcal{N}\left(\overline{u}_i, \frac{\sigma_u^2}{m_i}\right)\right. \tag{2}$$

The smoothing models (1) and (2) produce smoothed relative risks, whose difference depends on the structure of the incidence. Nonetheless, the principle of the two models results in a tendency towards a systematic decrease in the extent of the relative risks provided by the SIR; the decrease being all the more pronounced when the observed number of cases of a disease is low. It is therefore useful to base the choice of model on objective criteria. A first possible criterion relies on identification of the

characteristics of the SIRs, namely the existence of heterogeneity among the SIRs (Potthoff–Whittinghill test (Elliott et al. 2000)), the absence of spatial autocorrelation (Moran statistic (Elliott et al. 2000)) pointing towards model (1), and its presence towards model (2). A second method of selecting a model is to compare the deviance information criterion (DIC) of each of the two models and then select the one with the smallest DIC (Spiegelhalter et al. 2002). The DIC, the Bayesian equivalent of penalised likelihood criteria, is composed of two parts: one depends on the likelihood and describes the adequacy of the model to the data, and the other is a penalty linked to the complexity of the model (through an estimation of the effective number of parameters). Finally, a third approach consists in comparing the variances of the *U* and *V* components of model (2) (Mollié 1996): if these variances are very different, the component with the greatest variance provides the bulk of the information; the second component is actually relatively similar between the different spatial units. The two variances σ_v^2 and $\frac{\sigma_u^2}{m_i}$ are not directly comparable because while the first is marginal, the second is conditional. Therefore, we compare the empirical variances s_v^2 and s_u^2 of the a posteriori distribution of the random effects *V* and *U*.

Distribution of Hyperparameters σ^2_v and σ^2_u

The amplitude in the variability of the relative risks, in its non-spatial component, is controlled, a priori, by the hyper-parameter σ^2_v, whereas the parameter σ_u^2 allows control of the conditional variability of the relative risks. The Bayesian methodology associates a probability distribution to each of these parameters called the '*hyperpriori*' whose characteristics need to be specified (Wakefield 2000b; Mollié 1996).

Most of the time, the σ^2_v and σ^2_u parameters are associated with a non-informative distribution, called a '*prior wave*', interpreted as a state of ignorance, that is, not favouring any particular a priori value. For analytical reasons, a Gamma distribution is used for the inverse of the parameters σ^2_v and σ^2_u, denoted as σ^{-2}_v and σ^{-2}_u, respectively, representing the precisions. We considered the Gamma distribution: Ga (0.01; 0.01) as proposed by Wakefield et al. (Wakefield 2000b). In order to verify the sensitivity of the estimates to the choice of hyperparameters, we also considered the distribution Ga (0.5; 0.0005) used by Lawson et al. (Lawson 2003b), as well as a distribution Ga (0.015; 0.001). The difference between these three distributions is due to the a priori variability in the relative risks. Using the Mollié approach (Mollié 1996), we check that this a priori variability in relative risk is assumed to be high in the first case, being on average in the interval (0.1; 16) and supposed to contain 95% of the relative risks. It is assumed to be lower in the second case with an interval of (0.9; 1.1) and is intermediate in the third case with an interval of (0.5; 2).

Regression Models with Covariates

Models (1) and (2) are supplemented by taking into account one (or more) explanatory variable(s) (X) which may have the effect of reducing the contribution of the latent variables V and U. The extent of this reduction is related to the effect of the variable(s) X on the distribution of the incidence. Analytically, for a single explanatory variable, we obtain the two models (Lawson 2003b):

$$\log\left(\theta_i\right) = \mu + \beta \times X_i + V_i \qquad V_i \underset{idd}{\sim} \mathcal{N}\left(0, \sigma_v^2\right) \tag{3}$$

$$\log\left(\theta_i\right) = \mu + \beta \times X_i + U_i \qquad V_i \underset{idd}{\sim} \mathcal{N}\left(0, \sigma_v^2\right) \qquad U_i \left| U_j \;\; i \neq j \sim \mathcal{N}\left(\overline{u}_i, \frac{\sigma_u^2}{m_i}\right)\right. \tag{4}$$

The contribution of variable X is evaluated by comparing the DIC of models (1) and (3) or (2) and (4) according to the model that does not contain the covariate.

A complementary means of evaluating the contribution of variable X is to consider the modification of the empirical variance of the latent variable V (model (1)) or latent variables U and V (model (2)). More broadly, 'bottom-up' reasoning, based on variation in the DIC and empirical variances, can be done for the integration of other explanatory variables.

The Data

Our spatial analyses focus on incident cases of lung cancer in men (4409 new cases) and skin melanoma in women (1261 new cases) diagnosed in the county of Isère during the period 2006–2014. The population of Isère was 1.234 million inhabitants in 2010. The county is divided into 735 spatial units (aggregated units for statistical information: called 'IRIS' *Ilots Regroupés pour l'Information Statistique* in French) with sub-municipal division for municipalities with more than 5000 inhabitants, the IRIS being the same as the municipality otherwise). During the period 2006–2014, no new cases of lung cancer in men were observed in 12.5% of the spatial units, which represent 2.5% of the Isére population. For skin melanoma, no new cases of skin melanoma were observed in women in 32.1% of the spatial units, or 13.5% of the population of Isère.

The level of social deprivation within each IRIS unit was estimated using the European Deprivation Index (EDI), an aggregate index that measures social inequalities in a comparable way across different European countries. In this study, the French version of the EDI, based on the 2007 census, was used to assign a social deprivation score to each spatial unit (Pornet et al. 2012). The EDI was selected as a continuous variable that takes into account the estimated score in each spatial unit. This choice was validated by also considering the national quintiles of EDI.

To consider complementary information to the EDI that might explain variability in the distribution of risk, we added another variable. For lung cancer in men, we used the variable 'Urban' which distinguishes, on one hand, the city centres and suburbs (75% of the Isère population) from rural spatial units and isolated towns (25% of the Isère population, the reference modality in the model). For skin melanoma, we used the Breslow index (corresponding to melanoma thickness) to account for early or late diagnosis. In our study, we considered the average value of the Breslow index of incident cases from three large areas within the county. This variable is a stratification variable unless it is considered that early diagnosis may induce overdiagnosis leading to a higher incidence level. In any case, from a statistical point of view, this epidemiological distinction has no consequences for modelling.

The Results

SIR, Smoothed SIR and Choice of Bayesian Model

The estimated SIR varied between 0 and 4.7 for lung cancer and between 0 and 11.4 for skin melanoma. Taking into account the DIC criterion, the model adopted for the Bayesian estimation approach for smoothed SIRs was identical for both cancer sites and corresponded to the integration of the heterogeneity and spatial autocorrelation components (Table 4.1, column 2). This choice was confirmed by Potthoff–Whittinghill heterogeneity and Moran autocorrelation tests, which were significant for the two cancers studied. Smoothed SIRs with the $U + V$ model varied between 0.55 and 1.6 for lung and 0.7 and 1.8 for melanoma. For both cancer sites, the spatial component was the most informative with a high empirical variance (Table 4.2, column Ga (0.01, 0.01)). The percentage of total variance taken into account by the spatial component was 61% for the lung and 74% for melanoma.

Table 4.1 DIC criteria according to model and hyper-a-priori parameters

	Ga(0.01; 0.01)	Ga(0.01; 0.001)	Ga(0.5; 0.0005)
Lung cancer, male			
Model U	3180.3	3180.7	3186.9
Model $U + V$	3153.7	3154.7	3156.0
Model $U + V$ + EDI	3125.8	3127.7	3129.6
Model $U + V$ + EDI + habitat	3127.4	3130.2	3131.5
Skin melanoma, female			
Model U	2096.0	2098.5	2099.7
Model $U + V$	2073.7	2072.4	2072.4
Model $U + V$ + EDI	2044.8	2044.3	2043.7
Model $U + V$ + EDI + Breslow	2036.3	2036.7	2036.5

Table 4.2 Empirical variance of U and V by hyper-a-priori parameters

	Ga(0.01; 0.01)		Ga(0.015; 0.001)		Ga(0.5; 0.0005)	
	Empirical variance and 95% CI		Empirical variance and 95% CI		Empirical variance and 95% CI	
Lung, male						
Model						
U + *V*						
V	0.0273	[0.0078; 0.0527]	0.0271	[0.0041; 0.0535]	0.0141	[0.0002; 0.0455]
U	0.0430	[0.0200; 0.0698]	0.0422	[0.0181; 0.0712]	0.0512	[0.0206; 0.0826]
U + *V* + EDI						
V	0.0304	[0.0085; 0.0543]	0.0332	[0.0058; 0.0562]	0.0341	[0.0085; 0.0580]
U	0.0145	[0.0025;0.0359]	0.0114	[0.0006; 0.0348]	0.0068	[0.0001; 0.0305]
U + *V* + EDI + urbanY/N						
V	0.0316	[0.0116; 0.0545]	0.0327	[0.0024; 0.0577]	0.0350	[0.0099; 0.0598]
U	0.0142	[0.0027; 0.0343]	0.0111	[0.0003; 0.0380]	0.0072	[0.0001; 0.0313]
Skin melanoma, female						
Model						
U + *V*						
V	0.0217	[0.0047; 0.0628]	0.0161	[0.0008; 0.0540]	0.0056	[0.0002; 0.0414]
U	0.0607	[0.0227; 0.1113]	0.0641	[0.0257; 0.1150]	0.0630	[0.0231; 0.1158]
U + *V* + EDI						
V	0.0166	[0.0034; 0.0483]	0.0072	[0.0004; 0.0342]	0.0033	[0.0002; 0.0190]
U	0.0439	[0.0110; 0.0835]	0.0465	[0.0127; 0.0897]	0.0426	[0.0077; 0.0842]
U + *V* + EDI + Breslow						
V	0.0188	[0.0040; 0.0502]	0.0127	[0.0006; 0.0500]	0.0068	[0.0002; 0.0341]
U	0.0161	[0.0021; 0.0473]	0.0074	[0.0002; 0.0378]	0.0033	[0.0001; 0.0195]

This description of the results of modelling is usefully supplemented by looking at the maps of smoothed SIRs as well as at the components *V* and *U* (or, more exactly, their exponentials so as to be on the same scale as the relative risk). It is readily seen that the application of the smoothing method makes SIR maps more readable, with the revelation of a strong spatial pattern for both lung cancer and skin melanoma (Fig. 4.1, column 1). It is also possible to check the preponderance of the spatial component. Thus, the maps of the spatial components show high contrast for

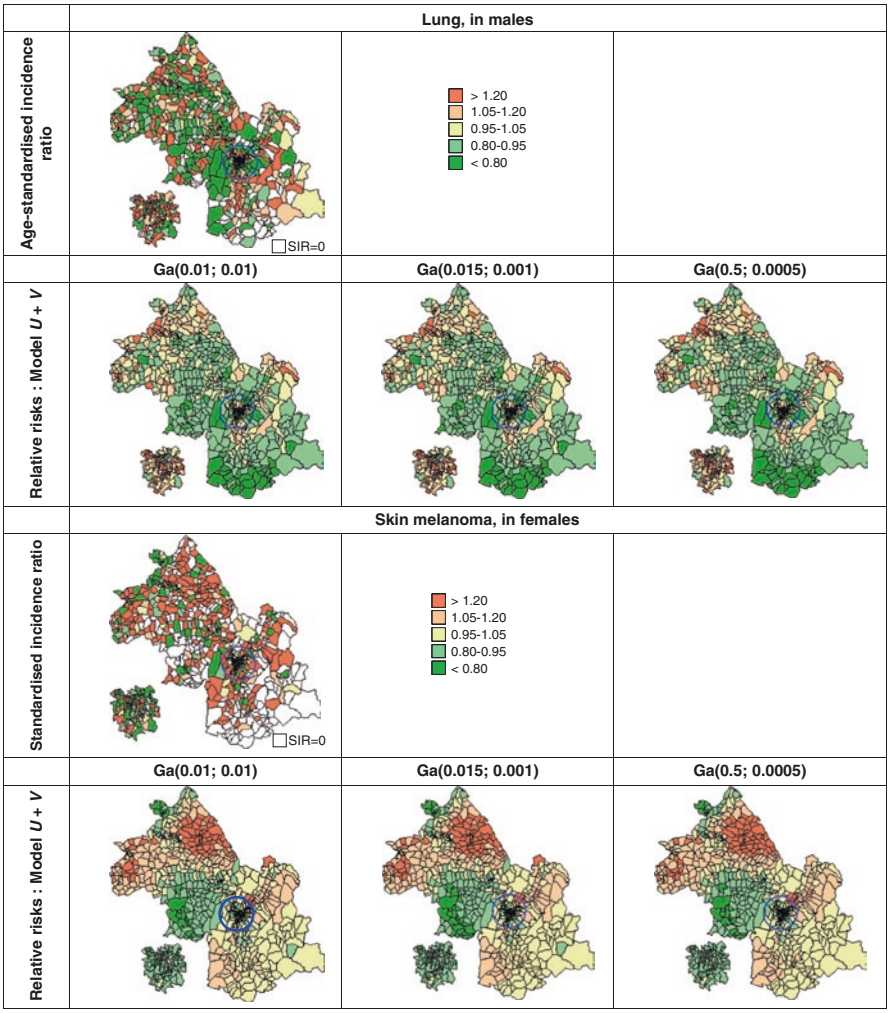

Fig. 4.1 Age standardised incidence ratio and relative risks according to hyper-priori parameters by cancer

both cancers (Figs. 4.2 and 4.3, column 1, lines 1 and 2). In addition, the heterogeneity component reveals specific features in certain spatial units for lung cancer.

The integration of EDI into the model with spatial components and heterogeneity reduces the value of the DIC for both cancer sites (Table 4.1). This finding logically confirms the map of SIRs in terms of EDI quintiles in the county of Isère for these two cancer sites (Fig. 4.4). The integration of the EDI variable decreases the variance of the spatial components for lung cancer and the variance of the *U* and *V* components for skin melanoma (Table 4.2). The map of the heterogeneity component remains similar to the model without EDI for lung cancer, while that of the

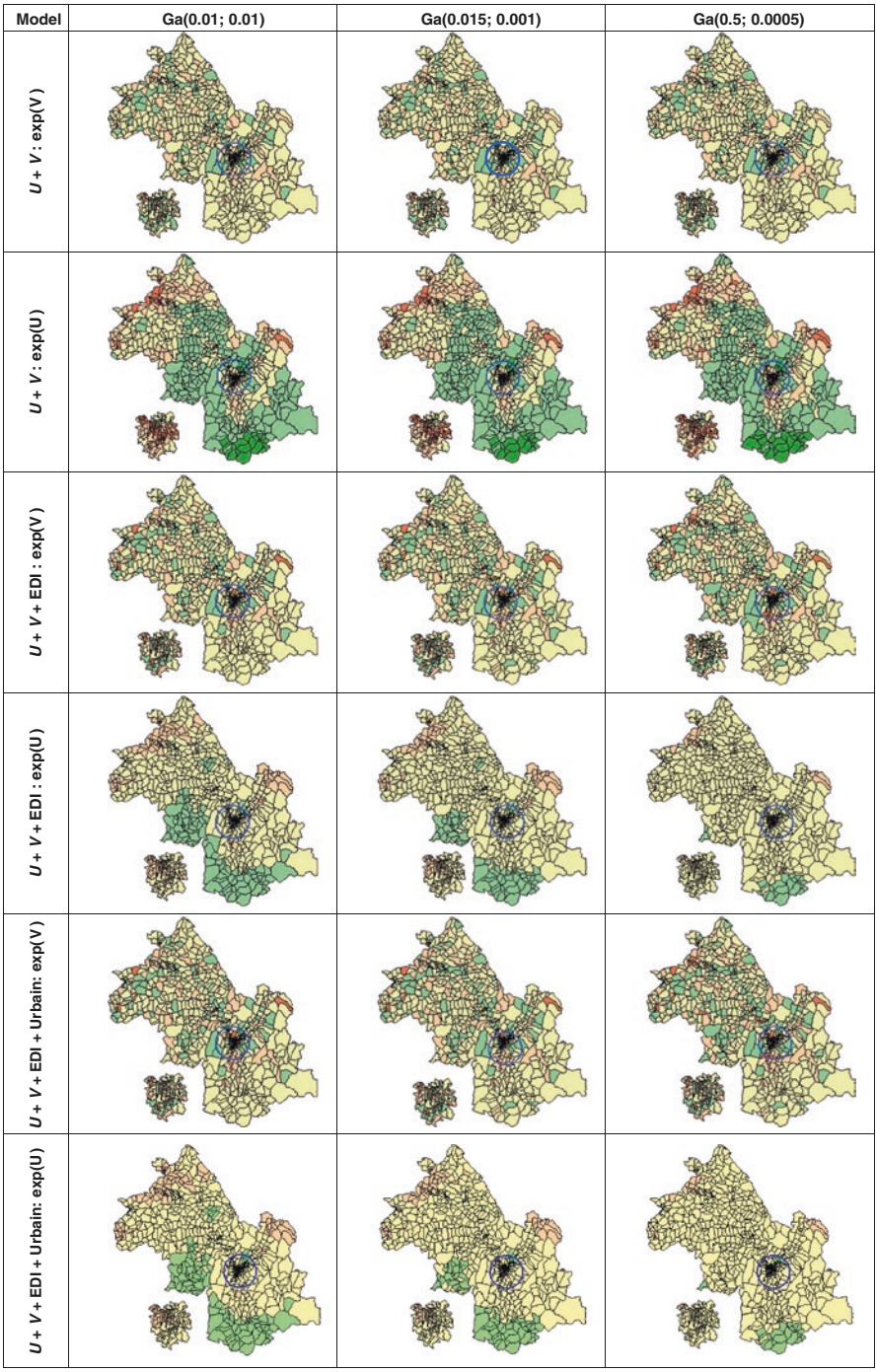

Fig. 4.2 Exponentials of *V* and *U* according to Bayesian models and hyper-a-priori parameters (lung cancer, in men)

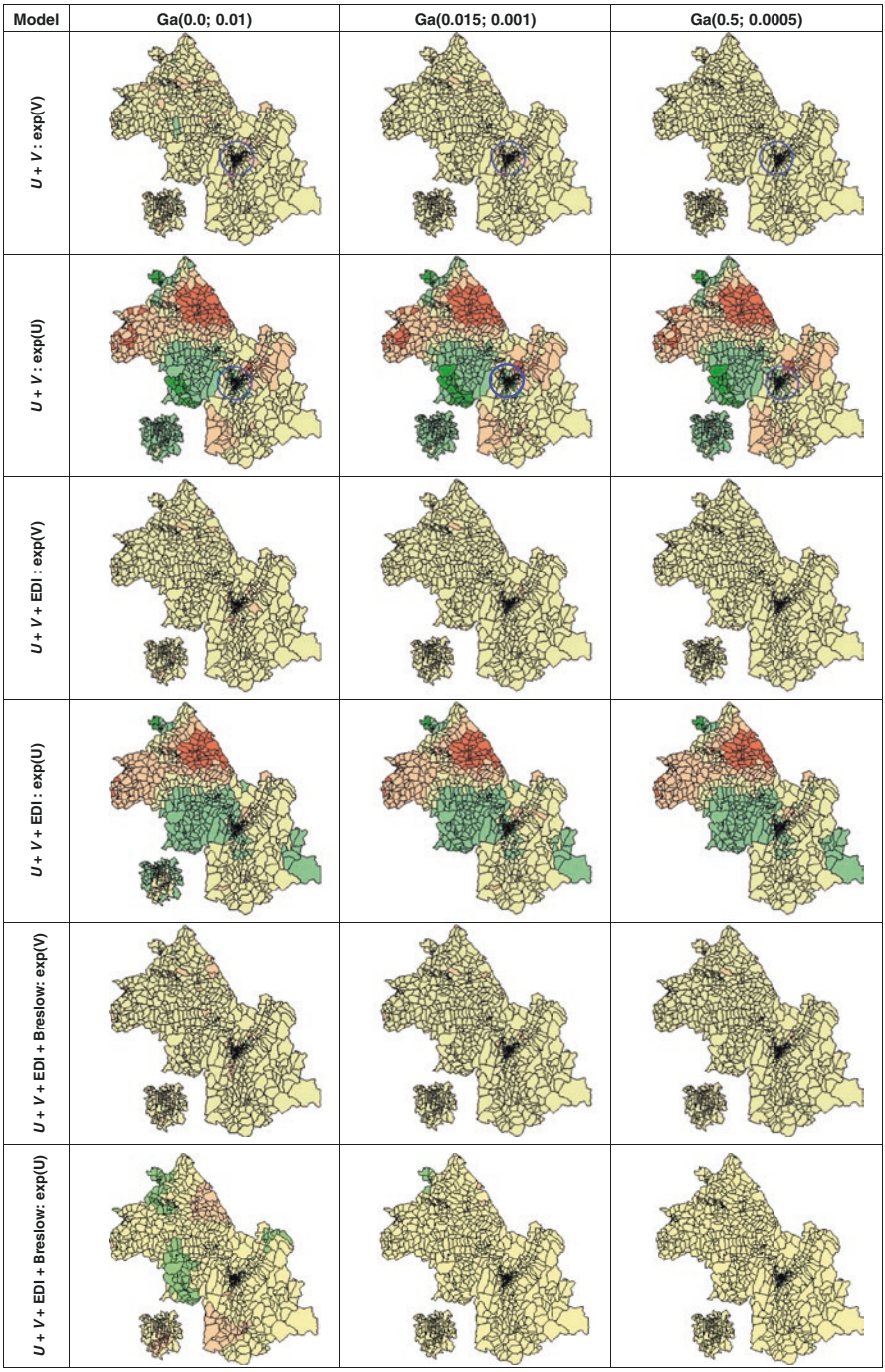

Fig. 4.3 Exponentials of V and U according to Bayesian models and hyper-a-priori parameters (skin melanoma, in women)

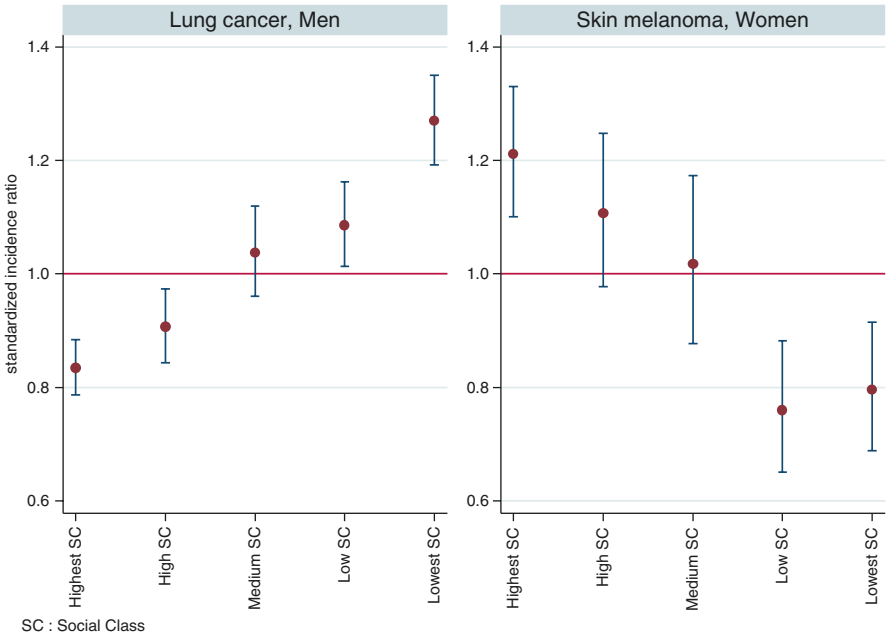

Fig. 4.4 Standardised incidence ratio by quintile of European Deprivation Index (EDI)

autocorrelation component becomes less well-contrasted (Fig. 4.2, column 1). Taking into account information on the level of social deprivation reduces the contrasts and the number of spatial units with visible over-incidence and sub-incidence. We note more particularly that consideration of the EDI makes it possible to reduce the spatial contrasts for lung cancer in the Grenoble conurbation (zoomed area), where there are numerous spatial units with disadvantaged communities. For skin melanoma, taking EDI into account modifies certain parts of the map: the eastern part of the Grenoble conurbation (east of the zoomed zone) becomes neutral; this result is particularly interesting since we know that the east of the agglomeration is characterised by a relatively high socioeconomic level. Apart from this, the map of the spatial component has contrasting IRIS units and groups of such units (Fig. 4.3).

At this stage, it is useful to find additional factors to reduce the residual information accounted for by the latent variables. For lung cancer, the 'Urban' variable considered above did not reduce the DIC nor the empirical variances (Tables 4.1 and 4.2), which led to maps similar to those of the model with EDI (Fig. 4.2). For skin melanoma, taking into account the Breslow index over large areas reduced the DIC and the empirical variance corresponding to the spatial component. The map that included this last component became poor in contrast and that with the heterogeneity component remained 'neutral' (Fig. 4.3).

Regression Coefficients for the Explanatory Variables

The table showing the regression coefficients for EDI, Breslow index and 'Urban' index shows that only the effect of the 'Urban' variable is not significant (Table 4.3). The values of the parameter estimates indicate that the risk of lung cancer increases with social deprivation and the risk of skin melanoma decreases with social deprivation. The estimation of the coefficients varies little with the inclusion of the Breslow index for melanoma and the 'Urban' variable for lung cancers. For the Breslow index, the risk decreases statistically significantly with the increase in the score (≡ increase in thickness) while the risk increases, non-significantly, with the level of urbanisation.

Sensitivity Analysis on the Choice of Hyper-Parameters

Whatever the hyper-parameter values fixed a priori, we note that the choice of models is identical according to the DIC criterion (Table 4.1). Similarly, the estimates of the regression coefficients for the EDI, the Breslow index and the 'Urban' index are similar irrespective of the values of the hyperparameters (Table 4.3).

Table 4.3 Regression coefficients according to models and hyperpriors for V and U

	Regression Coefficient and 95% IC		Regression Coefficient and 95% IC		Regression Coefficient and 95% IC	
	Ga(0.01; 0.01)		Ga(0.01; 0.001)		Ga(0.5; 0.0005)	
Lung, male						
Model						
$U + V$ + EDI						
B_EDI	0.0361	[0.0266; 0.0453]	0.0366	[0.0272; 0.0458]	0.0372	[0.0280; 0.0461]
$U + V$ + EDI + urbanY/N						
B_EDI	0.0355	[0.0258; 0.0450]	0.0360	[0.0262; 0.0456]	0.0364	[0.0269; 0.0457]
B_urbanY/N	0.0231	[−0.0674; 0.1123]	0.0241	[−0.0638; 0.1132]	0.0262	[−0.0627; 0.1129]
Skin melanoma, female						
Model						
$U + V$ + EDI						
B_EDI	−0.0542	[−0.0726; −0.0362]	−0.0541	[−0.0724; −0.0362]	−0.0544	[−0.0725; −0.0365]
$U + V$ + EDI + Breslow						
B_EDI	−0.0494	[−0.0672; −0.0320]	−0.0488	[−0.0660; −0.0318]	−0.0489	[−0.0658; −0.0321]
B_Breslow	−1.1100	[−1.6410; −0.5604]	−1.1560	[−1.6610; −0.6621]	−1.0970	[−1.5180; −0.6299]

Concerning the empirical variances of heterogeneity and spatial components, there is a relative similarity in the estimates between Ga (0.01, 0.01) and Ga (0.015, 0.001) for lung cancer. For skin melanoma, the behaviour of empirical variances is more erratic depending on the 'hyperpriori' for skin melanoma. The Ga (0.5, 0.0005) law lowers the variability of the latent variables when the residual information is weak: after taking into account the EDI for the lung and the EDI and Breslow index for skin melanoma. As a result, the maps of heterogeneity and spatial components are quite similar, except for the spatial components $U + V +$ EDI (lung model) and $U + V +$ EDI + Breslow index (melanoma model) (Figs. 4.2 and 4.3).

Elements of Discussion

Many studies from around the world have described a link between social deprivation and cancer incidence (Bryère et al. 2018). For most cancers (e.g., lung), social deprivation induces an increased risk of cancer. Only a few cancerous sites (e.g., melanoma) are more common among people from a privileged background. An immediate way to show this link in a given geographical area is to take the social deprivation index band (e.g., a quintile) and to compare the level of incidence in the different quintiles (via indirect standardisation) by bringing together the basic geographical units (IRIS, municipality) with the same class of EDI.This approach leads to useful information but does not answer a number of questions: (i) Is the inclusion of a deprivation index, the EDI, introduced in a continuous form, a relevant way to consider this variable? (ii) Does consideration of deprivation allow the spatial differences in incidence to be explained: in other words, how does this take into account modifying the latent variables U and V? (iii) Does any complementary information reduce the unexplained part of the modelling? (iv) Is the variability of unexplained incidence still high when the available explanatory variables have been incorporated into the model? Is it, or not, spatially structured?

Bayesian modelling of the incidence makes it possible to provide readily interpretable maps of the risks. Thus, this type of modelling allows one to show strong spatial patterns in the distribution of the incidence of these two cancers. This modelling also makes it possible to assess the contribution of the inclusion of a deprivation index, the EDI, which was introduced in a continuous form. We were also able to verify that consideration by class (e.g. quintile), by increasing the number of parameters related to the categorisation of the EDI, is not relevant for lung and skin melanoma according to the DIC criterion. There is, therefore, a continuous increase/decrease (depending on the cancer) of the risk of cancer with the level of social deprivation.

Taking EDI into account can greatly reduce spatially structured contrasts of lung cancer incidence. In other words, the EDI takes into account the spatial variations in the incidence for this cancer and thus makes it possible to reduce the contribution of the latent variable U. The heterogeneity of the incidence, when not spatially organised, remains after the consideration of EDI.

For skin melanoma, spatial contrasts are partially attenuated in an area of the county where the population has, on average, a comfortable socioeconomic level. On the other hand, there still are pronounced spatial contrasts in other parts of the county after EDI has been taken into account.

For lung cancer, the inclusion of additional information, in this case, place of residence, does not provide relevant information to reduce the heterogeneity and spatial components. In other words, modelling of the incidence of lung cancer shows that its frequency is strongly related to deprivation, but deprivation explains only a part of the disparities.For skin melanoma, taking into account the Breslow index (in addition to the EDI) allows one to model a substantial part of the variability in the incidence of this cancer. The modelling results show that EDI captures some of the variability in incidence. The Breslow index, a probable marker of differences in diagnosis management, complements the role of deprivation.

The interpretation of these results, especially for EDI, the indicator of interest in this chapter, is complex. In a study of EDI in Slovenia, Lokar et al. (Lokar et al. 2019) showed that for most cancers, there is a similarity in results whether one uses an aggregate deprivation index per spatial unit or an individual deprivation index. On the other hand, Chauvin et al. (Chauvin et al. 2019) have shown that the use of aggregated indicators for the IRIS units cannot be used for any extrapolation in terms of individual inferences. Thus, the deprivation indicator (e.g., EDI) should be considered only as a proxy of individual behaviours.

Bayesian analyses are based on an a priori choice of parameters for the variances of latent variables. We chose a 'non-informative' distribution, that is, without prioritising any particular value. We took into account two other distributions inducing respectively smaller amplitude in the variability of the variances and a very small amplitude of this same variability. Similar to that shown by Mollié (Mollié 1996) in a sensitivity analysis, we were able to verify that the different choices for the hyperparameters do not influence the risk estimates. The same is true for the regression parameter estimates of the explanatory variables. On the other hand, the description of risk variations requires a choice of suitable parameters: the non-informative law is probably too conservative when the variability is low, as indicated by Wakefield (Wakefield 2000b). This is seen in our example for skin melanoma after taking into account the EDI and the Breslow index. Conversely, a very restrictive law can be conservative as illustrated by the model integrating EDI for lung cancer.

The estimation of Bayesian models requires the computation of integrals that do not have a simple analytical solution. Moreover, these integrals are usually calculated using Markov Chain Monte Carlo MCMC) iterative methods. We implemented this approach using WinBUGS software (Lunn et al. 2000). Another estimation method has been more recently introduced by Rue et al. (Rue et al. 2009), which consists of calculating integrals involved in estimating a posteriori distributions using Laplace approximations. This method, implemented in the Integrated Nested Laplace Approximation (INLA) software (Rue et al. 2009), is particularly efficient in terms of computing time (a few tens of seconds against a few tens of minutes for MCMC) and gives results generally very close to those of MCMC.

Conclusion

We have described and highlighted some determinants of the spatial distribution of lung cancer and skin melanoma. For this purpose, we used a fine subdivision of the studied area, which reduces the ecological fallacy. The associations found at a spatial level between the incidence of lung cancer and EDI, on the one hand, and the incidence of skin melanoma and EDI plus the Breslow index, on the other hand, are valid at the level of spatial units. We reiterate that at the aggregate level, only means are taken into account. It is also important to bear in mind that cancer is in the majority of cases a multifactorial disease that may be the result of genetic factors, personal risk factors (lifestyle), environmental or occupational exposure(s) that can only partially be taken into account by deprivation indexes, even if the association with the incidence is strong.

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Chapter 5
Social Disparities in Cancer Survival: Methodological Considerations

Aurélien Belot and Maja Pohar-Perme

Introduction

The observed survival data for a whole population, as provided by population-based cancer registries, is an invaluable tool for describing the cancer epidemiology at a population-level in a geographical area (Brewster et al. 2005). Quantifying the level of association between individual characteristics and their survival probability, as well as describing the time trends of survival, are useful results for patients, carers and policymakers. These results may also be useful to other researchers for generating hypotheses to search for ways of improving patients prognosis. However, those data also come with specificities which represent some interesting challenges to be tackled during the statistical analysis. We aim in this chapter to present these challenges as well as some of the statistical methods used and developed in this context. In the literature, these methods are usually known as 'relative survival', and we focus in this chapter on their use for describing socioeconomic disparities in cancer survival.

We start by describing the main challenges faced when analysing population-based cancer registry data in order to estimate cancer-specific quantities, therefore introducing the relative survival approaches. We then focus on the methods that could be used when it comes to describing socioeconomic disparities of cancer

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survival, starting from net survival and its non-parametric estimation and finishing with multilevel hazard-based regression models. An illustrative example will be used throughout the chapter.

Relative Survival Approaches

The first main challenge is that we aim to estimate and draw inference on cancer-specific quantities, while most population-based cancer registries do not have reliable information on the cause of death. Attributing the cause of death to a cancer may be easy in some specific cases (e.g. in randomised clinical trials), but it becomes more difficult to ascertain in the general population (Percy et al. 1981; Mant et al. 2006; Johnson et al. 2012; Piffaretti et al. 2016), especially in the older population where multi-morbidities are quite common. In addition, the coding of the cause of death may be rather different in one area compared to another, thus leading to potential problems for comparability. Therefore, rather than aiming to know the exact cause of death in our population of interest, methods were developed using external data to help to identify cancer-specific quantities (Berkson and Gage 1950; Ederer et al. 1961; Hakulinen 1982; Buckley 1984; Estève et al. 1990). This is what we will call here the 'relative survival methods', which may be seen as a subfield of the broader field of competing risks analysis (Pohar Perme et al. 2016; Belot et al. 2019).

The relative survival methods are based on the idea that if we compare (i) the mortality hazard observed in a given population of patients diagnosed with a given cancer to (ii) the observed mortality hazard in a population with identical demographic characteristics but without this cancer, we should see an excess of mortality that could be interpreted as *due directly or indirectly to the cancer under study*. However, we do not observe the *mortality hazard in a population with identical demographic characteristics but without this cancer*, that is, the other-cause mortality. Therefore, relative survival methods assume that for a given patient *i*, this latter quantity can be approximated with the *mortality hazard observed in the general population with identical demographic characteristics*. This quantity is obtained from lifetables and detailed according to some demographic characteristics (usually at least sex and age) and additional variables such as year, geographical region, and deprivation groups when available.

In equation form this leads to

$$\lambda_{obs,i}(t) = \lambda_{E,i}(t) + \lambda_{P,i}(t) \tag{5.1}$$

Therefore, we assume that the overall mortality hazard observed for a given cancer patient *i* can be written as the sum of an excess mortality hazard $\lambda_{E,i}(t)$ and the expected (population) mortality hazard with similar demographic characteristics, $\lambda_{P,i}(t)$.

To be able to interpret $\lambda_{E,i}(t)$ as the excess mortality hazard, the following conditions on $\lambda_{P,i}(t)$ must be met:

(a) The cancer-specific mortality hazard in the general population is sufficiently small compared to the population mortality hazard such that the cancer-specific mortality hazard in the general population can be ignored, and thus $\lambda_{P,i}(t)$ can be considered as the other-cause mortality hazard in our population. This is true when prevalence of the cancer is low or when the cancer of interest represents a negligible cause of death in the population because of a very low cancer-specific mortality hazard. This condition underlines the importance of analysing specific cancers separately rather than treating all cancers as a single disease (in such a case, the condition would clearly not be met). In addition, from an epidemiological and clinical point of view, analysing all cancers as a single disease would not make any sense, as different cancers have very different profiles and prognosis.
(b) The other-cause mortality hazard of the general population is equal to the other-cause mortality hazard in our population, within levels defined by the demographic characteristics available in the lifetable. In other words, the other-cause mortality hazard in our population does not depend on characteristics other than the ones available in the lifetable. For example, this might be problematic with smoking-related cancers as we know that the expected mortality hazard is different for smokers and non-smokers, while smoking behaviour might also be predictive for the excess mortality hazard. This condition is therefore more problematic in practice than condition (a), and some work has been done to address this issue (Goungounga et al. 2019; Rubio et al. 2019a; Touraine et al. 2020).

In relative survival methods, we aim to estimate the excess mortality hazard (EMH) $\lambda_{E,i}(t)$ and the population mortality hazard $\lambda_{P,i}(t)$ is considered as known (and is therefore included as a constant in the estimation process).

Net Survival

The Measure of Interest

When interested in the hazard of cancer patients, the excess hazard $\lambda_{E,i}(t)$ is the key quantity of interest, whereas the other cause hazard $\lambda_{P,i}(t)$ only acts as a nuisance parameter (Belot et al. 2019). The excess hazard $\lambda_{E,i}(t)$ can vary through time, so when reporting it, we often consider its cumulative value on the 'survival scale', i.e. $S_{N,i}(t) = \exp\left(-\int_0^t \lambda_{E,i}(u)\,du\right)$. This quantity is referred to as net survival and can be interpreted as the survival probability of cancer patients once the other causes of death have been removed.

Net survival is useful if we are interested in assessing and quantifying differences in cancer control between different countries/regions (or even different periods of time within a country) as it is not affected by the differences in population mortality hazard $\lambda_P(t)$ between countries/region.

Estimation

Some important progress has been made recently in this field, and, in particular, a non-parametric consistent estimator of net survival has been proposed: the Pohar-Perme estimator (Perme et al. 2012). The estimator relies on the use of inverse probability weighting using the population mortality hazard as obtained from the life tables. For each patient, those weights are calculated as the (inverse of the) probability of remaining at risk if the patient were exposed to population mortality hazard. Intuitively, these time-varying weights can be seen as correcting the sample as time passes (both the number of patients at-risk and the number of events) from the depletion of patients because of population mortality.

When estimating net survival, care must be taken when analysing a sample which includes very old patients (Pohar Perme et al. 2016). Indeed, for these very old patients, very little information is given in the data regarding their (long-term) net survival as the probability of dying from other causes is very high. Thus, the estimated net survival curves can have very wide confidence intervals or can even increase. This type of result simply tells the analyst that there is not enough information in the data. In practice, we could limit the analysis to patients not older than a certain age (which obviously depends on the life expectancy of the country considered) or we could limit the net survival estimates to a reasonable time since diagnosis in order to avoid estimating long-term net survival without enough information. Following the publication of the Pohar-Perme estimator, a test was developed to compare net survival distributions (Grafféo et al. 2016; Pavlič and Perme 2017) based on the same philosophy as the classical log-rank test. This statistical test allows testing the difference of net survival curves between groups, with a possibility of stratification to account for an important variable that affects the hazard of the compared groups.

Age-Standardisation for Improving Comparability

When interest lies in comparing net survival between two (or more) groups of patients, it is important to account for the differences in covariate distributions between groups. In most applications, we focus in practice on the difference in age distribution because age is a major determinant of cancer survival (Corazziari et al. 2004; Brenner and Hakulinen 2005; De Angelis et al. 2009; Sasieni and Brentnall 2017). Indeed, one group may be composed of older individuals than those in

another, and because age is an important predictor of net survival, accounting for the differences in age distribution is crucial. It may be done through age-standardisation (also called age-adjusted survival (Brenner and Hakulinen 2003, 2005; Gondos et al. 2006)). The principle of the direct method for age-standardisation is as follows: the sample is split according to some pre-specified age groups and the net survival is estimated within each age group. The age-standardised net survival is then obtained as a weighted average of these age-specific net survival estimates, and the weights used reflect the age distribution of some defined standard population. The International Cancer Survival Standard (ICSS) age distribution proposed by Corazziari and colleagues (Corazziari et al. 2004) is one of the most widely used standards.

Measuring the Socioeconomic Deprivation

Measuring and quantifying the level of deprivation for cancer patients is another challenge. Mainly for confidentiality reasons, it is very uncommon to be able to analyse population-based cancer registry data where deprivation variables (e.g. income, or education) are measured at the individual level. Methods have been developed to build area-based measures of deprivation which may be considered as a reasonable summary of material disadvantage (Morris and Carstairs 1991). It has been shown that the size of the area may have an important impact on the estimated deprivation gradient, advocating for the use of small areas (Woods et al. 2005). Area-based measures have the additional advantage that they encompass what is called the contextual level of deprivation, that is, the patients' social and economic environment (Diez Roux 2002; Subramanian 2004). Different area-based measures have been proposed over the years (Townsend et al. 1988; Carstairs and Morris 1989; Pornet et al. 2012; Guillaume et al. 2016). In the illustrative example detailed in this chapter, we have used the French version of the European Deprivation Index (EDI) (Launoy et al. 2018). Using deprivation measures quantified at the area level (rather than individual level) brings new challenges for modelling, which will be discussed later in this chapter.

Illustration – Part 1

We illustrate the relative survival methods with some data of 15–75-year-old men diagnosed with a lip–oral cavity–pharynx cancer between 1997 and 2010 in a French region (Basse Normandie) and followed up to the 30th of June 2013. We used life tables stratified by age, sex, calendar year and département (French administrative area). For the purpose of the illustration, patients with the value of EDI in the first two quintiles constitute the 'least deprived group' and patients in the higher three quintiles constitute the 'most deprived group'. The socioeconomic groups

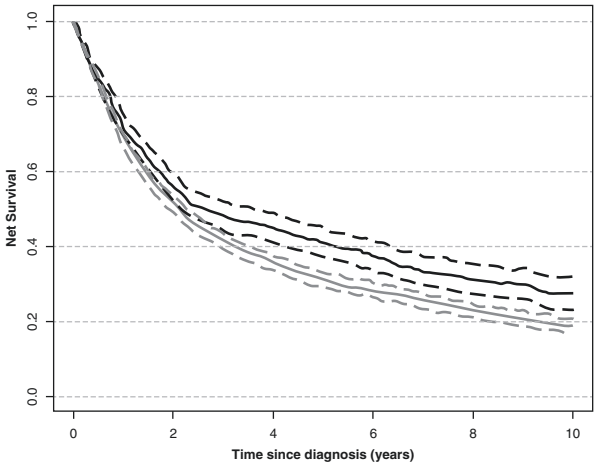

Fig. 5.1 Net survival estimates of 15–75-year-old men diagnosed with a lip–oral cavity–pharynx cancer between 1997 and 2010 in a French region (Basse Normandie), comparing the least deprived (black plain curve) to the most deprived group (grey plain curve), with their 95% confidence intervals in black and grey dashed curves, respectively

were based on the EDI defined at the 'IRIS' area level in France (geographical area of approximately 2000 inhabitants).

A first quantification of the association between socioeconomic deprivation and cancer survival would be to estimate the net survival of both groups. Applying the Pohar-Perme estimator, 5-year net survival of the least deprived group was 41.0% (95% Confidence Interval: [37.3; 45.0]) and 31.2% (95% CI: [29.3; 33.3]) for the most deprived group (see Fig. 5.1). At 10 years, the NS of each group respectively was 27.5% [23.5; 32.2] and 18.7% [16.7; 20.8]. The log-rank type test exhibits strong evidence of a difference between the two group-specific net survivals (Test statistic = 18.1, p-value < 0.01).

Quantifying the Association between Socioeconomic Deprivation and Excess Mortality

Non-parametric estimations of net survival, eventually split into groups according to some characteristics, represent the first descriptive step the analyst will follow. The following step for quantifying the association between the level of socioeconomic deprivation and cancer survival would usually involve regression modelling. Regression models permit describing how a quantity of interest is associated with some prognostic factors, such as age at diagnosis, and the patient's sex. For the excess mortality hazard as the quantity of interest, regression models have been the topic of many methodological developments and improvements (Hakulinen and Tenkanen 1987; Estève et al. 1990; Weller et al. 1999; Bolard et al. 2001; Giorgi et al. 2003; Dickman et al. 2004; Price and Manatunga 2004; Lambert et al. 2005; Nelson et al. 2007; Remontet et al. 2007; Cortese and Scheike 2008; Charvat et al. 2016; Fauvernier et al. 2019). We focus here on the following general form for the excess hazard, $\lambda_E(t, \boldsymbol{x}) = \exp(f(t, \boldsymbol{x}))$ (which is equivalent to $log(\lambda_E(t, \boldsymbol{x})) = f(t, \boldsymbol{x})$),

and where f is a function of time t that could also include specific functional forms for covariates included in the vector $\boldsymbol{x}$. These functional forms may include non-linear association(s) between continuous covariate(s) and the excess hazard and/or time-dependent association(s) between covariate(s) and the excess hazard. To parameterise these functional forms, regression splines will be our tool of choice (Perperoglou et al. 2019). Regression splines are a good compromise between mathematical simplicity and tractability while offering enough flexibility.

The Mortality Hazard

Before going into the details of regression hazard-based models (either used for the excess mortality or the overall mortality, that is, in the classical setting of survival), we aim to describe what the hazard is, how it should be interpreted, and why it represents an interesting quantity to report. The mortality hazard at a given time t is the instantaneous rate of death among people still at risk at that time. The hazard is expressed as the number of events per person-time (person-years or person-months, etc., depending on the time unit used for t). The hazard quantifies the 'force of mortality', and it may be seen, loosely speaking, as the 'speed of producing death' or as a 'probability of death per unit of time'. Given its definition, the mortality hazard may be higher than one. Graphical representation of the hazard helps to describe the natural history of the events happening over time. Because it is an instantaneous quantity, it brings new insights to the data as compared to the survival which is a cumulative quantity. Indeed, some specific behaviours of the 'force of mortality' may not be easily seen with a survival plot. When the hazard is approximately constant (say equal to λ) over a certain time interval dt, we can simplify its interpretation by going back to the probability scale. Indeed, when $\lambda * \mathrm{dt}$ is low, it may be directly interpreted as the (conditional) probability of death within the time interval dt, as the approximation $1 - exp(-\lambda * dt) \approx \lambda * dt$ holds for $\lambda * dt$ small.

Illustration – Part 2

For both deprivation groups, we obtained the excess mortality hazard by fitting a regression model separately in each group, assuming a cubic B-spline with one knot located at the median of the observed event times. The estimates of the EMH are shown in Fig. 5.2. The force of mortality is high in both groups, with a slight increase in the beginning, and then it continuously decreases up to 10 years after diagnosis. It does not reach 0 at 10 years, meaning that an excess mortality due to cancer still plays a role even 10 years after the diagnosis. For the most deprived, the excess mortality hazard reaches 0.4 death per person-year at 1 year after diagnosis. Therefore, assuming this hazard to be constant over a month (i.e. between 1 year

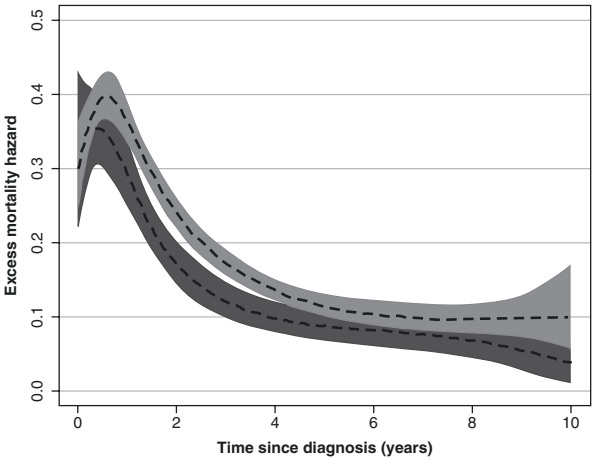

Fig. 5.2 Example of excess mortality hazard estimates (in person-years) of 15–75-year-old men diagnosed with a lip–oral cavity–pharynx cancer between 1997 and 2010 in a French region (Basse Normandie), comparing the least deprived (dark grey area & curve) to the most deprived group (light grey area & curve)

and 1 year and 1 month), it means that the probability of death within this month would be $0.4 * \frac{1}{12} = 0.033$.

Some Principles for Defining a Hazard-Based Regression Model

In order for the excess mortality hazard to be used to provide an unbiased estimate of the net survival, it is necessary to adjust for all the demographic variables defining the population lifetable (Danieli et al. 2012; Perme et al. 2012). Usually, for a given country, the lifetable is detailed at least according to sex, age and year. Therefore, the regression model needs to incorporate those variables as predictors, in addition to the socioeconomic deprivation variable which is our exposure of interest. However, in practice, some variables are not strongly associated with the expected mortality hazard, such as the year of diagnosis, if we are analysing data with a small range of diagnosis years. In other situations (as in our illustrative example), the data were observed in a small region of the given country, thus avoiding the need to adjust for the geographical area in the regression model.

It is good practice to analyse the variables in their original form rather than dichotomising or categorising continuous variables. Because the association between a prognostic factor and the excess mortality hazard may be complex, regression splines are useful (Therneau and Grambsch 2000; Gauthier et al. 2019; Perperoglou et al. 2019). These flexible functions allow analysing continuous variables with potential non-linear association with the mortality hazard. Another important element to consider when modelling (excess) mortality hazard is the proportional hazards assumption. Indeed, it is quite common to see in practice that the hazard ratio (HR) of a given covariate is varying with time, and therefore the PH assumption is violated (Therneau and Grambsch 2000). Again, in that situation, regression splines are useful to define time-dependent (log) HR by simply adding an

interaction term between a regression spline of time and the considered covariate in the linear predictor.

Finally, when the measure of deprivation is an area-based measure, multilevel modelling is an appropriate approach for deriving correct statistical inference as it accounts for the statistical dependency between patients who share similar characteristics because they live in the same area across which the ecological deprivation index is defined (Diez Roux 2001; Subramanian 2004; Duchateau and Janssen 2008; Hubbard et al. 2010; Charvat et al. 2016; Belot et al. 2018). Recently, a mixed-effect regression model for the EMH has been developed, which allows following the aforementioned general principles (Charvat et al. 2016). In a mixed-effect model for survival data (also called shared frailty model or random effect model), the estimated parameters should be interpreted *conditionally* on the random effect; that is, they have a 'subject-specific' interpretation (Hu et al. 1998; Diggle et al. 2002; Rabe-Hesketh and Skrondal 2012a, chap. 6, Rabe-Hesketh and Skrondal 2012b, chap. 10.8; Hardin and Hilbe 2013). It compares individuals conditionally on the same level of the random effect. In other words, to make comparisons between two individuals, we must hold the random effect to the same value. This interpretation differs from marginal models, which have a population-average interpretation (it compares observations 'across all the clusters') (Diggle et al. 2002; Hardin and Hilbe 2013).

After considering those general principles, the choice between different models is an issue the analyst will be faced with when analysing real data. This choice should be a mixture of subject matter knowledge and data-driven strategy. For example, it is well known that age is an important predictor for EMH and that the association between age at diagnosis and EMH is quite often non-linear (1-year increase in age at diagnosis is not the same for a 50-year-old patient as a 70-year-old patient). Proportional hazards assumption is also quite rarely true for the variable age at diagnosis. Therefore, one could assume that its default model would always include a non-linear and time-dependent association between age at diagnosis and the EMH. Model-building strategy (e.g. forward, backward, etc. (Royston and Sauerbrei 2007; Wynant and Abrahamowicz 2014; Maringe et al. 2019)) as well as information criterion (e.g. the Akaike Information Criteria, AIC) could be useful tools (Burnham and Anderson 2002). The use of a model selection strategy would nevertheless call for a refined methodology when deriving variances of the estimated coefficients in order to account for the model selection strategy (Buckland et al. 1997; Efron 2014), but this topic goes beyond the scope of the current chapter.

Illustration – Part 3

Given all these considerations, and assuming the analysis is conducted separately in men and in women, a candidate model for the EMH could be:

$$\lambda_E\left(t,\boldsymbol{x}\middle|w\right)=\lambda_o\left(t\right)\exp\left(g\left(a\right)+h\left(t\right)a+\beta y+m\left(EDI\right)+n\left(t\right)EDI+w\right) \quad (5.2)$$

where $\lambda_o(t)$ is the baseline hazard, a the age at diagnosis, y the year of diagnosis, EDI the European Deprivation Index and w the random effect (with mean 0 and standard deviation σ) defined at the area level. The (logarithm of the) baseline hazard $\lambda_o(t)$ and the functions h and n were modelled with cubic B-splines with knots located at 1 and 5 years, and the non-linear functional forms g and m were modelled using quadratic splines with one knot (located at 70 years for age at diagnosis and at 0 for EDI). With this model, we assume that the association between the year of diagnosis y and the EMH can be summarised with the simple linear and time-fixed term, β, while the association between age a and the EMH is far more complex (with both non-linear and time-dependent components). We also assumed a non-linear and time-dependent association for the EDI. The between-areas variability is accounted for through the random-effect parameter w (also called shared frailty in the field of survival analysis), which is assumed to follow a Gaussian distribution with mean 0 and variance σ^2 (Charvat et al. 2016; Belot et al. 2018).

For the EDI (our exposure of interest), we can investigate the form of association that better describes the observed data by fitting models with different EDI-EMH associations. We could fit a model with (i) a simple time-fixed regression coefficient for EDI (Lin-PH), or with (ii) a non-linear association (NLin-PH), or with (iii) a linear but time-dependent association (Lin-NPH), or with (iv) a non-linear and time-dependent association (as in Eq. (5.2)). In our illustrative example, the final retained model among those four candidates was obtained using the Akaike Information Criteria. The model with the lowest AIC was the one with a non-linear but time-fixed association (NLin-PH). From this model, we could depict the relation between the EDI and the EMH through a plot of the HR according to the EDI (Fig. 5.3). In LOCP cancers in men, the EHR increased according to EDI values but then plateaued for people living in the more deprived areas (e.g. conditionally to the

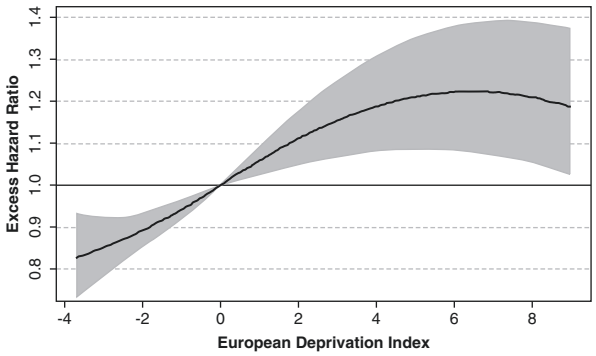

Fig. 5.3 Conditional excess hazard ratio of the European Deprivation Index for lip–oral cavity–pharynx cancer in men with 95% confidence intervals (shaded area), after adjusting for age at diagnosis and year of diagnosis. We limited the EDI values on the x-axis to the 5th and 95th percentiles of the observed EDI distribution. Adapted from Belot et al. (2018). Some modifications to the figure were made. (https://doi.org/10.2147/CLEP.S150848, licensed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/)

other covariates and the random effect, patients living in an area with an EDI = 6 have an EMH equal to 1.2 time the EMH of patients living in an area with EDI = 0). The estimated standard deviation of the random effect was $\sigma = 0.23$ (95% CI: [0.15;0.35]), with evidence of between-cluster variability. However, the estimated standard deviation of the random effect per se is difficult to interpret and developing a measure to quantify the strength of clustering (Oliveira et al. 2016) in the specific context of flexible modelling of the EMH remains an area for further methodological research (Belot et al. 2018).

Discussion

In this chapter, we discussed some of the tools for describing socioeconomic inequalities on cancer survival using population-based cancer registry data. We emphasised the use of relative survival approaches to enable estimation of net survival by socioeconomic subgroup, using the non-parametric consistent estimator developed by Pohar-Perme and colleagues (Perme et al. 2012; Pohar Perme et al. 2016). A log-rank type test may be the first useful step for evaluating the level of evidence that we observe in the data about a difference of net survival curves between socioeconomic subgroups (Grafféo et al. 2016; Pavlič and Perme 2017). In the free software R, the package `relsurv` would allow performing this first step (Perme and Pavlic 2018). A natural following step to quantify the socioeconomic inequalities would be fitting a regression model for the excess mortality hazard (Estève et al. 1990). We described the use of flexible hazard-based regression models to capture the complex association between the prognostic factors and the EMH, benefiting from the good properties of regression splines for non-linear and time-dependent associations (Bolard et al. 2001; Giorgi et al. 2003; Remontet et al. 2007). In the context of socioeconomic inequalities, area-based measures are quite commonly used, mainly for practical reasons but also because they encompass more information than individual deprivation, such as the patient's social and economic environment ('contextual variables') (Diez-Roux 1998; Diez Roux 2001; Subramanian 2004). Therefore, analysing such variables calls for multilevel modelling as the '*health status of residents in the same neighbourhood may be correlated, thus violating the independence assumptions of traditional regression models'* (Hubbard et al. 2010). An approach dealing with all these challenges has recently been proposed for modelling the EMH while accounting for the hierarchical structure of the data through the use of a shared frailty (Charvat et al. 2016; Belot et al. 2018). The R package *mexhaz* has been developed as a companion to these methodological developments. It should be mentioned that if only a small number of areas have more than one patient belonging to it in your dataset, the hierarchical structure may be ignored and thus an EMH without random effects may be used.

We focussed in this chapter on net survival and EMH models, but alternative and complementary measures could also be used to give a full picture of the situation (Belot et al. 2019). For example, the number of life-years lost due to cancer or the

crude probabilities of death from cancer and from other causes (also known as absolute risks or cumulative incidence functions in the classical competing risks setting) are additional measures which have their own merits. The latter quantifies the actual prognosis of cancer patients, while the former quantifies how many years would be lost due to the disease and due to other causes (as compared to an immortal cohort) (Belot et al. 2019).

The field of relative survival remains an active research area and many other tools than the ones presented here have been developed. We mentioned here the general principles of parameterising EMH with the use of model-building strategies and information criterion. Whatever strategy has been chosen, assessing the quality of the fit of the EMH is an additional step that could be done, and two methods have been proposed in the literature (Stare et al. 2005; Danieli et al. 2017). With the goal of analysing survival trends while flexibly modelling the association between continuous covariates and the EMH, Fauvernier et al. proposed a penalised hazard model using multidimensional splines. This approach has the advantage of modelling simultaneously non-linear and time-dependent effects, as well as the interactions of the continuous covariates considered (Fauvernier et al. 2019). Thus, it does not rely on a model-building strategy but reaches its computational limit when analysing more than four covariates. Another class of model (Rubio et al. 2019b) recently proposed for the EMH takes advantage of a general hazard structure and includes many well-known hazard model structures as special cases (e.g. proportional hazards or accelerated failure time models). This model has been extended to analyse data when condition (b) of assumption (1) is in doubt because of the use of insufficiently stratified life tables (Rubio et al. 2019a), while other approaches are also available (Goungounga et al. 2019; Touraine et al. 2020). This problem of insufficiently stratified life tables may arise when the analyst is investigating socioeconomic disparities in cancer survival without using deprivation-specific specific life tables. In this case, sensitivity analysis to evaluate the robustness of the results regarding different scenarios of deprivation-specific life tables should be conducted (Ito et al. 2014; Antunes et al. 2016). While many methodological developments have been achieved regarding analysing population-based registry data to explore socioeconomic inequalities in cancer survival, there is now a need for studies (and therefore data) that use socioeconomic measures defined at both the individual level and the area level (Sloggett et al. 2007). Moreover, we believe that future studies aiming to explain rather than describe socioeconomic inequalities of cancer survival should apply causal mediation analysis (Li et al. 2016). By doing so, effective interventions could be put in place in order to reduce the inequalities in cancer survival.

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Part II
Social Disparities in Cancer Incidence and Survival — Reports

Chapter 6
Social Disparities in Cancer Incidence Among Adults in Europe

Vesna Zadnik, Sonja Tomšič, Ana Mihor, and Eero Pukkala

Background

People's health is intimately linked with the social and economic conditions in which they live. People further down the social ladder are at higher risk of several—but not all—serious illnesses and premature death than those closer to the top. Accordingly, socioeconomic deprivation is recognised as one of the important predictors of many cancers. Inequalities are observed between countries, as well as within countries, irrespective of whether they belong to the low- or high-income country group (Vaccarella and Mackenbach 2020).

Social inequalities in cancer incidence are viewed as a consequence of social inequalities in the distribution of cancer risk factors and the access to preventive measures among certain social groups; defined by either their social class, ethnicity, education, income, wealth, occupation, living conditions or other indicators of socioeconomic status (SES). This view stems from observations that inequalities in cancer incidence can be at least partly attributed to inequalities observed in health-related behaviour and other 'proximal causes', such as smoking and alcohol, diet, exercise, reproductive behaviour, infectious agents (e.g. hepatitis viruses, human papilloma viruses) or exposure to occupational and environmental factors (Sarfati 2019; Vaccarella and Mackenbach 2020). Depending on the specific cancer, socioeconomic status can exert its influence during different life stages, from the prenatal period to

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adulthood (Vaccarella and Mackenbach 2020). According to the WHO Commission on Social Determinants of Health, underlying health inequalities, including in cancer morbidity and mortality, are 'inequalities in the conditions of daily life and the fundamental drivers that give rise to them: inequities in power, money and resources' (the so-called causes of the causes) (European Commission 2013).

Two landmark International Agency for Research on Cancer (IARC) publications (Kogevinas et al. 1997; Vaccarella et al. 2019) have addressed cancer inequalities. The first, published in 1997, was a comprehensive review of inequalities across the cancer continuum within developed countries, along with social class theory, methodological issues and investigation of putative (mostly what could be considered proximal) causes, compiling the primary evidence base. The compounded evidence from 1997 showed that cancer incidence is affected by SES, with some locations associated with higher SES (colon, breast, ovary, melanoma, brain in men) and others with lower SES (lung, upper aerodigestive system, oesophagus, stomach, liver, cervix), while the rest were not related to SES or the evidence was inconclusive. The recently published IARC report from 2019 updated the evidence base and the theoretical frameworks but paid more attention to medium and low-income countries, between-country differences, as well as actions and policies to reduce cancer inequalities.

To address cancer inequalities, we need accurate data. Registration of cancer cases in population-based cancer registries is a prerequisite for effective monitoring of social inequalities (Sarfati 2019). In this chapter, the focus is on within-country inequalities in European countries that are members of the European Network of Cancer Registries (ENCR), an organisation which strives to improve the quality and comparability of data on cancer across Europe. Most of the available data come (for now) from Northern and Western European countries, in contrast with the paucity of studies from Southern and especially Eastern Europe.

Registries ideally collect information on every single case of cancer diagnosed in a given population. This allows the most accurate calculation of incidence, survival and mortality (Parkin 2006), as well as creating cohorts of individuals stratified by explanatory variables. Data linkages with other population-based databases have opened the door for collecting new variables on cancer patients that traditionally were not part of the cancer registration process. As to the measurement of SES, two main methods are adopted, distinguished by applying individual or area-level measures of SES using proxy measures. In the Nordic countries, registry information is linked via a personal identifier to other databases and registers containing data on education, labour, taxation statistics, etc., which provide data on SES on an individual level. SES is often represented as a combination of several direct SES indicators, for example, highest level of education attained, annual household disposable income, occupational group, household tenure or other characteristic. Many other European countries have, either due to technical or privacy issues, not been able to use linkage methods or rely more on national/regional deprivation indices. They adopt an area-level approach whereby each individual's SES is determined based on administratively defined areas (e.g. postcode, voting district) by assigning all inhabitants a value of an area-based composite deprivation measure (area-SES as a proxy

for individual-level SES). The area-level SES measure consists of several domains and indicators (e.g. percentage of unemployed, percentage with low education, percentage of blue-collar workers, percentage of people claiming financial benefits, crime rates) and is typically grouped into quintiles of deprivation from lowest to highest.

It is estimated that almost 4 million cancers, not counting non-melanoma skin cancers, were diagnosed in Europe in 2018. The most common were cancers of the breast, colon-rectum, lung, prostate and bladder, and melanoma of the skin (Ferlay et al. 2018). Numerous epidemiological studies published over the past two decades have provided further evidence of an association between SES and incidence of all of the most common cancers in European countries. Recently, a comprehensive review of population-based epidemiological studies published in this millennium investigating social inequalities in cancer incidence in Europe has been published by Mihor et al. (2020). We summarise their main conclusions and add some further insights and references. In order to highlight the large burden of disease that could potentially be attributed to SES in Europe, in this chapter, the cancers are grouped according to the direction of association found: cancers associated with low socioeconomic status are reported first, followed by those that are associated with high socioeconomic status and finally those where no association with socioeconomic status has been confirmed. An overview is offered through a graphical presentation of associations with Fig. 6.1. We generated a figure of cancer locations which specifies by using three semi-quantitatively defined categories the observed: (i) direction of association (no association, increased risk for low SES, decreased risk for low SES, or combinations of these); and (ii) range of most commonly reported estimates of RR for low compared to high SES—no association if most RRs were not significantly different from 1, slightly increased (decreased) risk if most RRs were <1.25 (>0.8), moderately increased (decreased) risk if most RRs were 1.25–1.5 (0.8–0.66) and strongly increased (decreased) risk if most RRs were >1.5 (<0.66).

Cancers Associated with Low Socioeconomic Status

Lung cancer is the most common cancer among cancers associated with low socioeconomic status. There is a more than threefold variation in lung cancer incidence among European countries; the countries presenting with high incidence rates are different when considering male or female lung cancers (European Commission 2020). By far, the most significant factor influencing trends in lung cancer incidence is tobacco smoking, which is thought to be the main cause of lung cancer in the vast majority of cases. Smoking is socially determined and was once more widespread among high compared to low SES groups. In many places, this pattern has shifted towards lower SES groups, though even today, there might be societies in Europe where the former distribution is seen (Pampel 2005).

A recent systematic review by Mihor et al. (2020) identified 16 large European registry-based studies that used individual SES indicators to assess relative risk for

Low compared to High SES			Estimate of Relative Risk		
↔	↑	↓	●	●	●
no variation	increased risk	decreased risk	<1.25 >0.8	1.25–1.5 0.8-0.66	>1.5 <0.66

Cancer	Number* of studies	Men RR		Women RR	
		Direction	Size	Direction	Size
Lung & trachea	20.5	↑	●	↑	●
Head & neck	15.5	↑	●	↑	●
Esophagus	10	↑	●	↔↑	●
Stomach	14	↑	●	↑	●
Liver & gallbladder	7	↑	●	↑	●
Pancreas	11	↔↑	●	↔↑	●
Cervix	20.5			↑	●
Bladder	9	↑	●	↑	●
Kidney	10	↑	●	↑	●
Malignant melanoma of skin	15	↓	●	↓	●
Non-melanoma skin	7	↓	●	↓	●
Breast	18.5			↓	●
Prostate	19	↓	●		
Testis	10.5	↔↓	●		
Thyroid	7	↔↓	●	↔↓	●
Colon & rectum	17.5	↓↔↑	●	↓↔↑	●
Uterus	6.5			↓↔↑	●
Ovary & fallopian tubes	9			↓↔↑	●
Haematological	9	↔		↔	
Central nervous system	9.5	↓↔↑	●	↓↔↑	●

Fig. 6.1 Overview of associations between location-specific cancer incidence and socioeconomic status in Europe (Source: compiled based on results from the systematic review by Mihor et al. (2020)). SES socioeconomic status, RR relative risk. *Calculation of number of studies: complete overlap of data with respect to time period in the same European country was weighted 0, partial overlap in the time period was weighted 0.5, no overlap in the time period was weighted 1

lung cancer across SES group strata and an additional 14 that applied (also) area-level SES indicators for the same purpose. Unequivocally, their findings point to an increased risk of cancer in men and women with low SES, irrespective of the type of SES measure used. Importantly, there is a clear gradient of incidence inequalities found across the many different categories of SES, from lowest through middle to highest. Overall, it appears that the association of increasing risk for lung cancer with decreasing social advantage is stronger for men compared to women. Some investigations also considered the association stratified by the histology of lung cancer. Squamous and small cell carcinoma were found to be associated with SES, whereas adenocarcinoma and large cell carcinoma were less so (Ekberg-Aronsson et al. 2006; Bennett et al. 2008).

Because the unequal distribution of smoking across SES is thought to contribute most to lung cancer inequality, adjusting for smoking and other known socially determined causes of lung cancer is imperative to establish whether low SES has

any independent effects on increased incidence—something not many studies in Europe have attempted. Regarding smoking, one study found that it accounted for 64% of the excess risk in low SES women (Braaten et al. 2005), while another found that in men, the risk was increased in low SES individuals irrespective of their smoking status, even in never-smokers (Ekberg-Aronsson et al. 2006). Within a large multi-centric EPIC cohort consisting of individuals from nine European countries (Menvielle et al. 2009), along with smoking, the role of diet in explaining socioeconomic inequalities was also investigated. Smoking was able to explain between 50% and 70% of educational inequalities in lung cancer, while diet did not explain any. Smoking was able to explain a larger percentage of the lung cancer inequality in countries with higher incidence rates (i.e. in Northern compared to Southern Europe), reflecting the historical smoking pattern. The remaining inequality might primarily be explained by occupational exposures (Menvielle et al. 2010). It remains to be investigated whether any other factors contribute to lung cancer incidence inequality, assuming the unexplained portion is not entirely due to the residual confounding of smoking.

The distribution of *head and neck cancers (lips, oral and nasal cavity, sinuses, pharynx and larynx)* is influenced by trends in their main risk factors, tobacco smoking and alcohol consumption. Considering SES, several European studies have shown that the entire group of head and neck cancers is strongly associated with lower SES, mainly determined by education on the individual level or by combined deprivation indices on the area level (Mihor et al. 2020). The association is much stronger for men than women. Two multi-centre case-control studies (Conway et al. 2010, 2015) investigating head and neck cancers adjusted the observed educational inequality for alcohol and tobacco consumption along with fresh fruit and vegetable intake. Approximately 30% of the educational inequality was unexplained, meaning there might be other pathways through which SES exerts its influence on the incidence of these cancers.

Most of the European research on *oesophageal* and *stomach cancer* and SES points to higher risks with lower social standing. Yet again, the incidence in women seems to be less influenced by SES level than in men (Mihor et al. 2020). Different risk factors have been identified for the two major histological types of oesophageal cancer (adenocarcinoma and squamous carcinoma) as well as for cardia and non-cardia stomach cancer. Adenocarcinoma in the cardia has been associated with the same risk factors as oesophageal adenocarcinoma (diet), while the occurrence of non-cardia adenocarcinoma is linked to infection with *Helicobacter pylori*, and oesophageal squamous carcinoma is associated with similar risk factors as head and neck cancers (smoking and alcohol). The burden of oesophageal squamous carcinoma and non-cardia stomach cancer is considerably higher compared to the other two subtypes, which skews the results of any pooled epidemiological analysis in their favour (Arnold et al. 2015; Colquhoun et al. 2015). Considering the association with SES level, insufficient information comes from studies that do not control in the design and/or analysis for the above-mentioned main subtypes of oesophageal and stomach cancers. The results on relatively scarce research on the association of

liver, gallbladder and *pancreatic cancer* incidence and SES suggest that those cancers are associated with low socioeconomic status. Their aetiology is poorly understood, which is also reflected in inconclusive findings regarding SES inequality.

A mainly sexually transmitted infection with oncogenic *Human papilloma virus* (HPV) types is considered a prerequisite for the development of *cervical cancer*. Despite changes in sexual behaviour leading to increases in HPV infection rates, cervical cancer incidence has been decreasing dramatically in most of Europe during the past decades due to the introduction of organised screening with cervical Pap smears or HPV testing, which also enables the detection of precancerous lesions. A contributing risk factor for cervical cancer is smoking, which is thought to influence the progression of a persistent infection to invasive carcinoma (International Collaboration of Epidemiological Studies of Cervical Cancer 2006; Fonseca-Moutinho 2011). Sexual behaviour, screening participation and smoking are known to be differentially distributed across the SES spectrum, and therefore it is not surprising that there is a consistent strong negative association between affluence and risk of invasive cervical cancer diagnosis (Mihor et al. 2020).

Smoking as the most important known risk factor is the major driver of *bladder cancer* incidence rates. The risk is also increased by exposure to occupational carcinogens, most notably aromatic amines, and certain chronic parasitic infections that, however, are not common in Europe (Cumberbatch et al. 2018). There is a lack of data in Europe regarding the contributory power of known and potential risk factors to the observed SES inequality in bladder cancer incidence (Mihor et al. 2020). Drawing from what we know about SES inequality in lung cancer, a large proportion of the inequality is likely attributable to smoking. Known and potential risk factors for *kidney cancer* include hypertension, smoking, obesity, alcohol, physical inactivity and occupational exposure to certain chemicals. All the above-mentioned factors are associated with SES. Based on available European population-based research in the past 20 years, Mihor et al. (Mihor et al. 2020) concluded that lower SES is associated with a higher incidence in both sexes but slightly more strongly in women.

Cancers Associated with High Socioeconomic Status

Breast cancer is the most common cancer among cancers associated with high socioeconomic status. There is a more than twofold variation in female breast cancer incidence among European countries (European Commission 2020). The countries presenting with the lowest incidence rates are mainly in the east and southeast of the continent. Risk factors are well established and include genetic/familial predisposition, height and reproductive factors (such as age at menarche and menopause, age at first birth, parity and breastfeeding), which relate to the cumulative years of menstruation, use of oral contraception and postmenopausal hormone therapy, high BMI (protective before and a risk factor after menopause), physical inactivity, alcohol and smoking (McPherson et al. 2000; Hamajima et al. 2002;

Hankinson et al. 2004; Dossus et al. 2014). Many of them are considered as highly variable across socioeconomic strata. A recent systematic review by Mihor et al. (2020) identified 20 large European registry-based studies that used individual SES indicators to assess relative risk for female breast cancer across SES group levels and an additional 10 that applied (also) area-level SES indicators for the same purpose. Consistently, studies find that women with high SES have a higher risk of breast cancer. Almost all of the excess risk can be explained by known reproductive risk factors. Different analyses indicated education (and the underlying causal association between higher education and delayed childbearing) as the most important driver of the observed SES gradient. Age at first birth and parity account for up to 50% of inequality (Menvielle et al. 2011). Some of the inequality might also be attributable to differential participation in mammographic screening though the contribution is thought to be small because organised screening now is widespread in Europe and results in smaller SES differences in participation than the opportunistic type of screening (Braaten et al. 2005; Menvielle et al. 2011; Meijer et al. 2013).

Aside from family history, hormonal factors and race, risk factors for *prostate cancer* are poorly understood. Incidence trends are largely influenced by the availability of opportunistic screening for prostate cancer by prostate-specific antigen (PSA) testing. Many European studies found lower prostate cancer incidence in lower SES classes, irrespective of the SES measure used. (Mihor et al. 2020). Even though there are few available studies in Europe that aimed to investigate directly factors explaining this association, it is thought to primarily coincide with greater use of opportunistic PSA testing. PSA testing without clinical indication seems to be least common in men with the lowest level of education (Karlsen et al. 2013). The association between high SES and the increased incidence is very strong for less advanced disease, whereas the incidence of more advanced prostate cancer is either less increased (Pukkala and Weiderpass 2002; Shafique et al. 2012) or even much lower among the affluent (Kilpeläinen et al. 2016).

For *testicular cancer*, high areal deprivation and low occupational social class were linked to lower seminoma and non-seminoma incidence in England and Finland (Pukkala and Weiderpass 2002; National Cancer Intelligence Network 2014; McNally et al. 2015). In Finland, a pronounced narrowing of the gap since 1970 was evident, and similar findings of a closing gap have been reported in other countries (Pukkala and Weiderpass 2002). If and to what extent potential prenatal (e.g. in utero exposure to environmental endocrine disruptors leading to cryptorchidism) or postnatal risk factors (such as diet, exercise and exposure to heat (McGlynn and Trabert 2012)) could explain these observations and trends remains unclear.

The vast majority of *skin cancers* are attributable to UV radiation, either natural from the sun or artificial in tanning beds. *Skin melanoma* is associated more with high intermittent exposure and sunburns, while *squamous cell carcinoma* is linked to chronic exposure (Gandini et al. 2005; Moan et al. 2015). Intermittent exposure is thought to be more prevalent in higher SES groups who more often engage in recreational activities with high UV exposure, such as during holidays, while outdoor workers with regular sun exposure rarely get sunburns. Chronic UV exposure

has been a marker of occupational exposure in low SES groups. Studies in Europe consistently show malignant melanoma risk is higher in men and women of higher social standing, measured using different SES indicators, most often level of education or areal deprivation (Mihor et al. 2020). Sub-analysis by body parts showed that SES is primarily associated with trunk and limbs melanoma, whereas there was no gap found for head and neck melanoma. This is in line with the intermittent exposure theory (Pérez-Gómez et al. 2008). Association of non-melanoma skin cancer, especially basal cell carcinoma, which is known to be underreported in cancer registries, and SES has been studied much less than melanoma. In the published studies, both basal and squamous cell carcinomas are also associated with higher SES. It remains unknown whether greater access for the affluent to individual screening is driving the gap in skin cancer incidence, especially in view of reports of possible overdiagnosis on account of classifying benign, atypical lesions as malignant (Erickson and Driscoll 2010).

The increasing incidence of *thyroid cancer*, most notably of the papillary type, is thought to be driven mostly by improved detection of asymptomatic small cancers via biopsy (Pellegriti et al. 2013). In some European countries, greater affluence was associated with a higher incidence (Braaten et al. 2005; Smailyte et al. 2015; Hoebel et al. 2018). The positive association, when found, is likely artificial and only present due to more affluent people having better access to diagnostic procedures. Known and potential causes for thyroid cancers, such as ionising radiation, persistent organic pollutants, dietary iodine, nitrates, obesity and autoimmune disorders (Pellegriti et al. 2013), are unlikely to be more prevalent in high compared to low SES groups.

Cancers Not Clearly Associated with Socioeconomic Status

Most established risk factors for *colorectal cancer* are lifestyle-related, such as low fibre and high red and processed meat diet, overweight and obesity, and lack of physical activity, as well as alcohol and tobacco use (Dekker et al. 2019). Leading up to the 21st century and even as recently as 2014, two predominant overall SES patterns were found whereby incidence was higher among the affluent in Europe (European pattern) and among the deprived in the United States (American pattern) (Aarts et al. 2010; Manser and Bauerfeind 2014). Newer European studies reviewed by Mihor et al. (Mihor et al. 2020) provided evidence that, at least in certain Northern and Western European countries, a reversal of the European pattern towards the American pattern is underway.

Keeping in mind that colorectal cancer is not a uniform disease but the three distinct segments—proximal colon, distal colon and rectum—differ somewhat with respect to carcinogenesis and risk factors (Li and Lai 2009), analysis by subsite (and controlling for known lifestyle factors) is important to better understand colorectal cancer SES inequalities. In the EPIC cohort, for example, a lower risk of colorectal cancer in lower educated groups was found to be most pronounced for proximal

colon, with no association for rectal cancer (Leufkens et al. 2012). Adjustment for smoking, body mass index (BMI), physical activity, alcohol, intake of vegetables, fruit, fibre, energy from fat and non-fat, red meat, processed meat and fish lowered all estimates, but each factor alone did not contribute much to inequality. Differences between men and women were found, which could also result from differential effects of risk factors, since there have been reports, for example, that compared to females, males benefit more from physical exercise in terms of colorectal cancer risk reduction (Sormunen et al. 2016).

Cancers of the uterus, fallopian tubes and ovaries share some of the risk factors with breast cancer, such as reproductive factors and postmenopausal hormone therapy use (Salehi et al. 2008; Dossus et al. 2010). Some European studies (Mihor et al. 2020) found an increased incidence of these cancers in high SES groups, though many more found no association, or occasionally even lower incidence. Therefore, it is uncertain if and how SES is associated with these cancers. It should be stressed that the aetiology of epithelial ovarian cancer has been found to vary according to histological subtype, and different factors influence the risk of different subtypes (Gates et al. 2009). Further research should aim to answer which subtypes are associated with SES.

There are practically no known aetiological factors for *haematological cancers*, aside from a possible role of infections with viruses such as *Epstein-Barr virus* (EBV), *Human herpesvirus 8* (HHV-8) and *Human t-cell leukaemia virus type 1* (HTLV-1) in lymphomas and exposure to benzene, ionising radiation and obesity in leukaemia (Zeeb and Blettner 1998; Roman and Smith 2011; Mazzarella et al. 2019). Associations with higher SES have previously been reported for Hodgkin lymphoma, though European studies from the past two decades do not show evident SES variations (Mihor et al. 2020). Adjustment for aetiological risk factors in studying associations with SES has not been performed yet, and therefore it is impossible to speculate on the underlying causes for occasional findings of an association with haematological malignancies—they could eventually turn out to only be chance findings.

Incidence of *central nervous system (CNS) tumours* is on the rise, which can be attributed to increased detection but could also reflect a real increase due to hitherto unknown reasons (Patel et al. 2019). Associations for CNS tumours with SES are very inconsistent—both positive, negative or none have been found in Europe (Mihor et al. 2020). In order to better understand whether SES is linked with CNS tumours, this should be investigated by specific subtypes, which presumably differ in aetiology.

Conclusions

Overall, as seen in Fig. 6.1, the burden of many specific cancer types is distributed unequally with respect to SES, and many of the most common types show a negative or positive gradient with various SES indicators, both individual as well as areal

level, which capture different aspects of affluence and deprivation. Cancers of the lung, head and neck, oesophagus, stomach, liver and gallbladder, pancreas, kidney, bladder and cervix uteri are associated with lower affluence in Europe, whereas skin, breast, prostate and thyroid cancers are disproportionally more often diagnosed in highly affluent individuals or those living in areas with the lowest deprivation levels. No convincing associations are currently seen for haematological cancers, testicular cancer and tumours of the central nervous system. There is a shifting association observed for colorectal cancer, with northern Europe now experiencing higher incidence among the deprived, while in the south, a reverse pattern remains.

The higher burden in the deprived, which is more pronounced in men than in women, is of particular concern because the cancers with the highest incidence in the low-SES individuals—lung, head and neck and stomach cancers—also carry low survival. Lifestyle-related factors have the largest (proximal) contributory power in driving these inequalities within European populations. To remedy the situation, it is important to address the underlying 'causes of the causes' in addition to developing SES-tailored preventive approaches.

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Chapter 7
Social Disparities in Survival from Breast Cancer in Europe

Pamela Minicozzi, Michel P. Coleman, and Claudia Allemani

Introduction

Breast cancer is the most common cancer and the main cause of death from cancer among women in Europe and worldwide (Bray et al. 2018).

The third cycle of the CONCORD programme (CONCORD-3) updated the global surveillance of cancer survival to include patients diagnosed during the 15-year period from 2000–2014 with one of 18 malignancies, including breast cancer. It included individual data on more than 37.5 million cancer patients from 322 population-based cancer registries in 71 countries and territories worldwide (Allemani et al. 2018). The main outcome measure was five-year net survival: this is the cumulative probability of surviving at least 5 years from diagnosis, after correction for mortality due to other causes of death. Net survival is usually expressed as a percentage for convenience.

The results show that five-year net survival for adult women (aged 15–99 years) diagnosed with breast cancer has varied widely in Europe, both between countries and over time. Age-standardised five-year net survival for women diagnosed during 2000–2004 ranged from 65% (95% confidence interval [CI] 63–66%) in Lithuania to 87% (83–92%) in Iceland. For women diagnosed 10 years later, during 2010–2014, the range was from 71% (69–72%) in the Russian Federation to 89% (85–93%) in Iceland (Allemani et al. 2018).

CONCORD-3 also showed that survival varies widely within countries, although in most countries, these regional differences have narrowed over time (Fig. 7.1). Germany, France, Italy and the United Kingdom are exceptions. In these countries, regional variation in five-year net survival for women diagnosed during 2010–2014

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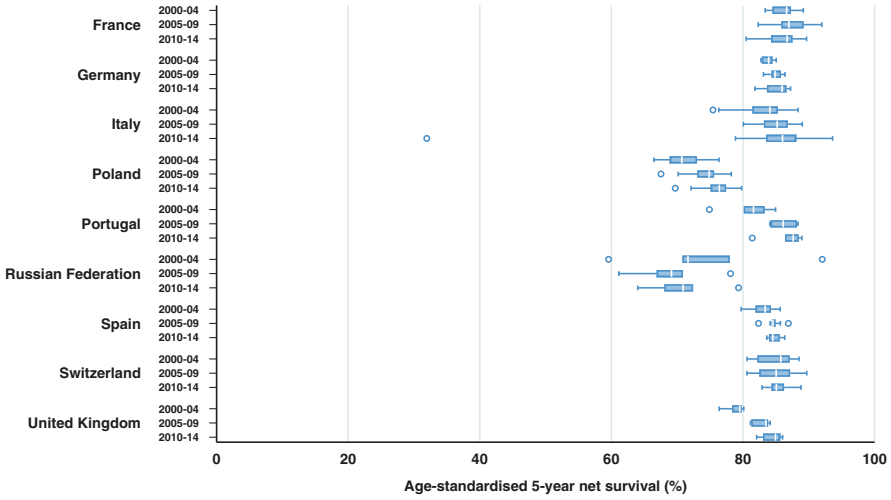

Fig. 7.1 Range in age-standardised five-year net survival (%) for adult women (15–99 years) diagnosed with breast cancer during 2000–2014: European countries with regional cancer registration (CONCORD-3)

had changed very little from the variation seen among women diagnosed during 2000–2004.

These data reveal wide disparities in breast cancer outcomes across Europe. Population-based cancer survival is a key indicator of the overall effectiveness of health systems in managing care and treatment for all cancer patients. However, there are significant inequalities in the availability of and access to high-quality cancer care (Aapro et al. 2017). The inequalities in cancer survival arise within societies.

The determinants of population-based cancer survival differences can be divided into two groups. Factors related to the social environment include the availability and organisation of diagnostic facilities, organised mass screening, adequate treatment facilities, and sufficient numbers of doctors and other health personnel. Factors related to the individual cancer patient include socioeconomic status, serious concomitant disease at diagnosis [comorbidity], lifestyle factors such as smoking, alcohol use and physical activity, and race/ethnicity (Sant et al. 2015).

A worldwide review of all cancers in the late 1990s found that patients in lower social classes had consistently lower survival than those in higher social classes (Kogevinas and Porta 1997). A more recent worldwide review found that part of the association between socioeconomic groups and cancer survival is attributable to unfavourable stage distribution at diagnosis and lower access to optimal treatment (Woods et al. 2006). However, the authors underlined that more investigations were needed: (i) on patients characteristics, such as nutrition and comorbidities that may interact with treatment decisions and with the outcome; and (ii) on how socioeconomic differences are associated with access to health services, participation in screening programmes and, ultimately, to differences in cancer survival.

We conducted a PubMed literature search to investigate the current state of the art on this topic. The search terms used were designed to identify references that indexed or mentioned: (i) breast cancer, (ii) survival, (iii) a European country and (iv) socioeconomic or social status, or their synonyms. All European countries were included as search terms. Only articles published in the 10 years up to December 2019 and explicitly showing results on socioeconomic differences in survival were selected.

Literature Review

We selected 648 articles for abstract review, of which 144 were selected for full-text review (flow chart in Fig. 7.2). Of these, 42 were finally included in our review. The studies varied widely in the calendar period of diagnosis examined, as well as the sample size, statistical methods, definition of socioeconomic status and the co-variables included in the analyses, as well as between the countries included. The main results and key descriptors are summarised in Table 7.1.

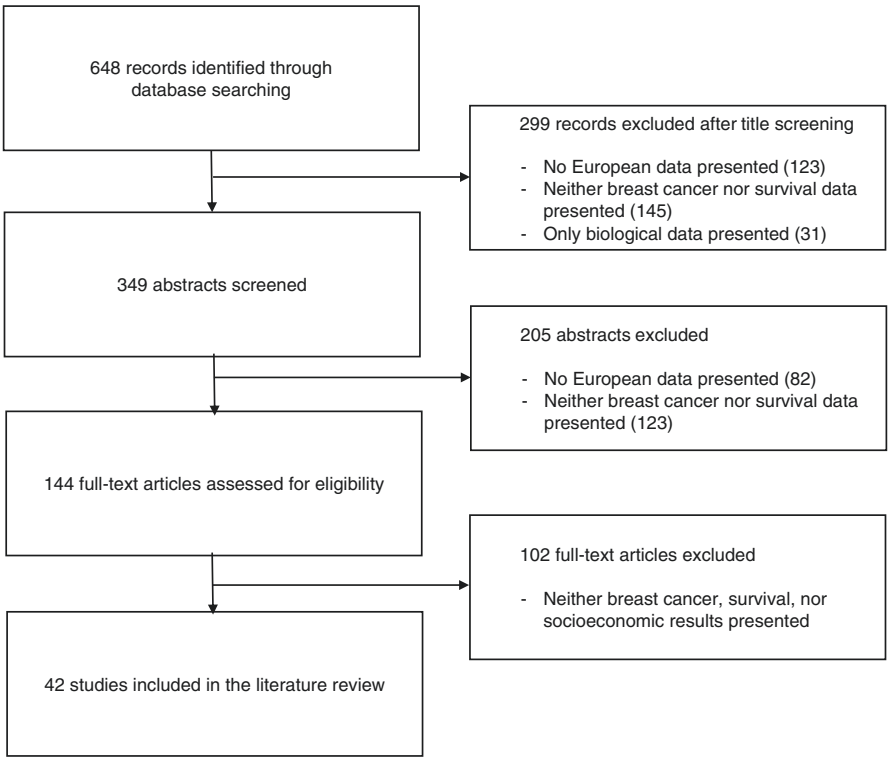

Fig. 7.2 Flow chart of the study selection process

Table 7.1 Description of the studies included in the literature review, including country involved, data source accessed, study population, statistical methods applied, socioeconomic measures used, and any further information considered in relation to socioeconomic survival estimates, together with main study results

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Belot et al. 2018) (France)	Calvados and Manche population-based cancer registries	Women diagnosed during 1997–2010	Net survival	Area deprivation [based on the European Deprivation Index based on (country-specific) census variables]	–	1-year net survival varied from 97% in most affluent to 95% in most deprived women; 5-year net survival varied from 87% in most affluent to 85% in most deprived women; 10-year net survival varied from 81% in most affluent to 75% in most deprived women
(Lyratzopoulos et al. 2011) (UK)	Office for National Statistics for residents of England and Wales Hospital Episodes Statistics data	Women diagnosed during 1971–2006	Relative survival	Area deprivation index [based on Carstairs index and the Index of Multiple Deprivation, according to period of diagnosis]	Year of diagnosis	The deprivation gap (i.e. the absolute difference between survival estimated for most deprived and that estimated for most affluent women) in five-year relative survival reduced over time (from around −10% in 1973 to approx. −7% in 2003) *(A negative value means that survival in most deprived women was lower than that estimated for most affluent women)*
(Exarchakou et al. 2018) (UK)	National Cancer Registry National Cancer Registration and Analysis Service in Public Health England Office for National Statistics Health and Social Care Information Centre	Women aged 15–99 diagnosed in England during 1996–2013	Net survival	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Year of diagnosis	Although survival increased from 1996 to 2013 (e.g. survival for most affluent women was 91% in 1996 and 98% in 2013), it remained consistently lower among more deprived than among most affluent patients. The deprivation gap in 1-year net survival remained unchanged in 1996–2013 (−3.2%* over the entire period)

(Dalton et al. 2019) (Denmark)	Income Statistics Register, Danish Cancer Registry, Central Population Registry	Women aged ≥20 years diagnosed during 1987–2009, with available information on income	Relative survival	Individual disposable income	Year of diagnosis	five-year relative survival varied from 67% in most affluent to 55% in most deprived women in 1987 *(data extracted from graphics)* five-year relative survival varied from 78% in most affluent to 71% in most deprived women in 2013 *(data extracted from graphics)*
(Syriopoulou et al. 2017) (UK)	National Cancer Registry	Women diagnosed during 1998–2013	Average loss in life expectancy Percentage of life lost	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis	Average loss in expectation of life for each deprivation group ranged from 5 to 6 years from least to most deprived women. Results varied with age at diagnosis, being slightly lower for 70-year olds or older. Proportion of life lost varied from 22% to 27% from least to most deprived women. Results varied with age at diagnosis, being higher for 70-year olds or older.
(Rutherford et al. 2015) (UK)	National Cancer Registry Data	Women aged 30–99 diagnosed in England and Wales during 1999–2009	Life expectancy estimated (by using flexible parametric excess hazard regression models)	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis	*Age at diagnosis*: *60 years* The difference in life expectancy with and without cancer was estimated to be 4.7 and 4.9 years for the least and most deprived groups, respectively The proportion of the deprivation gap in number of years remaining that is due to differences in relative (cancer) survival was approx. 28%; thus, over two-thirds of the deprivation gap in differential life expectancy was explained by differences in other-cause survival.

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Berger et al. 2012) (France)	*ONLY abstract*	Women diagnosed and treated in the Institut Curie during 1981–2001	Cox proportional hazards regression models for all-cause survival	Socioeconomic status was determined from district of residence, median income for town of residence corrected by the consumption unit and body mass index	Period of diagnosis, age at diagnosis	Hazard ratio [HR] = 0.93* for high-income women compared to low-income women After adjusting for age at diagnosis and period of diagnosis, the risk of cancer death decreased for patients residing in districts with median income greater than 15,770 € (HR = 0.92*)
(Nur et al. 2015) (UK)	England Cancer registry, Office for National Statistics	Women aged 15–99 years diagnosed in England during 2001–2005	Net survival weighted least-squares regression models	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis	The deprivation gap in 1-year net survival widened with increasing age at diagnosis (−0.8%* for 15–44-year olds to −4.8%* for 75–99-year olds) This also happened for patients diagnosed up to 74 years for five-year net survival (deprivation gap: −5.2%* for 15–44-year olds to −8.3%* for 65–74-year olds, but −5.1* for 75–99-year olds) and 10-year net survival (deprivation gap: −5.7%* for 15–44-year olds to −8.9%* for 65–74-year olds, but −7.4* for 75–99-year olds).

(Beiki et al. 2012) (Sweden)	Swedish nationwide registers	Women diagnosed during 1961–2007	Cox proportional hazards regression models for cause-specific survival	Education	Period diagnosis, age at diagnosis, immigrant status or immigrants' daughter status	Women with the highest number of years of education had approx. 30% higher risk of dying from breast cancer than women with the lowest number of years of education *(data not shown in the paper)* Compared to native Swedes, no significant differences were evident in the risk of dying from breast cancer among immigrants (hazard ratios [HRs] range: 0.99–1.03) and immigrants' daughters (HRs range: 0.85 to 0.98), according to years of education after adjusting for age and period of diagnosis

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Rutherford et al. 2013) (UK)	Eastern Cancer Registration Information Centre	Women diagnosed in the East of England during 2006–2010	Relative survival No. of avoidable deaths (by using flexible parametric excess hazard regression models)	Area deprivation index [based on the Index of Multiple Deprivation]	Stage at diagnosis	5-year stage-specific survival was quite similar across deprivation quintiles 1–4 (e.g. approx. 90% for stage II, approx. 60% for stage III and 18–20% for stage IV), but decreased for most deprived women, i.e. deprivation quintile 5 (e.g. approx. 85% for stage II, approx. 50% for stage III and approx. 10% for stage IV). No differences in five-year survival were evident for stage I tumours across deprivation quintiles 1–5. Socioeconomic differences in stage explained nearly all of the deprivation differences in relative survival found between women in deprivation quintiles 3 or 4 and those in deprivation quintile 1 (most affluent). Eliminating stage differences only removed about half of the survival inequalities found for most deprived women with respect to most affluent women Equalising stage at diagnosis for women in deprivation quintiles 2–5 to that observed for women in deprivation quintile 1, no. of avoidable deaths were approx. 80 for women in deprivation quintiles 2 and 3, 120 in deprivation quintile 4, and 170 in deprivation quintile 5

(Bower et al. 2019) (Sweden)	Breast Cancer Data Base Sweden (including Breast Cancer Quality Registers from the Stockholm/ Gotland, Uppsala/ Orebro and North healthcare regions)	Women diagnosed during 1992–2012	Loss in expectation of life (by using flexible parametric excess hazard regression models)	Education	Age at diagnosis Stage at diagnosis	Life years lost in low, middle and high education groups vary from 9.90, 9.69, 9.11 for 45-year olds to 2.28,1.89, 2.11 for 75-year olds, respectively. Considering the cohort of 3843 women diagnosed in a typical calendar year with breast cancer, removing differences in stage distribution would result in postponing 25 deaths beyond 5 years from diagnosis, compared to a postponement of 26 deaths when removing differences in stage-specific survival. Considering the whole life span of women with breast cancer, 573 life years could be gained if differences in stage at diagnosis were eliminated, in comparison to 692 life years when removing stage-specific survival.
(Aarts et al. 2013) (Netherlands)	Eindhoven Cancer Registry	Women diagnosed in Eindhoven during 1991–2008	Cox proportional hazards regression models for all-cause survival	Education	Period of diagnosis, age at diagnosis, stage at diagnosis	HR = 1.5 for women with low education level compared to those with high education level, after adjusting for year of diagnosis, age and stage at diagnosis

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Baker et al. 2010) (UK)	Ninewells Hospital Medical School database	Resected Caucasian patients diagnosed in 1997–2001, with frozen tissue stored in the regional tissue bank	Kaplan Meier estimates and Cox proportional hazards regression models for cancer-specific survival and disease-free survival	Area deprivation index [based on Carstairs index, grouped as 1st–9th deciles and 10th decile]	p53 mutation tumour grade, stage at diagnosis (tumour size, lymph nodal status) oestrogen receptor status, HER2, triple negative tumour	Women in deprivation decile 10 were more likely to have a relapse (HR = 3.7*) or die (HR = 6.1*) compared to those in deciles 1–9, after adjusting for all the considered variables Within the p53-mutant patients, those in deprivation decile 10 were more likely to have a relapse (five-year survival: 24% vs 72%) or die (five-year survival: 20% vs 55%) compared to those in deciles 1–9, after adjusting for all the considered variables (excluding p53 mutation)
(Morris et al. 2017) (UK)	West Midlands Breast Screening Quality Assurance Reference Centre, Hospital Episode Statistics, General Practice Research Database	Women aged 50–70 diagnosed during 1989–2006 in the West Midlands region of England	Net survival	Area deprivation [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis, comorbidity lifestyle (alcohol habits, smoking habits, body mass index [BMI])	5-year net survival ranged from 94% in most affluent women to 83% in most deprived women *(data extracted from graphics)* 10-year net survival ranged from 88% in most affluent women to 72% in most deprived women *(data extracted from graphics)* This disadvantage in prognosis for most deprived women was present irrespective of the woman's obesity, alcohol, smoking or comorbidity status

(Morris et al. 2016) (UK)	West Midlands Breast Screening Quality Assurance Reference Centre Hospital Episode Statistics National Breast Screening Service records	Women aged 50–70 years diagnosed during 01/04/1989–31/03/2011 who were continuously eligible for screening from the age of 50 up to either 65 or 70 years and who would have received their first invitation letter from their 50th birthday onwards	Flexible parametric excess hazards regression models to estimate the excess hazard rate ratio (EHR)	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis, stage at diagnosis (tumour size, nodal involvement, presence of metastases), year of diagnosis *(as a proxy of screening history)* tumour characteristics (histology) treatment (surgery and time to surgery) comorbidity	*Women with non-screen detected cancer* The excess hazard of death from breast cancer, within 5 years of diagnosis, was 64% higher in most deprived women compared to most affluent women (EHR = 1.64*, adjusted for age and year of diagnosis) *Women with screen-detected cancer* The excess hazard of death from breast cancer, within 5 years of diagnosis, was more than double among screen-detected women (EHR = 2.12*, adjusted for age and year of diagnosis). These hazard rate ratios reduced by approx. 10% for non-screen-detected women and by approx. 25% for screen-detected women, after adjustment for stage of disease. Tumour characteristics and treatment did not have any notable impact. The inclusion of comorbidity reduced the excess hazard rate ratios slightly in both screen-detected (EHR = 1.39*) and non-screen detected (EHR = 1.54*) women.
(Ward et al. 2018) (UK)	UK cancer registry regions (West Midlands, Northern and Yorkshire), Office for National Statistics database Hospital Episode Statistics database	Women aged ≥70 years diagnosed during 2002–2010	Cox proportional hazards regression models and Royston-Parmar restricted cubic splines models for cause-specific survival	Deprivation index (no further information)	Stage at diagnosis (tumour size, lymph nodal status), treatment (surgery, endocrine therapy) comorbidity	HR = 1.26* for most deprived women compared to most affluent women, after adjusting for comorbidity, stage and treatment

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Redaniel et al. 2012) (UK)	UK General Practice Research Database (GPRD)	Women who were registered in the GPRD during 1987–2007	Cox proportional hazards regression models for all-cause survival	Area deprivation [based on the Index of Multiple Deprivation]	Year of diagnosis age at diagnosis, region of residence, lifestyle (BMI, smoking and alcohol habits), oestrogen use	HR = 1.05 for most deprived women compared to most affluent women in the unadjusted model HR = 0.97 for most deprived women compared to most affluent women, after adjusting for all listed variables
(Walsh et al. 2014) (Ireland)	Cancer Registry database Hospital Inpatient Enquiry System	Women aged 15–99 years diagnosed during 1994–2008 in Ireland	Kaplan Meier estimates for cause-specific survival Cox proportional hazards regression models for cause-specific survival	Area deprivation index [based on the SAHRU index based on the 3409 electoral divisions in the Republic of Ireland]	Year of diagnosis age at diagnosis, stage at diagnosis method of presentation *(screening history)* grade, tumour morphology hormonal status comorbidity lifestyle (smoking habits), region of residence	*15–49-year olds* 5-year cause-specific survival ranged from 90% in most affluent women to 83% in most deprived women *65–99-year olds* 5-year cause-specific survival ranged from 75% in most affluent women to 70% in most deprived women HR = 1.33* for most deprived women compared to most affluent women, after adjusting for age at diagnosis HR = 1.18 for most deprived women compared to most affluent women, after adjusting for all variables listed

(Larsen et al. 2015) (Denmark)	Danish Breast Cancer Database Danish Diet, Cancer and Health Study Danish registries	Postmenopausal women included in the Danish Diet, Cancer and Health Study (i.e. women aged 50–64 years between December 1993 and May 1997, born in Denmark, and living in the Copenhagen or Aarhus area and replying positively to the invitation to the study) diagnosed during 1993–2008	Cox proportional hazards regression models for all-cause survival	Education income	Stage at diagnosis (tumour size, lymph node status, no. of positive lymph nodes, malignancy) grade hormone receptor status comorbidity lifestyle at baseline (BMI, waist circumference, diabetes, smoking and alcohol habits) lifestyle at diagnosis (BMI, diabetes, smoking and alcohol habits)	HRs for women with low education level compared to those with high education level ranged from 1.40*, after adjusting for age at diagnosis, to 1.24 also adjusting for stage at diagnosis, receptor status, BMI, comorbidity, diabetes, and smoking and alcohol habits. HRs for women with low income compared to those with high income ranged from 0.96, after adjusting for age at diagnosis, to 0.93 also adjusting for stage at diagnosis, receptor status, BMI, comorbidity, diabetes, and smoking and alcohol habits

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Morris et al. 2015) (UK)	West Midlands Breast Screening Quality Assurance Reference Centre, Hospital Episode Statistics National Breast Screening Service records, the National Mortality Database	Women aged 50–70 years, diagnosed during 1989–2011 and invited for screening	Net survival	Area deprivation index [based on the Townsend score and the Income Domain of the Index of Multiple Deprivation, according to the period of diagnosis]	Screening history	five-year net survival ranged from 90% in most affluent women to 87% in middle/most deprived women. *Women with screen-detected cancer*: five-year net survival ranged from 94% in most affluent women to 89% in middle/most deprived women *Women whose last screening attendance had resulted in a negative screen and had not yet been invited to a subsequent screening*: five-year net survival ranged from 86% in most affluent women to 81% in middle/most deprived women *Women whose cancer was diagnosed after having previously had a negative screen, but who had not attended their most recent screening appointment*: five-year net survival ranged from 81% in most affluent women to 77% in middle/most deprived women *Women who had never presented for screening*: five-year net survival ranged from 73% in most affluent women to 62% in middle/most deprived women

(Woods et al. 2016) (UK)	West Midlands Breast Screening Quality Assurance Reference Centre Hospital Episode Statistics National Breast Screening Service records	Women aged 50–65 years in 1997–2006 and ≤51 years in 1997	Net survival	Quintiles of the regional distribution of the percentage of unemployment in their small area of residence	Stage at diagnosis screening history	five-year net survival in most affluent women (quintiles 1–2): 93% (99% screen-detected cancer, 88% non-screen detected cancer) five-year net survival in most deprived women (quintiles 3–5): 89% (96% screen-detected cancer, 84% non-screen detected cancer) Most deprived women in both screening groups experienced lower survival than that experienced by most affluent women. In particular, most deprived women diagnosed with regional non-screen detected diseases had the lowest net survival (approx. 80%)
(Davies et al. 2013) (UK)	Thames Cancer Registry London Cancer Screening Quality Assurance Reference Centre (QARC) NHS Cancer Screening Programme NHS Central Register via the Office for National Statistics	Women aged 50–64 diagnosed during 1998–2005 in London	Net survival	Area deprivation [based on the Index of Multiple Deprivation]	Screening history	five-year net survival ranged from 90% in most affluent women to 82% in most deprived women. *Women with screen-detected cancer*: five-year net survival ranged from 98% in most affluent women to 94% in most deprived women *Women who had never presented for screening*: five-year net survival ranged from 85% in most affluent women to 73% in most deprived women *(data extracted from graphics)*

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Aarts et al. 2011) (Netherlands)	Population-based screening program database (BoBZ) Eindhoven Cancer Registry (IKZ)	Women eligible for screening diagnosed during the overlapping regions of the BoBZ and IKZ in 1998–2006 with invasive breast cancer or DCIS	Cox proportional hazards regression models for all-cause survival	Socioeconomic status [based on individual fiscal data on the economic value of the home and household income]	Age at diagnosis stage at diagnosis treatment (surgery, radiotherapy, systemic therapy) comorbidity	*Women with screen-detected cancer*: five-year survival ranged from 90% in most deprived women to 92% in most affluent women (HR for most deprived compared to most affluent women = 1.32* after adjusting for age and stage; 1.23 also adjusting for comorbidity and treatment) *women with interval cancer:* five-year survival ranged from 78% in most deprived women to 90% in most affluent women (HR for most deprived compared to most affluent women =1.47* after adjusting for age and stage; 1.45 also adjusting for comorbidity and treatment) *women with non-screen detected cancer*: five-year survival ranged from 73% in most deprived women to 80% in most affluent women (HR for most deprived compared to most affluent women =1.22 after adjusting for age and stage; 1.17 also adjusting for comorbidity and treatment)

(Puliti et al. 2012) (Italy)	Tuscan Cancer Registry	Women aged 15–69 years diagnosed during 1985–2000	Cox proportional hazards regression models for all-cause survival	Area deprivation index [based on national census data]	Period of diagnosis *(as a proxy of screening history)*, age at diagnosis, stage at diagnosis (pathological T and N stages)	The deprivation gap in 10-year survival between most deprived and most affluent women aged <50 years at diagnosis decreased from 12% in 1985–1986 to 10% in 1996–2000 The deprivation gap in 10-year survival between most deprived and most affluent women aged 50–69 years at diagnosis decreased from 12% in 1985–1986 to −1% in 1996–2000 In the first two calendar periods (1985–1986, 1991–1996), the differences in the risk of death between most deprived and most affluent women disappeared (HRs around 1) after adjusting for stage at diagnosis, both in <50-year olds and 50–69-year olds. As regards the last period (1996–2000), the same was for 50–69-year olds, but the risk doubled in most deprived compared to most affluent <50-year-old women

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Pacelli et al. 2014) (Italy)	Regional breast cancer registry census individual database hospital discharge records	Women aged 30–69 years diagnosed during 1997–2003 in Emilia-Romagna region	Cox proportional hazards regression models for all-cause survival	Socioeconomic indicators [based on education level]	Period diagnosis *(as a proxy of screening history)*, age at diagnosis, stage at diagnosis	*Transitional period (1997–2000)* five-year survival ranged from 87% in most deprived to 94% in most affluent 30–49-year-old women (HR for most affluent compared to most deprived women = 0.75, after adjusting for stage and age at diagnosis) five-year survival ranged from 87% in most deprived to 91% in most affluent 50–69-year-old women (HR for most affluent compared to most deprived women = 0.64, after adjusting for stage and age at diagnosis) *Consolidation period (i.e. after the full implementation of the screening programme; 2001–2003)* The above-mentioned differences decreased in both 30–49-year olds (range: 89–93%; HR = 0.63, after adjusting for stage and age) and 50–69-screening target population (range 95%–93%; HR = 1.23, after adjusting for stage and age), thus disappearing completely among women in the age-group invited to screening

(Feller et al. 2017) (Switzerland)	Swiss National Cohort National Institute for Cancer Epidemiology and Registration cancer registry data; Federal Statistical Office	Women diagnosed with invasive or in situ breast cancer in December 2000–December 2008	Subhazard ratio (by using competing risk regression models based on Fine and Gray's proportional hazard regression models)	Education Urbanity (urban/rural area)	Age at diagnosis, stage at diagnosis, place of residence *(canton with organised and non-organised screening)* nationality (Swiss, non-Swiss) civil status	Differences in survival among least and more deprived women were still evident (subhazard ratios = 1.22*) after adjusting for age at diagnosis, civil status, nationality, stage at diagnosis, urbanity, and screening availability.
(Rachet et al. 2010) (UK)	National Cancer Registry	Women diagnosed during 1996–2006 in England and Wales	Relative survival variance-weighted linear regression	Area deprivation index [based on the Index of Multiple Deprivation]	Period of diagnosis *(as a proxy of screening history)*	The deprivation gap in 1-year relative survival between most deprived and most affluent women was −4%* in 1996 and −3%* in 2006 The deprivation gap in 3-year relative survival ranged from −6.7%* in 1996–2000 to −4.7%* in 2004–2006 Mean absolute change (%) in the deprivation gap in 1-year relative survival within the three periods (pre-cancer plan [1996–2000], initialisation [2001–2003], implementation [2004–2006]) was stable and not negative, meaning that the deprivation gap has not widened. Similar results were found for the deprivation gap in 3-year relative survival

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Li et al. 2016) (UK)	Northern and Yorkshire Cancer Registry Hospital episode statistics	Women diagnosed during 2000–2007	Net survival G-computation procedures to estimate the proportion of the effect of deprivation on survival mediated by stage, and on survival mediated by treatment	Area deprivation index [based on the Index of Multiple Deprivation]	Stage at diagnosis, treatment (surgery)	1-year net survival ranged from 97% in most affluent women to 94% in most deprived women five-year net survival ranged from 86% in most affluent women to 76% in most deprived women Stage-specific survival estimates were consistently lower in most deprived patients. Large deprivation gap existed for the 1-year net survival in stage IV, and for the five-year net survival in stages II–III Most deprived women were almost three times more likely to die within 6 months after diagnosis than the most affluent women (odds ratio = 2.77*) Stage accounted for about one-third of the total effect of deprivation at 6 months and 1 year (proportion mediated: 35% and 30%, respectively). This proportion decreased to just over a tenth at 3 and 5 years since diagnosis (12% and 14%, respectively). The main mediation analysis found no evidence for the effect of deprivation on mortality mediated through differential treatment
(Downing et al. 2007) (UK)	Northern and Yorkshire Cancer Registry; Information Service database	Women diagnosed during 1998–2000 in Northern and Yorkshire regions of England	Cox proportional hazards regression models for all-cause survival	Area deprivation index [based on the Townsend score]	Age at diagnosis stage at diagnosis treatment (surgery, type of surgery)	Living in most deprived areas was associated with an increased risk of death for all women overall (HR = 1.08* per quartile increase in Townsend score, after adjusting for age and stage at diagnosis) and for those undergoing a breast-conserving surgery (HR = 1.1.3*), but not for those undergoing mastectomy (HR = 1.04) or not resected (HR = 1.03)

(Eaker et al. 2009) (Sweden)	Regional Breast Cancer Register of the Uppsala social database the Multi-Generation Register the Cause of Death Register	Women aged 20–79 diagnosed during 1993–2003	Kaplan Meier estimates for cause-specific survival (CSS) Cox proportional hazards regression models for cause-specific survival Relative survival (RS)	Education, socioeconomic index (based on occupational group), employment status, income, home ownership, and welfare	Period of diagnosis, Age at diagnosis, stage at diagnosis (number of lymph nodes examined, tumour size, lymph node involvement, distant metastases) proliferation status, oestrogen and progesterone receptor status, detection mode, treatment (surgery, radiotherapy, chemotherapy, hormonal therapy), type of clinic	five-year CCS (RS) ranged from 86% (85%) in women with low level of education to 91% (92%) in women with high level of education (HR for women with high level compared to low level of education = 0.65*, after adjusting for age, stage at diagnosis, and period of diagnosis; HR = 0.68* adjusting also for diagnostic intensity, tumour characteristics, and treatment) HRs for 20–49, 50–65 and 66–79 years old women with high level of education were 0.51*, 0.64* and 0.76, respectively Five-year CCS (RS) ranged from 87% (88%) in women with low socioeconomic index to 91% (92%) in women with high socioeconomic index (HR for women with high socioeconomic index compared to women with low socioeconomic index = 0.61*, after adjusting for age, stage at diagnosis, and period of diagnosis) Five-year CCS (RS) ranged from 86% (86%) in women with low income to 90% (90%) in women with high income (HR for women with high income compared to women with low income = 0.76*, after adjusting for age, stage at diagnosis, and period of diagnosis)

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
						Five-year CCS (RS) ranged from 86% (85%) in women who did not own their own home to 89% (89%) in women who owned their own home (HR for women who did compared to women who did not own their own home = 0.82*, after adjusting for age, stage at diagnosis, and period of diagnosis) Five-year CCS (RS) ranged from 88% (88%) in women without welfare status to 83% (83%) in women with welfare status (HR for women with welfare status compared to women without welfare status = 1.40*, after adjusting for age, stage at diagnosis and period of diagnosis) The social gradient in the risk of death for women with high level of education compared to women with low level of education did not vary markedly across the diagnostic intensity variables investigated (HRs around 0.60*); was somewhat small among women with high proliferation (HR = 0.82) and large (HR = 0.80) tumours, but great among women with low proliferation (HR = 0.53*), hormone sensitive tumours (HR = 0.54*) and small tumours (HR = 0.50*), was present for all treatment variables (HRs ranged 0.60*-0.70*), except for breast-conserving surgery associated with (HR = 0.83) or not associated with (HR = 0.80) radiotherapy

(Redaniel et al. 2013) (UK)	West Midlands Cancer Intelligence Unit inpatient Hospital Episode Statistics the Office of the National Statistics	Women, aged 15 years or older, diagnosed during 1996–2009 with localised stage undergoing surgical resection	Relative survival Generalised linear regression models to estimate the Relative Excess Risks of death (RER)	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis, period of the waiting time targets (*as a proxy of screening history*); stage at diagnosis, grade, histology, treatment (waiting time from diagnosis to first curative surgery) region of residence, ethnicity	High risk of death for most deprived women compared to most affluent women (HR = 1.28*, after adjusting for age, ethnicity, place of residence, waiting time from diagnosis to first curative surgery, stage, grade, histology and period)
(Jack et al. 2009) (UK)	Thames Cancer Registry, Hospital Episode Statistics, National Health Service Central Register through the Office for National Statistics	Women diagnosed during 1998–2003 in South East England	Cox proportional hazards regression models for all-cause and cause-specific survival	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis, stage at diagnosis, treatment (surgery, radiotherapy, chemotherapy, hormone therapy) ethnicity	Living in most deprived areas was associated with an increased risk of death compared to living in most affluent areas (HR = 1.36*, after adjusting for age and ethnicity; HR = 1.25*, adjusting also for stage and treatment).

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Bastiaannet et al. 2011) (Netherlands)	Netherlands Cancer Registry Netherlands Institute for Social Research	Women diagnosed with invasive and or in situ breast cancer in 1995–2005	Cox proportional hazards regression models for all-cause survival Relative survival Generalised linear regression models to estimate the Relative Excess Risks of death (RER) No. of avoidable deaths for each socioeconomic group relative to the highest socioeconomic group	Area socioeconomic status score [based on income, employment and education]	Year of diagnosis, age at diagnosis stage at diagnosis (T-stage, N-stage, M-stage, tumour size) histology, tumour grade, treatment (surgery, adjuvant treatment)	Low socioeconomic status was associated with worse survival, even stratified for tumour size or stage of disease. 10-year observed survival ranged from 65% in most affluent women to 58% in most deprived women (HR for most deprived women compared to most affluent women = 1.10*, after adjusting for all listed variables) 10-year relative survival ranged from 79% in most affluent women to 74% in most deprived women (RER for most deprived women compared to most affluent women = 1.19*, after adjusting for all listed variables) For the lowest socioeconomic group, 777 deaths out of 3748 excess deaths due to cancer within 5 years could be avoided if the survival was equally high as in the highest socioeconomic group
(Davies et al. 2010) (UK)	Thames Cancer Registry local screening programme Hospital Episode Statistics	Women diagnosed during 2001–2005 in London	Cox proportional hazards regression models for cause-specific survival	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Age at diagnosis, stage at diagnosis, treatment (surgery, chemotherapy, radiotherapy, hormone therapy), ethnicity place of residence	HR = 1.45* for most deprived women compared to most affluent women, after adjusting for age, stage, ethnicity, treatment, and place of residence

(Davies et al. 2016) (UK)	Inpatient Hospital Episode Statistics NHS, Princess Grace Hospital Breast Services	Women diagnosed during 2005–2011	Cox proportional hazards regression models for all-cause survival	Area deprivation index [based on the Income Domain of the Index of Multiple Deprivation]	Year of diagnosis, age at diagnosis, stage at diagnosis, place of treatment (private providers only, private and public providers, public providers only), treatment (surgery, radiotherapy, chemotherapy, hormonal therapy)	HR = 1.37* for most deprived women compared to most affluent women, after adjusting for age at diagnosis and place of treatment HR = 1.22 for most deprived women compared to most affluent women, after adjusting for age at diagnosis, stage, year of diagnosis, treatment and place of treatment
(Skyrud et al. 2016) (Norway)	Cancer Registry of Norway Norwegian Patient Register	Women diagnosed during 2002–2011	Generalised linear regression models to estimate the Relative Excess Risks of death (RER)	Highest education level achieved within 1 year of diagnosis, household income 1 year prior to diagnosis	Age at diagnosis stage at diagnosis, place of residence *(as a proxy of health services regions)* treatment (surgery, radiotherapy) comorbidity	RER = 0.60* for women with high level of education compared to women with low level of education, after adjusting for sex, age, tumour stage, household income, surgery, radiotherapy and health services region RER = 0.68* for women with high income compared to women with low income, after adjusting for sex, age, tumour stage, education, surgery, radiotherapy and health services region After adjusting for comorbidity and all variables mentioned before, there was only one regional variation that remained unexplained, which could result from inequalities in the quality of cancer care delivered by the relevant health services regions

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Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Quaglia et al. 2011) (Italy)	Liguria Region CR	Women diagnosed during 1996–2000	Cox proportional hazards regression models for all-cause survival Generalised linear regression models to estimate the Relative Excess Risks of death (RER)	Regional Deprivation Index	Period of diagnosis age at diagnosis stage at diagnosis (tumour size, lymph nodal status), oestrogen receptor status, treatment (surgery, chemotherapy, radiotherapy, hormonal treatment, lymphadenectomy)	Most deprived women experienced a poorer prognosis (five-year relative survival = 77%) than women with higher socioeconomic status (five-year relative survival = 89%). RER = 2.34* for most deprived women compared to most affluent women, with no adjustments. RER decreased to 1.82, after adjusting for age, incidence period, tumour size, lymph nodes, oestrogen receptor status and treatment
(Redaniel et al. 2015) (UK)	Merged Cancer Registry, Office for National Statistics database Hospital Episode Statistics database	Women aged ≥15 years diagnosed during 1998–2009	Relative survival	Area deprivation index [based on the Index of Multiple Deprivation]	Age at diagnosis, calendar period *(as proxy for screening history)*, histology, tumour differentiation, -no. consultations, treatment, comorbidity, diagnostic interval, region of residence, ethnicity	HR = 1.20 for more deprived women compared to most affluent women, after adjusting for all listed variables

(Lillini et al. 2011) (21 European countries)	EUROCARE 3 Study OECD database WHO-HFA database EUROSTAT database	Women diagnosed during 1990–1994	Relative survival Linear regression models considering relative survival as dependent variable and socioeconomic and health care-related (SEH) indicators as independent variables	SEH factors belonging to macro-economy	health technologies and medical resources labour market	Survival was strongly associated with the availability of clinical facilities (Computed Tomography Scanners [coefficient = −0.009*]), to the organisation of the healthcare systems (% of labour force in Services [coefficient = −0.023*]), and to factors describing the sociodemographic environment where the patient lives (Total Public Expenditure [coefficient = −0.013*]) The linear regression model explained a large part (R^2 = 70%) of the geographic variability in survival among European countries
(Dialla et al. 2015) (France)	Côte d'Or breast and gynaecological Cancer Registry	Women diagnosed during 1998–2009 and residing in Côte d'Or	Relative survival	Area deprivation index [based on the French European Deprivation Index (FEDI)], Urbanity (urban/rural area) distance from the place of residence to the nearest cancer radiology centre		five-year survival ranged from 88% in most deprived women to 93% in most affluent women five-year survival was 91% in women living in an urban area and 90% for women living in a rural area five-year survival ranged from 89% in women living ≥9 km from the nearest cancer radiology centre to 93% in women living <2 km from the nearest cancer radiology centre

(continued)

Table 7.1 (continued)

Reference (Country)	Data sources	Study population	Statistical methods	Socioeconomic measure	Further investigated variables[a]	Main survival results
(Verkooijen et al. 2009) (Switzerland)	Geneva Cancer Registry, Cantonal Population Office	Women diagnosed during 1990–2005	Cox proportional hazards regression models for cancer-specific survival	Socioeconomic indicator based on the woman's last occupation or, for the unemployed, that of the spouse	Age at diagnosis, stage at diagnosis, method of detection *(screening history)*, grade, oestrogen receptor status, treatment (surgery, radiotherapy, chemotherapy, hormonal therapy), family history	After adjusting for all listed variables, there was still a trend towards lower mortality risk among women with a positive family history compared to women with a negative family history (HR = 0.84, overall; HRs ranged from 0.58 to 0.92 according to socioeconomic status), in particular among women with high socioeconomic status (HR = 0.58)
(Brooke et al. 2017) (Sweden)	Swedish Cancer Register Longitudinal Integration Database for Health Insurance and Labour Market Studies	Women, aged 65–79 years, with a child aged ≥30 years diagnosed during 2001–2010	Relative survival Flexible parametric regression models to estimate the excess hazard rate ratio (EHR)	Offspring's education Offspring's disposable income	Year of diagnosis, country of birth, mothers' education level, mothers' income, partners' education level, number of children, sex of child, age of child in year prior to mother's diagnosis, −proximity of residence between mother and child, marital status	10-year overall survival (relative survival) ranged from 69% (89%) in women with offspring's education >14 years to 58% (79%) in women with offspring's education <12 years (EHR = 1.69* for women with offspring's education <12 years compared to women with offspring's education >14 years, after adjusting for all listed variables and offspring's disposable income) 10-year relative survival ranged from 65% (87%) in women with offspring with high income to 66% (85%) in women with offspring with low income (EHR for women with offspring with low income compared to women with offspring with high income = 1.06, after adjusting for all listed variables and offspring's education level)

[a]Any further information considered in relation to socioeconomic survival estimates

Thirty-three studies (79%) were conducted in Northern Europe (Denmark, Ireland, Norway, Sweden, the Netherlands, UK), five (12%) in Central Europe (France, Switzerland) and three (7%) in Southern Europe (Italy). One study involved 21 countries.

Most studies used population-based cancer registry data, together with information from national statistics databases. Only one study used information from hospital databases (Baker et al. 2010).

Crude survival estimates (e.g. survival from cancer or all causes of death combined) or hazard ratios were provided by 20 studies. Twenty-two studies presented either net or relative survival estimates, or the relative excess risk of death (sometimes called excess hazard rate ratios). Five studies only provided the number of avoidable deaths or the average loss in life expectancy, estimated with regression survival models.

Survival was examined in relation to various indices of socioeconomic status. Ten studies used education level, home ownership or household income. Three studies considered occupational group or type of employment, but most studies considered tertiles, quintiles or deciles of a socioeconomic status score, usually based on summaries of individual fiscal data for residents in a given area and assigned to each patient living in that area, using her postcode of residence at diagnosis. The scores of socioeconomic status were derived with different variables in each country, typically income and occupation, but sometimes educational level, home rental or ownership status, the economic value of the home, the social class or the civil status (single, married, divorced, etc.).

Differences between the studies were also evident in the additional variables investigated to assess socioeconomic differences in survival. Some studies only reported results on socioeconomic differences in survival, overall or over time. Others considered the age of the women at diagnosis, the tumour stage at diagnosis, tumour characteristics (e.g. histology or hormonal status), and modality of cancer detection (screen-detected vs. non-screen detected). Comorbidities were analysed with or without lifestyle factors. Other studies also investigated treatments or the familial and social environment.

In line with the results for all cancers combined, survival from breast cancer was higher for less deprived (more affluent) women than more deprived women at 1, 5 and 10 years after diagnosis (Belot et al. 2018). However, although survival has generally increased over time, the absolute change in the deprivation gap (i.e. the difference between the five-year survival estimate for the most affluent and the most deprived women) was stable or only slightly smaller for women diagnosed more recently (Lyratzopoulos et al. 2011; Exarchakou et al. 2018; Dalton et al. 2019; Rachet et al. 2010). In other words, over 20 years since these differences in survival were first identified, more deprived women with breast cancer continue to have lower survival and shorter life expectancy than more affluent women with the same disease (Syriopoulou et al. 2017; Rutherford et al. 2015).

Potential explanations for socioeconomic differences in survival can be separated into three main groups: those related to characteristics of the patient and the tumour, to the healthcare system and to the wider social environment.

Patient and Tumour Characteristics

Place of Birth and Age at Diagnosis

Breast cancer is generally more common among more affluent women (Nur et al. 2015). However, more deprived women are generally older at diagnosis: less often aged under 50 years and more often aged 65 years or over (Nur et al. 2015; Walsh et al. 2014).

It has been observed that the deprivation gap in short-term (one-year) breast cancer survival tends to be wider among older women (Nur et al. 2015), but socioeconomic inequalities in survival remain evident up to 10 years after diagnosis in all age groups (Berger et al. 2012; Nur et al. 2015).

A slightly different result has been reported from Sweden, where social gradients in breast cancer survival were of similar magnitude for women aged 20–49 and 50–65 years, and no statistically significant socioeconomic differences in survival were evident among women aged 66–79 years (Eaker et al. 2009).

Lower survival among cancer patients with lower social position may in part be attributed to differences in nationality and/or ethnicity. However, one Swedish study found no significant differences in the risk of dying from breast cancer between native Swedes and immigrant women or their daughters at each level of education (Beiki et al. 2012). Further possible explanations include more advanced stage or higher levels of comorbidity at diagnosis among more deprived women (Dalton et al. 2019), or socioeconomic disparities in participation in screening programmes and in the management of the primary tumour or any recurrence, especially among the elderly (Nur et al. 2015).

Disease Stage at Diagnosis

The stage or extent of disease at diagnosis is a crucial contributory factor to the duration of survival. Notable socioeconomic differences in the distribution of stage at diagnosis have been reported, with more affluent women generally being diagnosed with less advanced tumours (Eaker et al. 2009; Quaglia et al. 2011; Berger et al. 2012; Bower et al. 2019), irrespective of age at diagnosis (Rutherford et al. 2013).

Five-year relative survival estimates at each stage at diagnosis were comparable among the deprivation quintiles 1–4 but were approximately 10% lower in the fifth, or most deprived, quintile (Rutherford et al. 2013). This suggests that a substantial reduction in the number of premature deaths among women with breast cancer could be achieved if inequalities in stage at diagnosis could be eliminated (Rutherford et al. 2013; Bower et al. 2019; Aarts et al. 2013). Although differences in stage at diagnosis explained most of the survival differences between women in deprivation quintiles 3, 4 and 5, eliminating differences in the distribution of stage would only

be expected to remove about half of the inequalities in survival between women in the most deprived and most affluent groups (Rutherford et al. 2013; Li et al. 2016).

Cell Proliferation Rate and Molecular Markers

Since the beginning of the twenty-first century, many clinical trials and hospital-based studies have shown that breast cancer is a heterogeneous disease, with gene expression patterns or immunohistochemical determination of oestrogen (ER) and progesterone (PgR) receptor expression, human epidermal growth factor receptor 2 (HER2) over-expression, and cell proliferation status identifying distinct subtypes that are also characterised by different outcomes. Differences in cancer survival between these groups have been confirmed at the population level. Women with hormone-positive (ER+ or PgR+), HER2-negative (HER2-) tumours, or tumours with low cell proliferation rate, experience better survival than women diagnosed with hormone-negative (ER- and PgR-), HER2+, or tumours with a high cell proliferation rate (Minicozzi et al. 2013).

Less-educated women seem to be diagnosed more often with tumours that have a high proliferation rate (Eaker et al. 2009) and less often with hormone-positive tumours than women with higher levels of education (Walsh et al. 2014). More deprived women with breast cancer are also less likely to be HER2-negative.

It has also been found that even after adjusting for age, period of diagnosis and stage at diagnosis, the same socioeconomic differences in survival were still present among women with hormone-positive tumours or tumours with a low cell proliferation rate (Eaker et al. 2009).

It has been suggested that the p53 mutation, which may have aberrant responses to inflammatory stress, with therapeutic consequences, may partly account for the worse prognosis in more deprived women (Baker et al. 2010). Among women with the p53 mutation, those in the most deprived group (the tenth decile) were more likely to relapse, or to die, than those in deciles 1–9.

Lifestyle and Comorbidity

Women diagnosed with breast cancer in more deprived groups are more likely to be current smokers or ex-smokers and to have a higher body mass index (BMI) but are less likely to be current drinkers (Morris et al. 2017; Larsen et al. 2015). While some authors have observed that women living in more deprived areas have higher levels of comorbidity when diagnosed with breast cancer (Dialla et al. 2015), such as diabetes (Redaniel et al. 2012), others have not found any association between deprivation and comorbidity (Morris et al. 2017).

However, the deprivation gap in survival for women with breast cancer was present irrespective of obesity, alcohol consumption, smoking habit or comorbidity

(Morris et al. 2017). Adjustment for characteristics of the woman, her tumour and any comorbidity had little influence on socioeconomic differences in survival (Morris et al. 2016; Ward et al. 2018), but adjustment for lifestyle, represented by metabolic indicators, smoking and alcohol habits, does reduce the deprivation gap to some extent (Larsen et al. 2015; Redaniel et al. 2012; Walsh et al. 2014).

These findings suggest that improvements in lifestyle might improve survival among women with lower socioeconomic position (Larsen et al. 2015).

Factors Related to the Healthcare System

Screening

Inequalities in the use of breast cancer screening services between socioeconomic groups defined by education level have been described in several European countries (Palencia et al. 2010). These inequalities are more marked in countries that do not have organised cancer screening programmes.

However, adherence to breast cancer screening recommendations is variable. Women living in deprived or rural areas, and those who live far from screening centres, are less compliant with screening recommendations (Ouedraogo et al. 2014), as well as women who are obese or diabetic (Constantinou et al. 2016).

In the Netherlands, *in situ* tumours (mostly screen-detected) were more commonly seen among more affluent women, suggesting higher attendance at the screening programme (Bastiaannet et al. 2011). By contrast, in one region of England, the proportion of regional and advanced tumours was particularly high in the most deprived women with screen-detected tumours (Morris et al. 2016). These women also had larger tumours than those diagnosed in more affluent women with screen-detected tumours. The authors suggested that deprived women may use screening as an entry point to the healthcare system, after they are already symptomatic, more often than women in more affluent categories.

Studies in London and Ireland (Davies et al. 2013; Walsh et al. 2014) have shown that more deprived women were less likely to have presented via screening. Similar results have been seen in France, where for women diagnosed during 1998–2009, residence in a deprived area was linked to advanced stage at diagnosis only among those aged 50–74 years (Dialla et al. 2015). This suggests socioeconomic disparities in participation in organised breast cancer screening programmes. In England, women in the most deprived group also appeared to wait longer for a hospital appointment after the general practitioner's referral (Downing et al. 2007) and to experience somewhat longer delays between the last breast-related consultation and diagnosis, although the difference was not significant (Morris et al. 2017).

The deprivation gap in breast cancer survival has been reported by many authors, whether the tumour is screen-detected or not (Morris et al. 2015, 2016; Davies et al. 2013; Woods et al. 2016; Aarts et al. 2011). However, among screen-detected women, the deprivation gap in survival was either similar to (Morris et al. 2015;

Woods et al. 2016) or somewhat smaller than (Morris et al. 2016; Aarts et al. 2011; Davies et al. 2013) the deprivation gap in survival among women whose tumour was diagnosed clinically, even after correction for lead-time bias and potential overdiagnosis (Morris et al. 2015).

Two studies in Italy, in Tuscany and Emilia Romagna, have shown that, after adjustment for stage, the risk of death from breast cancer becomes similar across the socioeconomic spectrum 10 years after the introduction of a screening programme for women. These changes were seen among women in the age range invited to screening (50–69 years), but not among women diagnosed under the age of 50 years (Puliti et al. 2012; Pacelli et al. 2014). These studies suggest that the screening programmes successfully reduced socioeconomic inequalities in early detection, shortened the time to diagnosis and improved the quality of treatment in more deprived groups, thus producing greater equity in breast cancer survival.

However, since socioeconomic differences in survival remain evident after participation in a screening programme has been taken into account (Rachet et al. 2010; Feller et al. 2017), they could be related to the lack of timely screening, which could lead to delayed diagnosis and a larger tumour burden at diagnosis (Siddharth and Sharma 2018). Some authors have concluded that the type and quality of treatment provided could also play a role, although a few studies have found no effect of treatment on socioeconomic survival differences (Morris et al. 2016; Li et al. 2016).

Further investigations are required of the timeliness and appropriateness of treatment, adherence to treatment and the quality of clinical follow-up between women with breast cancer in the different social groups, together with the influence of these variables on cancer care.

Treatment and Access to Care

Substantial differences in access to treatment exist both between and within European countries, and they contribute to differences in cancer survival (Siddharth and Sharma 2018).

For example, in England, the most deprived women appeared to have to wait a longer time from diagnosis to surgery than the most affluent women (Downing et al. 2007; Morris et al. 2016, 2017), although those findings were not confirmed after selecting women with localised stage disease who only underwent surgical treatment (Redaniel et al. 2013). Furthermore, women receiving some or all of their care within private provider(s) were often living in the most affluent area, as well as being younger, non-screen detected and less often diagnosed at an early stage, than women who were treated in public hospitals (Davies et al. 2016).

One Italian study found that women with a very low socioeconomic status who were diagnosed with invasive breast cancer during 1996–2000 in Liguria were less likely to be treated with curative intent or according to current guidelines (Quaglia et al. 2011). In particular, more deprived women in the Northern and Yorkshire

region of England who were diagnosed during 1998–2000 were less likely to receive surgery, and when they did receive it, were less likely to have breast-conserving surgery (Downing et al. 2007), or to receive radiotherapy or chemotherapy, according to a Swedish study of women who were diagnosed during 1993–2003 in the Uppsala/Örebro region (Eaker et al. 2009).

By contrast, another Italian study found that socioeconomic indicators (education, occupational status and housing characteristics) showed only a marginal independent effect on indicators of the pathway of care relative to timeliness, for 50- to 69-year-old women diagnosed in Piedmont during 1995–2008 (Zengarini et al. 2016).

After taking into account age and stage at diagnosis, the association between socioeconomic status and survival was stronger among women who underwent breast-conserving surgery as part of treatment with curative intent than those who underwent mastectomy (Downing et al. 2007). It is striking that socioeconomic differences in survival have been shown to persist even after a wide range of factors have been taken into account, including the waiting time from diagnosis to surgery (Redaniel et al. 2013), chemotherapy, radiotherapy and hormonal treatment (Eaker et al. 2009; Jack et al. 2009; Davies et al. 2010; Bastiaannet et al. 2011), place of treatment (private vs. public hospital) (Davies et al. 2016), and health service region (Skyrud et al. 2016), although these adjustments do all contribute to reducing socioeconomic inequalities (Jack et al. 2009; Eaker et al. 2009; Quaglia et al. 2011; Davies et al. 2016; Aarts et al. 2011). However, they seem to disappear after considering the diagnostic interval, that is, the time from primary care presentation to definitive diagnosis (Redaniel et al. 2015), thus suggesting that differences in access to medical services do play a role. Examples include the availability of clinical facilities (e.g. computed tomography scanners), the organisation of the healthcare system (e.g. percentage of the labour force working in health services) and factors describing the sociodemographic environment where the patient lives (e.g. total public expenditure), all of which are associated with survival (Lillini et al. 2011), as well as differences in access to specialist centres, especially given that women often have to travel long distances (Dialla et al. 2015; Gentil et al. 2012), ease of travel to appointments, flexibility of work, other commitments and the level of social support (Morris et al. 2016).

Factors Related to the Social Environment

Familial Environment

According to one study using data from the Irish National Cancer Registry (Walsh et al. 2014), no more than half of the socioeconomic gap in breast cancer survival can be explained by the available information on patients and tumour

characteristics, and treatment, that is, age, stage, comorbidities at diagnosis, hormonal status and all treatments administered. This suggests that other factors or mechanisms may be involved.

When women are diagnosed with breast cancer, it can affect the emotional, physical, psychological and social well-being of their families, as well as the women themselves (Gluck and Mamounas 2010). This may be reflected in lifestyle changes during treatment or reduction of household income (e.g. through the personal costs of receiving treatment, or restriction of the woman's ability to work).

Breast cancer impacts society both directly (e.g. through health system costs: expenses associated with treatment) and indirectly (e.g. through the loss of labour productivity). All these aspects may contribute to socioeconomic differences in survival among women with breast cancer. However, cultural factors within the family may also play a role.

It has been noted that the presence of a positive family history of breast cancer eliminated socioeconomic differences in access to screening and optimal treatment, but this did not translate into a reduction in socioeconomic differences in breast cancer survival (Verkooijen et al. 2009). In fact, among more deprived women, the presence of a family history increased the probability of being detected at an earlier stage compared with deprived women who did not have a family history. However, most deprived women were those with the lowest positive effect of having a family history on the risk of death from their breast cancer. The authors argued that a possible explanation includes socioeconomic differences in lifestyle, as mentioned above. Thus, the positive effect of improved access to screening and optimal treatment associated with a positive family history may be offset by the higher prevalence of unfavourable lifestyles among the most deprived women.

It has also been found that lower education level among adult children of mothers with a breast cancer diagnosis is associated with poorer survival, independently of the mother's education level or income (Brooke et al. 2017). This association was stronger among women diagnosed at an earlier clinical stage. These results suggest that health awareness or the ability to interpret information, rather than material resources, may be particularly important in improving outcome.

Social Relationships

Favourable associations have also been observed between positive developments in romantic relationships and hobbies and death from breast cancer. Similarly, higher breast cancer mortality has been reported in relation to negative life events, even after adjusting for characteristics of the patient and the tumour, lifestyle and socioeconomic status (Heikkinen et al. 2017). It would seem that social interaction with and support from friends and family are particularly important in times of illness, and they may contribute to disparities in cancer outcomes.

Comment

The relation between breast cancer survival and the characteristics of the woman and her tumour, including biological, lifestyle, social and health-seeking factors, is complex (Fig. 7.3). Thus, differences in women's baseline characteristics, primary care consultation patterns, symptom presentation, and the time intervals between the first report of symptoms and the eventual diagnosis, and then between diagnosis and the start of treatment, all contribute to socioeconomic differences in breast cancer survival. Factors related to the behavioural norms or education of the woman's children (Torssander 2014) or causes of death other than breast cancer (Rutherford et al. 2015) are plausibly correlated with these differences.

It is insufficient to concentrate attention on one small area within a complex whole. Rudolf Virchow (1848), the founder of cellular pathology, pointed out a long time ago: Medicine is a social science, and politics is nothing else but medicine on a large scale. "Medicine, as a social science, as the science of human beings, has the obligation to point out problems and to attempt their theoretical solution: the politician, the practical anthropologist, must find the means for their actual solution" (Munro 2014). Thus, the ultimate goal of research is not only to improve our understanding of a problem but also to show how research findings can be translated into clinical benefits, in particular into interventions that deliver benefits to more socioeconomically deprived patients through earlier diagnosis and better treatment, follow-up and rehabilitation, in order to improve cancer outcomes overall, as well as to reduce the socioeconomic gap in survival (Dalton et al. 2019).

Virtually all the studies we have reviewed suggest that socioeconomic inequalities in breast cancer survival remain even after controlling for stage at diagnosis,

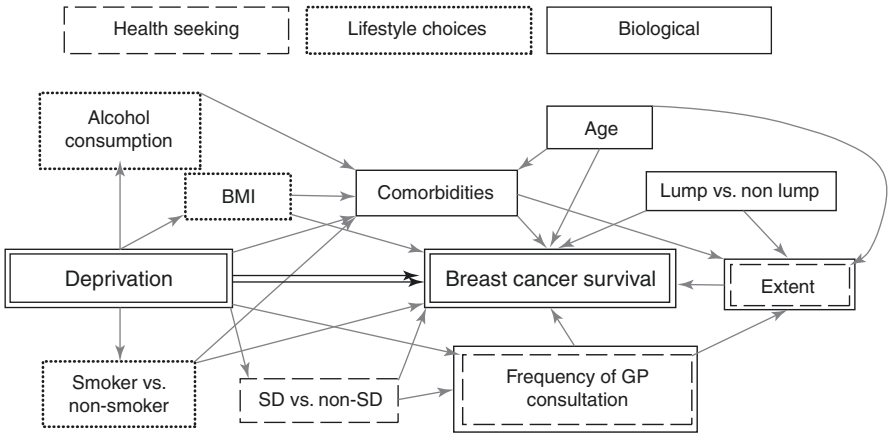

Fig. 7.3 Potential links between deprivation and breast cancer survival and the woman's biological, lifestyle and health-seeking characteristics. SD screen-detected, non-SD non-screen-detected. (Reprinted from Morris et al. (2017), Fig. 1, licensed under the terms of the Creative Commons Attribution License [https://creativecommons.org/licenses/by/4.0/])

treatment, hormonal receptors, the woman's lifestyle, comorbidities at diagnosis and screening attendance. Deeper insight into the complex inter-relation between these factors and breast cancer survival is required. Studies must include all these factors, together with the social environment, as well as socioeconomic status. Studies of this type could contribute to a better understanding of socioeconomic inequalities in breast cancer survival, and they would be expected to offer more useful information for public health interventions.

Recommendations

Demographic factors, socioeconomic conditions and clinical aspects should be considered together in research, policy and clinical or public health interventions aimed at reducing socioeconomic inequalities in breast cancer survival.

Clinicians should address the broader environment and social context of patient care, at the same time as integrating the increasing molecular understanding of cancer. They also need to be aware of the educational context of their patients with breast cancer and to pay particular attention to women who require extra support. Further improvements are needed in the quality of care in healthcare facilities that are not reference or tertiary centres, and to the distribution of these specialised centres in European countries, to avoid aggravating socioeconomic differences in outcome. Screening programmes should be more closely adapted to the personal and social characteristics of the women they serve. Better research will be required to pinpoint the causes that underlie socioeconomic differences in survival, especially in those European countries where this important issue has never been considered.

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Chapter 8
Social Disparities in Survival from Prostate Cancer in Europe

Rafael Fuentes-Raspall and Malcolm M. Mason

Introduction

In comparison with other cancer sites discussed in this book, social disparities that influence the survival of prostate cancer patients in Europe are probably more clearly understood under the umbrella term of socioeconomic status (SES). This is the main definition used in this chapter. SES is a factor that is not frequently studied regarding the incidence and survival of cancer patients. It is a multifactorial concept that includes elements with many modifying factors. Social disparities are classically considered in relation to educational level, financial income and even racial differences. However, several more related variables should be considered.

Measuring SES is as difficult as quantifying a concept like quality of life. Because the vast majority of papers focus on data from cancer registries, a lack of precise information regarding education level or economic income has to be offset by what is taken to be a valid surrogate.

While several tools exist to assess quality of life, such as the simple Karnofsky Performance Status to validated tests such as the EORTC-QLQ C30 and the SF 36, similar instruments to assess SES are lacking (Karnofsky et al. 1948; https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf; Ware et al. 1993). However, a recent addition to the evaluation arsenal is the European Deprivation Index (EDI) that was developed by the European Union Statistics on Income and Living Conditions (EU-SILC) (Pornet et al. 2012a). As detailed

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previouly, the EDI may be used to assess whether an individual is deprived on the basis of having access to enough resources to obtain the following needs: diet, type of living conditions, amenities or services (Belot et al. 2018).

It is well known for some types of cancer such as lung cancer and gastrointestinal cancer that smoking or alcohol abuse are risk factors and prognostic factors that mostly affect the lower social class. Similar risk factors have not been associated with prostate cancer, despite the fact that some recently published data showed a possible association between cardiovascular risk and prostate cancer and dietary factors such as excess consumption of foods rich in fat. These foods tend to be consumed more by the more socioeconomically advantaged in society, so prostate cancer tends to be associated with the higher SES classes (Leong et al. 2020; Wilson and Mucci 2019).

SES has been studied in relation to the survival of cancer patients in various scenarios, and it has been reported that cancer patients from socioeconomically disadvantaged groups have poorer survival than those from socioeconomically advantaged groups (Woods et al. 2006; Rachet et al. 2008). The comprehensive review published by Woods et al. (2006) covered papers from different countries and regions worldwide with a definition of tumour-related factors, patient factors and the healthcare system as possible causes of social differences. Despite the apparent economic uniformity in European countries, large disparities exist when comparing economic resources, level of education and access to public health systems. This may even be the case in regions and different socioeconomic groups within the same country (Felay et al. 2018; Tomic et al. 2018; Pokhrel et al. 2010; Tron et al. 2018).

Prostate cancer risk at an individual level is divided into low risk (clinical stage T1–2, prostate-specific antigen (PSA) <10 ng/ml, and Gleason score (GS) ≤6, intermediate risk (T1–2, Gleason score 7 and/or PSA 10 to <20 ng/ml), high risk (T3 and/or Gleason score 8-10 and/or PSA 20 to <50 ng/ml, regionally metastatic (T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases (M0 or Mx) and distant metastases (PSA ≥100 ng/ml, or M1). Tomic et al. (2018) defined other risk categories: very low risk (age < 75, cT1, Gleason score ≤6, PSA <10 ng/ml, PSA density <0.15, number of biopsy cores positive for cancer ≤4, cancer extension at biopsy <8 mm) and very high risk (T4, 50 ≤ PSA < 200 ng/ml, any N or M0) (Tomic et al. 2018). Nevertheless, despite the existence of these prognostic factors associated with survival in cancer patients, anatomical extension of the disease at the time of diagnosis remains the most important factor for the vast majority of tumours, including prostate cancer (Gospodarowicz et al. 2016; Herden et al. 2018; Zou et al. 2018). Therefore, any factor associated with diagnostic delay and upgrading tumour to a more advanced stage at diagnosis is what finally will impact negatively on survival.

The increasing use of PSA testing has dramatically raised the incidence of prostate cancer, particularly in societies where access to a PSA blood test is easier. An extremely early diagnosis of prostate cancer prolongs survival. Tumours detected by PSA testing in asymptomatic subjects fall into the low-risk groups, and treatment by surgery or radiotherapy is highly successful. This contrasts with cases detected

as a consequence of symptomatic tumours, generally in more advanced stages, which are less amenable to treatment of curative intent (Zou et al. 2018; Lerhmann-Lerche et al. 2019; Berglund et al. 2012).

The impact of SES on survival has received growing attention over the past decade. Different tumour types have been investigated, including cervical, breast and colorectal. Probably the first paper studying prostate cancer and social class was published as early as 1965 by Richardson (Richardson 1965). Another of the earliest papers was published in 1994 by Clark et al., and they found no differences in survival due to SES in a US military population (Clark and Thomson 1994).

Instruments Used in Europe to Measure SES in Prostate Cancer

In Europe, several teams in epidemiology have addressed the issue of SES in relation to the incidence of cancer and survival. Most of the studies until now have not focused on prostate cancer but rather on the most common cancer locations in men and women. Unfortunately, not all research groups use the same measuring system; therefore, direct comparisons between countries or geographical areas are hazardous. Only one paper in the European context has exclusively analysed prostate cancer, and it was from Switzerland. The surrogate used to measure SES was a division into three levels of occupation, and patients were classified by their 'last known occupation' (Rapiti et al. 2009). The Danish study by Oksbjerg et al. included the 15 most common cancers, and SES was determined by 'income quintiles' with the lowest and highest 20% of the total. Income considered was that during the year preceding diagnosis (Oksbjerg et al. 2019).

In a Finnish study of 27 tumour locations, the surrogate of SES was educational level divided into three categories (Pokhrel et al. 2010). However, in a paper focusing on England and Wales, the so-called deprivation gap was calculated according to a more sophisticated system in which they used the Carstairs score for the time period from 1986–1999 and the deprivation quintile score income domain from the National Assembly for Wales (Coleman et al. 2004; Carstairs 1995).

In Germany, the German Index of Multiple Deprivation was applied to study SES and survival with cancer. The Index covers seven domains: income, employment, education, district revenue, social capital, environment and security (Jansen et al. 2014).

A Belgian study of a population including all types of cancer measured SEP (socioeconomic position) based on educational level, employment status and housing conditions (Hagedoom et al. 2018). Finally, EDI was used by a French team to establish an ecological index divided into five quintiles and supported by the European Union Statistics on Income and Living Conditions (EU-SILC) (Tron et al. 2018).

In summary, there is no agreed standardised way to measure SES in Europe, and different methods have been proposed in order to classify social groups, most of them including several forms of income, employment and education. Even though

a system able to meet all the methodological needs does not exist, it seems reasonable to adopt a system able to provide comparable results in the different territories that compose Europe. In this regard, the European Deprivation Index could be a sound candidate, as proposed by Tron et al. (Tron et al. 2018). Table 8.1 summarises the European studies.

Survival with Prostate Cancer According to SES in Europe

To our knowledge, Richardson in the United States was the first in 1965 to analyse the impact of SES and survival in prostate cancer and paved the way for subsequent studies (Woods et al. 2006; Richardson 1965). In Europe, published data from population-based registries are quite recent, with most papers being published after 2004 and concerning Northern Europe. In our review, with the exception of Switzerland, we were unable to find any information on the area covered by the SUDCAN collaborative study (Rapiti et al. 2009; Grosclaude et al. 2017).

The vast majority of data provided in this review is based on papers in which prostate cancer is one of the most common cancer locations. To our knowledge, only one paper from Switzerland was dedicated to prostate cancer in a European country (Rapiti et al. 2009). The paper published by Coleman et al. studied a total of 20 tumour locations in England and Wales up to 2001. Data were obtained from a population-based registry covering 2.2 million patients, and the main outcome analysed was the deprivation gap. Deprivation was divided into five groups, and the time period from 1986 to 1990 was subdivided into three different intervals (1986–1990, 1991–1995 and 1996–1999). Cancer survival, as a whole, increased over time for the majority of tumours. However, despite an increase in overall survival from prostate cancer, there was a considerable and increasing difference in the deprivation gap: −3% every 5 years, reaching −7.2% by 1996–1999. The increase in survival after prostate cancer is probably a consequence of systematic PSA testing after 1990. In addition, access to PSA testing also became greater among the more affluent groups (Coleman et al. 2004; Evans and Moller 2003).

In Belgium, a study by Hageddom et al. analysed 'socioeconomic position' in relation to site-specific cancer mortality. The maximum age of the cohort was 40 years, which limited the power of the study and the time period was from 2001 to 2011. Interestingly, neighbourhood deprivation was significantly associated with mortality for all cancer and most of the specific sites except for prostate cancer. The authors found that female breast cancer, male colorectal cancer and prostate cancer were not associated with neighbourhood deprivation (Hagedoom et al. 2018).

Another interesting paper from France during the period between 2006 and 2009 studied a total of 19 tumour sites registered in the FRANCIM (French Network of Cancer Registries) covering a total of 189,657 tumours. Again, this was not a prostate-specific study, but prostate cancer was one of the sites included. The main tool used was the EDI (Pornet et al. 2012b). Regarding prostate cancer, the

Table 8.1 Summary of European studies evaluating social inequalities in cancer and including prostate cancer

Author	Tumour type	Country	Time period	Measures
Coleman et al. 2001 (Karnofsky et al. 1948)	All	England & Wales	1986–1999	Deprivation gap; Carstairs score
Hagedoom et al. (https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf)	All	Belgium	2001–2011	SEP; educational level, employment status, housing conditions
Tron et al. (Ware et al. 1993)	All	France	2006–2009	Europe Deprivation Index
Rapiti et al. (Pornet et al. 2012a)	Prostate	Switzerland	1995–2005	'last known occupation'
Oksbjerg et al. (Belot et al. 2018) Marsa et al. (Woods et al. 2006)	All Prostate/ Testicular	Denmark	1987–2009 1994–2003	Income quintiles Education, income, social class and others
Pokhrel et al. (Leong et al. 2020)	All	Finland	1971–2005	Educational level
Jansen et al. (Wilson and Mucci 2019)	All	Germany	1997–2006	German Index of Multiple Deprivation

deprivation gap at 1 year and 5 years of age-standardised net survival was 0.5 and 3.0, respectively, showing a negative gradient with increasing deprivation for prostate, breast, colorectal and corpus uteri cancer sites (Tron et al. 2018).

The paper by Rapiti et al. is probably the only one dedicated to prostate cancer in Europe and the only population-based study of a country included in the SUDCAN group (Grosclaude et al. 2017). Of note, the paper included some disease variables generally not found in tumour registries such as disease stage, Gleason score, type of treatment, screening or symptom detected, nationality, and private versus public health service. All of these data were compared with low, middle and high SES. In agreement with previous studies, prostate cancer patients with low SES had a two-fold higher risk of death than patients with high SES. Furthermore, patients with low SES were older, with higher tumour grade and more advanced disease at the time of diagnosis.

A higher incidence of prostate cancer and better survival in patients in Europe with high SES were also found in a Danish study published in 2008. It reported a 25% increase in incidence amongst men with high SES, a finding replicated by a study from Germany (Oksbjerg et al. 2019; Jansen et al. 2014; Marsa et al. 2008).

Conclusions

An increased incidence of prostate cancer amongst men with high SES in European countries has been demonstrated, as evidenced by various scales acting in most cases as surrogates. However, little is known about tumour characteristics and incidence because comorbidities, TNM staging and other relevant biological factors are not generally registered by population-based registries, and only very few reports provide information about them. The overarching conclusion that can be drawn from the literature is that there is a clear gap in the survival of prostate cancer patients between those with higher and lower SES. A possible explanation for this is the increasing use of PSA screening associated with lower-stage disease among high SES populations, that is, the so-called Will Rogers phenomenon (Kogevinas et al. 1997; Feinstein et al. 1985).

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Chapter 9
Social Disparities in Survival from Lung Cancer in Europe

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Introduction

Worldwide, lung cancer was the most commonly diagnosed cancer in 2018 (11.6% of the total cases) for both sexes combined and the leading cause of cancer death (18.4% of the total cancer deaths). It is, therefore, the most frequent cancer and the leading cause of cancer death globally—rank it has held since 1985 (Bray et al. 2018). By sex, lung cancer was the most commonly diagnosed cancer and the leading cause of cancer death in males. Among females, lung cancer was the third most commonly diagnosed cancer (WHO International Agency for Research on Cancer 2019). Despite new biological insights and the considerable diagnostic and therapeutic efforts made in recent decades, lung cancer remains a deadly disease. It has

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one of the world's lowest survival rates out of all cancers, which stands especially low for patients in advanced stages. Five-year survival rates fluctuate substantially across countries, with estimates ranging from 10% to 20% (Francisci et al. 2015; Allemani et al. 2018).

In Europe, the panorama is somewhat similar. Lung cancer was the third most frequently diagnosed cancer in 2018, comprising 12.2% of the total new cancer cases, and was also the leading cause of cancer death accounting for 20.9% of the total deaths from cancer (European Comission ECIS 2019). Lung cancer survival is poor everywhere in Europe. According to EUROCARE-5 reports, the mean five-year age-standardised relative survival for lung cancer patients diagnosed in 2000–2007 was 13%. Five-year survival probabilities vary considerably among European countries, with the lowest estimate of 9% in the United Kingdom (UK) and Ireland, and the highest estimate of 15% in central Europe. Furthermore, lung cancer survival declines with advancing age at diagnosis, varies depending on the type of lung cancer and is better among women than men. Overall, cancer survival in Europe shows a consistent pattern mainly characterised by a generalised poor survival across countries, although a slightly increasing trend during recent years (De Angelis et al. 2014; Francisci et al. 2015).

Similarly to what occurs in incidence and mortality in Europe, lung cancer survival varies across a variety of social groups (Finke et al. 2018; Barta et al. 2019). Overall, social disparities in cancer survival have been reported in several countries and for different cancer sites in Europe. Unfortunately, these differences and their reasons have been examined less extensively for lung cancer than other cancer sites (Auvinen and Karjalainen 1997; Coleman 2014; Dean et al. 2018). Social inequalities in cancer are further discussed in Chap. 1 of this book. Briefly, each population has its history, culture, structure, and economic and social divisions, which influence how people are exposed to specific environmental and socioeconomic conditions and how the provision of health care is organized. Therefore, cancer survival across Europe is composed of a constellation of complex and interrelated factors that may explain survival differences (Finke et al. 2018; Marmot 2018).

During the past two decades, increasing attention has been drawn towards social disparities and the social determinants of health in population-based epidemiological studies. The World Health Organization's Commission on Social Determinants of Health defines the social determinants of health as 'the conditions in which people are born, grow, work, live, and age, including the healthcare system, and the wider set of forces and systems shaping the conditions of daily life'. These social determinants of health, directly driven by inequities in money, power and resources globally, explain most of the unjust and preventable health disparities observed both within and between countries (WHO Commission on Social Determinants of Health 2008). These disparities in health reflect social disparities in society, whether rich or poor (Wilkinson and Pickett 2010).

Lung cancer, because of its close ties with the tobacco epidemic, is considered to be particularly preventable through public health measures (Dela Cruz et al. 2011). According to results from the broadest research project on cancer survival in Europe, prevention should be a priority for lung cancer, as well as early diagnosis and

improved treatments (Francisci et al. 2015). Reducing the global burden of lung cancer, or any other cancer, requires not only more efficient prevention to reduce incidence but to also take action to improve survival (OECD 2019). Hence, it is crucial to gain information and gather evidence on the survival of lung cancer patients at all possible levels in order to help understand the intricate social disparities affecting survival in lung cancer across the European region.

Social Environment and Survival for Lung Cancer in European Countries

One of the major determinants of health is the social environment. Briefly, it encompasses the immediate physical, social and cultural setting in which people function and interact, and, as commented before, it is believed that several of its components are involved in cancer survival disparities (e.g. differences in socioeconomic status (SES), race/ethnicity, age, gender/sex identity, geographical location, access to healthcare services, etc.) (Barnett and Casper 2001; Polite et al. 2017).

Relationships between social disparities and poor survival are not attributable to mere chance, and a growing number of studies attest to this in the field of cancer (WHO International Agency for Research on Cancer 2019). Evidence supporting the need for reducing social inequalities in healthcare access and provision with a focus on healthcare equity has been mounting over time (Wilkinson and Pickett 2010). In this chapter, a considerable amount of the available evidence on the influence of the social environment on the differences in lung cancer survival across Europe is reviewed.

The Studies

Studies have increasingly reported social inequalities, mainly socioeconomic-related, with a consistently lower survival for the more deprived patients. Lung cancer survival, as well as that of any cancer, is known to vary across social groups (Kogevinas and Porta 1997; Woods et al. 2006; Finke et al. 2018). Social differences in the survival of patients with lung cancer, whether at the individual or neighbourhood level (i.e. spatially aggregated, usually at the census tract level), have been examined in 47 studies for this chapter. For each investigation, a general description of the study, the indicators used, and some brief comments on the results are collected in Tables 9.1 and 9.2, for the individual and the aggregate level, respectively.

Out of all studies reviewed, 36 out of 47 (76.6%) were carried out solely in Northwestern European countries, while only two studies covered several other European countries. The first one covered ten European countries and the second 19 European countries (Table 9.2). At an individual level, most studies were conducted

Table 9.1 Social differences in survival from lung cancer in Europe (individual measurements)

Reference; Country	Study design	Indicator(s)	Comments
Aarts et al. (2013); Netherlands	REG; PBC; 1991–2008; FU: 2009; NSCLC; *n* = 274; 15–75 years	Education level, health and health-related behaviours	Crude survival from NSCLC was the lowest in highly educated patients, but survival not associated with educational level. Association remained similar after including comorbidities and/or lifestyle behaviours
Berglund et al. (2010); Sweden	REG; PBC; 1996–2004; FU: 2006; NSCLC; *n* = 3370; 30–94 years	Socioeconomic, demographic and tumour characteristics, treatment and management	For all socioeconomic indicators, 1- and 3-year crude CSS longer among patients with high compared with low SES. Higher diagnostic intensity in patients with high compared with low education. Social gradients in time between referral and diagnosis in early-stage disease. Social differences in treatment even after adjustment for prognostic factors
Chirlaque et al. (2018); Spain	REG; PBC; 1995–1999 and 2000–2007; FU: 2003 and 2008; *n* = 28,090; ≥15 years	Socio-demographic and tumour characteristics, treatment and other prognostic variables	Lung cancer 5-year relative survival of 10.6%. No significant differences between age-standardised 5-year relative lung cancer survival for the 2 study periods, and no changes in prognosis detected as well. No significant sex differences in lung cancer relative survival. Survival 2 points lower than the European mean
Dalton et al. (2008); Denmark	REG; PBC; 1994–2003; FU: 2006; *n* = 21,492; 30–79 years	Socioeconomic, demographic and health-related indicators	Some indications of socioeconomic gradients in age-standardised relative survival when measured as a range of socioeconomic, demographic and health-related indicators. Short-term survival usually poorer in less advantaged groups. 5-year survival estimates similarly low in all groups
Dalton et al. (2015); Denmark	REG; PBC; 2004–2010; FU: 2011; *n* = 13,045; 51–81 years	Socioeconomic, demographic and health-related indicators, tumour stage and treatment	Patients with lower SES were less likely to receive first-line treatment. Differential treatment, stage, performance status and comorbidity partly explained social inequality in survival from lung cancer

Table 9.1 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Di Maio et al. (2012); Italy	Data from clinical trials; 1996–2005 (conduction of trials); FU: median 26.3 months; NSCLC; *n* = 1680; 29–86 years	Socio-demographic and tumour characteristics	Adjusted HR of death was 0.85 for patients with high education level. At multivariable analyses, female gender, better performance status and high education were independent predictors of longer overall survival
Grivaux et al. (2011); France	Prospective cohort study; 2000; FU: 2005–2006; *n* = 5447; all ages	Socio-demographic and tumour characteristics, health-related indicators and treatment	Percentage of deceased patients varied with socio-professional category. Excess mortality observed among the 202 farmers and the 651 unemployed patients (93.6% and 92.5%, respectively)
Holmberg et al. (2010); England, Norway and Sweden	REG; PBC; 1996–2004; FU: 2009; England *n* = 250,828, Norway *n* = 18,386, Sweden *n* = 24,886; 0–80+ years	Age, sex, country	In all subcategories of age and sex, 5-year cumulative survival was lower in England than in Norway and Sweden. Women had better survival than men in all strata of age and country
Hussain et al. (2008); Sweden	REG; PBC; 1990–2004; FU: 2004; *n* = 17,936; 30–64 years	Education level	Significant positive associations between education level and cancer survival for lung cancer
Kravdal (2000); Norway	Census and REG; PBC; 1955–1986; FU: 1960–1991; *n* = NA; 50–79 years	Education, income and occupation	Comparing low with high number of years of education, significant HRs ranged from 1.28 (pancreas, women) to 1.72 (bladder, men) with lung cancer within the interval. Differences were also observed by income and occupation and continued to be significant after accounting for stage of disease
Myrdal et al. (2009); Sweden	REG; PBC; 1995–2003; FU: 2004; NSCLC; *n* = 4345; 0–70+ years	Socio-demographic and tumour characteristics, health-related indicators, treatment and home county	In full multivariate model (all variables considered), male gender, age over 70 years, current smoking and non-squamous cell type of tumour, together with advanced stage, were all significantly related to poorer long-term survival. When type of treatment was excluded from the model, differences in survival between county centres were seen

(continued)

Table 9.1 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Nilsson et al. (1997); Sweden and Estonia	REG; PBC; 1974–1986 in Sweden and 1979–1985 in Estonia; FU: 1988 (Estonians in Sweden), 1989 (Estonians in Estonia) 1991 (Swedish population); males; *n* = 6588; all ages	Immigration (survival in Estonia vs survival of Estonian immigrants in Sweden vs survival in Sweden)	Estonians living in Sweden and general population of Sweden had higher cancer relative survival (7.2% and 6.0% respectively) than Estonians living in Estonia (5.2%)
Pagano et al. (2010); Italy	REG; PBC; 2000–2003; FU: 2006; NSCLC; *n* = 2259; all ages	Socio-demographic and tumour characteristics, and health-related indicators	Relationship between patients characteristics and survival analysed by adjusting for all the available covariates, including pattern of care. For early-stage, surgical pattern of care was a significant positive prognostic factor, whereas unmarried status and older age were negatively associated with survival
Pastorino et al. (1990); Italy	REG; PBC; 1976–1979; FU: ≥9 years; *n* = 222; 34–85 years	Socio-demographic and tumour characteristics, and treatment	Factors such as age, sex or social class did not affect survival when treatment was taken into account. Data show that surgical resection is the major determinant of survival
Pokhrel et al. (2010); Finland	REG; PBC; 1971–2005; FU: 2005; *n* = 66,014; ≥25 years	Education level and occupation	Survival consistently highest for patients with highest education and lowest for those with only basic education. Potentially health-conscious patients had even higher survival. Differences were in part attributable to less favourable distributions of tumour stages in the lower education categories
Rodríguez-Barranco et al. (2019); Spain	REG; high-resolution PBC; 2010–2011; FU: 2015; *n* = 1196; ≥15 years	Socio-demographic and tumour characteristics, comorbidity burden and healthcare factors associated with regional variability	Geographical differences in lung cancer survival between regions at 1-year since diagnosis. Evidence of regional differences in lung cancer late diagnosis and treatment received. Higher survival in females than males in both regions
Rosso et al. (1997); Italy	REG; PBC; 1981; FU: 1985–1992; *n* = 1505; ≥25 years	Educational level and housing tenure	Overall, individuals with university-level education displayed the highest survival

Table 9.1 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Salmerón et al. (2012); Spain	REG; PBC; 1995–1999; FU: 2004; *n* = 10,999; ≥15 years	Socio-demographic and tumour characteristics	Sex-related differences: age-standardised 5-year relative survival significantly higher in women (11.8%) than in men (9.2%). Among the youngest patients, conditional relative survival was 1.74 times significantly higher in women than in men Histologic type-related differences: some histology groups, such as squamous cell carcinoma and adenocarcinoma, presented better prognosis than others
Skyrud et al. (2016); Norway	REG; PBC; 2002–2011; FU: 2013; *n* = 24,565; ≤30 years	Socioeconomic, demographic and health-related indicators, tumour characteristics and treatment	RER of death of 0.89 for lung cancer, and of 0.27 for those receiving radical surgery. Sub-analysis of comorbidity showed the lowest RER of death for lung cancer. Statistically significant regional variations in RER of death, from the base model, for lung cancer
Smailyte et al. (2016); Lithuania	REG; PBC; 2001–2009; FU: 2009; *n* = 8812; 30–74 years	Education level	Lower survival rates among patients with lower educational levels
Vågerö and Persson (1987); Sweden	REG; PBC; 1961–1979; FU: 1979; *n* = 7817; 20–64 years	Occupation	No detectable differences in lung cancer survival probability by social class

REG population-based cancer registry data, *PBC* population-based cohort study, *FU* follow-up length, *NSCLC* non-small cell lung cancer, *n* sample size (lung cancer), *NA* not available, *CSS* cause-specific survival, *SES* socioeconomic status, *HR* hazard ratio, *RER* relative excess risk

in Scandinavia, whereas, at a geographical area-based level, most were conducted in the UK (mainly in England). Area-based studies use aggregates of several socioeconomic individual-level indicators as a proxy for individual SES. These area measures are referred to as indices of deprivation characterizing small geographical areas (i.e. census tracts) on a continuum from deprived to affluent.

In general, most studies used population-based cancer registry data and had a population-based cohort design. Twenty-one studies examined indicators on an individual level and 25 on an aggregate level, whereas only one examined both levels.

A few studies examined crude survival rather than disease-specific (either net or relative) survival, which was the most used analysis.

Table 9.2 Social differences in survival from lung cancer in Europe (aggregated measurements)

Reference; Country	Study design	Indicator(s)	Comments
Aarts et al. (2015); Netherlands	REG; PBC; 2001–2012; FU: 2014; NSCLC stage IV; *n* = 5428; all ages	Areal measure of deprivation (postal code level), tumour characteristics, stage, treatment (chemotherapy use) and comorbidity	Increasing administration rates of chemotherapy over the period 2001–2012 resulted in extension of median survival by 3 weeks
Berglund et al. (2012); England	REG; PBC; 2006–2008; FU: 2009; *n* = 15,582; 0–80+ years	Areal measure of deprivation (quintiles of the income domain of the 2007 ID at LSOA level), comorbidity burden, stage at diagnosis and treatment	No detectable socioeconomic differences in stage at diagnosis among lung cancer patients. Social differences in lung cancer management and survival existed, and could not be fully explained by differences in stage at diagnosis, comorbidity and treatment factors. In early-stage disease, social gradients in survival existed throughout follow-up, whereas in advanced disease, variations in survival were confined to the period immediately after diagnosis
Campbell et al. (2000); Scotland	REG; PBC; 1991–1995; FU: 1995; *n* = 19,449; all ages	Areal measure of deprivation (output area) and distance to nearest cancer centre	For lung cancer patients who survived at least 1 day after diagnosis, increasing deprivation associated with decreasing survival. Small settlement size was a significant advantage, even after adjusting for age, sex, deprivation and distance. Increasing distance from cancer centre significantly associated with poorer survival for lung cancer
Cheyne et al. (2013); UK	RCo; 2008–2010; FU: NA; *n* = 1432; 31–97 years	Areal measure of deprivation (LSOA level) stage and health-related indicators	No significant difference in lung cancer median survival or 1-year survival according to SES
Chouaïd et al. (2017); France	RCo; 2011; FU: 2013; *n* = 41,715; all ages	Areal measure of deprivation (quartiles of the SDI at municipality level) and comorbidity	1- and 2-year survival significantly lower in patients living in socially deprived areas compared to very privileged ones, but no difference observed with respect to population density. Age, sex and comorbidities associated with survival

Table 9.2 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Coleman et al. (2001); England and Wales	REG; PBC; 1971–1990; FU: 1995; n = 144,604; all ages	Areal measure of deprivation (quintiles of the Carstairs score at ED level)	Difference in survival between adults in the most affluent and most deprived categories from all cancers combined (including lung cancer) was 12.7% for 1-year survival and 11.1% for 5-year survival. Lung cancer survival at 5 years was 5% in men and women and had scarcely changed since the early 1970s
Coleman et al. (2004); England and Wales	REG; PBC; 1986–1990; FU: 2001; n = 107,317; 15–99 years	Areal measure of deprivation (quintiles of the 1991 Carstairs score and the IMD 2000 income domain score at electoral ward level)	5-year survival for lung cancer patients diagnosed 1996–99 was 6% in both sexes, not significantly better than a decade earlier. Survival in men significantly lower for the poor than the rich (deprivation gap −1.4%). Wider gap than for men diagnosed 1986–90, although not significant. Deprivation gap in survival for women diagnosed 1996–99 was small, and unchanged from a decade earlier
Ellis et al. (2012); England	REG; PBC; 1996–2006, FU: 2009; n = 83,839; 15–99 years	Areal measure of deprivation (quintiles of the income domain of the IMD at LSOA level)	Lung cancer was single largest contributor to total number of avoidable deaths, although deficit in survival between affluent and deprived patients was small (≈ 2%). ≥80% of avoidable deaths in the first 3 years occurred during first year after diagnosis. Avoidable deaths by sex revealed only small differences, although percentage of excess avoidable deaths was consistently higher in women
Ellis et al. (2014a); UK	REG; PBC; 2001–2005; FU: 2009; n = 145,206; ≥35 years	Areal measure of deprivation (quintiles of the IMD at LSOA level) and smoking habit	5-year net survival estimated with smoking-adjusted life tables 1.5% higher than survival estimated with unadjusted life tables for lung cancer. Impact of using smoking-adjusted life tables more pronounced in affluent patients, but small
Evans and Pritchard (2000); Europe/USA	PBC; Europe: 1983–1985; FU: 1995; n = 10 countries; 0–84 years	Areal measure of deprivation (country level) and GDP expenditure on health	Higher GDP health expenditure and longer survival rates for lung cancer and for each gender significantly correlated

(continued)

Table 9.2 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Forrest et al. (2015); UK	REG; PBC; 2006–2009; FU: ≥2 years; *n* = 22,967; all ages	Areal measure of deprivation (LSOA level), histology, timely GP referral, performance status and comorbidity	Socioeconomic inequalities in survival from lung cancer statistically explained by socioeconomic inequalities in receipt of treatment, but not by timeliness of referral and treatment
Iyen-Omofoman et al. (2011); UK	PCo; 2000–2009; FU: 2009; *n* = 12,135; all ages	Areal measure of deprivation (quintiles of the Townsend score at output area level)	Lung cancer survival did not differ across socioeconomic groups, but worsened with increasing age at diagnosis
Jack et al. (2006); UK	REG; PBC; 1998; FU: NA; *n* = 695; all ages	Areal measure of deprivation (IMD at ward level), tumour characteristics, health-related indicators and treatment	Residence in a more deprived ward associated with lower 1-year survival ($P = 0.0184$). No changes by adjustment for case mix variables but after further adjustment for treatment, trend was attenuated and no longer statistically significant ($P = 0.1935$)
Jansen et al. (2014); Germany	REG; PBC; 1997–2006; FU: 2006; *n* = 105,688; ≥15 years	Areal measure of deprivation (quintiles at district level)	5-year relative survival was lower in the most deprived districts than in all other districts combined. Inequalities persisted after adjustment for stage
Louwman et al. (2010); Netherlands	REG; PBC; 1997–2006; FU: NA; *n* = 12,945; all ages	Areal measure of deprivation (postal code level) and comorbidity	Crude 1-year survival of lung cancer patients from lower SES was worse compared with the highest SES. Relative contribution of comorbidity in explaining inequality in 1-year survival was 0% for lung cancer
Nur et al. (2015); England	REG; PBC; 2001–2005; FU: 2011; *n* = 145,532; 15–99 years	Areal measure of deprivation (quintiles of the income domain score of the IMD at LSOA level)	For lung cancer, the deprivation gap in 1-year survival narrowed with increasing age at diagnosis. The 'deprivation gap' in survival in patients diagnoses aged 15–44 years was ≥10% for 1-year survival in men and 1- and 5-year survival in women
O'Dowd et al. (2015); UK	PCo; 2000–2013; FU: 3 months; *n* = 20,142; ≥30 years	Areal measure of deprivation (quintiles of the Townsend score at output area level), smoking habit, comorbidity and urbanisation	Increasing age, male sex, socioeconomic deprivation, rural versus urban location and current smoking, were all independently associated with early death, although early death was less likely in ex-smokers compared with never smokers; and no association with comorbidity index, or living alone versus in a shared dwelling

Table 9.2 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Pollock and Vickers (1997); England	REG; PBC; 1987–1992; FU: 1992; n = 22,842; 40–99 years	Areal measure of deprivation (deciles of the Townsend score 1991 at ED level)	Lower lung cancer survival rates observed for the most deprived deciles compared with the most affluent deciles. Moderate effect, 5-year lung cancer relative survival rate ratio 1.18
Rachet et al. (2010); England	REG; PBC; 1996–2006; FU: 2007; n = 303,422; 15–99 years	Areal measure of deprivation (quintiles of the IMD 2004 at LSOA level)	Survival slightly improved for lung cancer, but inequalities in survival were still wide in 2006. Most of the socioeconomic disparities in survival occurred soon after cancer diagnosis, regardless of the cancer prognosis
Riaz et al. (2011); England	PBC; 2003–2007; FU: 2008; n = 150,939; all ages	Areal measure of deprivation (quintiles of the income domain of the IMD 2007 at LSOA level) and urbanisation	Lung cancer patients from a deprived area had lower survival than those from an affluent area. Survival higher in females than males in all urbanisation and socioeconomic deprivation groups
Rich et al. (2011); England	PBC; 2004–2008 (data entry); FU: 2008; n = 60,059; all ages	Areal measure of deprivation (LSOA level), demographic and tumour characteristics, stage and treatment	Socioeconomic disadvantage did not influence survival or access to surgery but was slightly related to a decreased use of chemotherapy
Schrijvers et al. (1995a); Netherlands	REG; PBC; 1980–1989; FU: 1991; n = 4591; all ages	Areal measure of deprivation (postal code level) and prognostic factors (stage at diagnosis, histologic type, treatment)	For lung cancer, 5-year relative survival rate higher in the higher SES groups, although the highest SES group had a lower 5-year relative survival rate than the second highest. Socioeconomic variation in survival not explained by the distribution of the prognostic factors stage, histologic type and treatment
Schrijvers et al. (1995b); England	REG; PBC; 1980–1989; FU: 1992; n = 40,279; 30–99 years	Areal measure of deprivation (quintiles of the Carstairs score 1981 at ED level)	Better survival amongst the affluent observed for lung cancer. Statistically significant adjusted HRs for the most deprived quintile compared to the most affluent (1.13 for lung). Addition of stage of diagnosis to multivariate models of relative survival did not change HRs much

(continued)

Table 9.2 (continued)

Reference; Country	Study design	Indicator(s)	Comments
Shack et al. (2007); Scotland	REG; PBC; 1986–2000; FU: 2004; *n* = 20,851; 15–99 years	Areal measure of deprivation (quintiles of the 1995 Carstairs score and the IMD 2004 at postcode sector level)	5-year survival improved for lung cancer and was significantly associated with a widening in the deprivation gap in survival
Sloggett et al. (2007)[a]; England and Wales	REG; PBC; 1981–1997; FU: 2000; *n* = 4271; ≥45 years	Individual SES indicators and areal measure of deprivation (ward level)	Socioeconomic differences for lung cancer survival confirmed by every indicator (social class, housing tenure, car access and ecological measure of deprivation)
Vercelli et al. (2006); Europe	REG; PBC; 1990–1994; FU: ≥5 years; *n* = 657,541; 65–84 years	Areal measure of deprivation (country level), macro-economic and labour force indicators and features of the healthcare systems	Survival for lung cancer not very well correlated with the affluence indicators or demographic factors. Statistically significant correlations between proportion of elderly married people and survival for lung cancer in men

REG population-based cancer registry data, *PBC* population-based cohort study, *FU* follow-up length, *NSCLC* non-small cell lung cancer, *n* study sample size, *RCo* retrospective cohort, *NA* not available, *PCo* prospective cohort, *ID* index of deprivation, *LSOA* Lower Super Output Area, *SDI* social deprivation index, *ED* enumeration district, *IMD* index of multiple deprivation, *GP* general practitioner, *SES* socioeconomic status, *GDP* gross domestic product, *HR* hazard ratio
[a]Study examined indicators both on an individual and an aggregate level

Results

A non-exhaustive but wide overview of the studies on social disparities in lung cancer survival is shown in Tables 9.1 and 9.2. There, an extract of the most relevant outcomes regarding lung cancer survival is presented for each study.

On an individual level (see Table 9.1), the majority of the studies focused on the SES or one or more of its main determinants (income, occupation and education). One study focused on immigration and lung cancer survival. Most of the studies adjusted for age and sex, while only accounted for any other confounding factors (e.g. stage at diagnosis, treatment, health-related indicators and behaviours, comorbidity and other prognostic factors, management, geographical location). The level of adjustment for prognostic factors was heterogeneous across studies. After age and sex, stage at diagnosis, treatment and comorbidity were the confounders most often included. Although strongly associated with lung cancer incidence, mortality and survival, and its contribution to socioeconomic inequalities in mortality (Gregoraci et al. 2017), smoking habit or status was only considered by a few studies. Because most of the individual studies were carried out in Scandinavia, where data are frequently extracted from cancer registries and linked to other registries to obtain SES and other data of interest, individual information on the smoking status

might not be available. In most studies, relative survival analysis using life tables was used to report lung cancer survival outcomes.

On an aggregate or area-based level (see Table 9.2), studies used a geographically aggregate measure of deprivation to gather information on social differences. Authors used a variety of indices to measure the deprivation experienced by people living in an area, and they did so at different geographical area levels, i.e. different population sizes, across studies. Most of the studies adjusted for age, sex and stage at diagnosis. Information on tumour characteristics and histology, treatment, comorbidity, smoking habit or status, performance status, health-related indicators, features of the healthcare system, timely general practitioner (GP) referral, distance to the nearest cancer centre, urbanisation, macro-economic and labour force indicators, geographical location and on gross domestic product (GDP) expenditure on health were also collected. Similar to what happened in the studies at an individual level, the degree of adjustment for prognostic factors was also heterogeneous across these types of studies. Age, sex and stage at diagnosis, treatment and comorbidity were the confounders most often included in the analyses. In most studies, relative survival analysis using life tables was used as the benchmarking method for estimating lung cancer net survival. Interestingly, the vast majority of these studies were conducted in the UK (mainly in England). In the UK, the deprivation index in cancer survival research has been used as a proxy for an individual-level measure for many years, assuming that people living in the same area may share some environmental factors. However, the correlation between individuals living in the same area (i.e. census tracts) is usually not considered due to methodological challenges. It is just recently that, under the relative survival setting, researchers are able to account for the within small geographic area effect in order to develop a multilevel approach with the small area as contextual level (Crowther et al. 2014). It is important to remark that significant geographical differences in lung cancer survival, as well as in incidence and mortality, exist among European countries and regions (Cheng et al. 2016; Wong et al. 2017; Barta et al. 2019). Lung cancer survival trends between 1995–1999 and 2000–2014 were generally flat, but survival increased by 5–10% in 15 European countries (Allemani et al. 2018). In Fig. 9.1, lung cancer survival estimates from most European countries (only reliable data) are shown. As can be seen in the figure, lung cancer survival across Europe is generally and consistently lower for Eastern and Southern countries than for Northwestern countries (Francisci et al. 2015; Allemani et al. 2018). These regional differences could reflect earlier stages of the tobacco epidemic in countries such as Bulgaria, Poland and the Russian Federation (Proctor 2001). However, the geographical differences in lung cancer survival might also be due to socioeconomic and educational inequalities, levels of human development index (HDI), and to a lower degree, country-specific GDP per capita, different patterns of healthcare organization and provision across Europe (Ellis et al. 2014b; WHO International Agency for Research on Cancer 2019; Belot et al. 2019). The relationship between tobacco and lung cancer is as much a social, economic and political problem as it is a problem of individual lifestyle (Gregoraci et al. 2017).

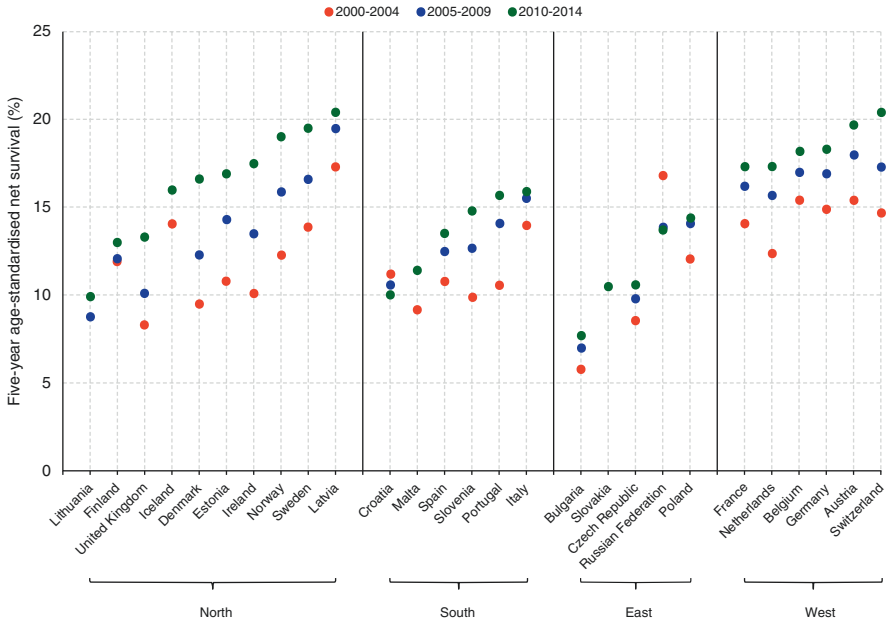

Fig. 9.1 Five-year age-standardised net survival (%): adults (15–99 years) diagnosed with lung cancer by calendar period of diagnosis (2000–2004, 2005–2009, 2010–2014) across European countries. (Source: Allemani et al. 2018—CONCORD-3)

Practically all of the studies, whether at an individual or aggregate level, documented a relationship between lung cancer survival and measures of social class, SES or deprivation. Broadly, it seems to be a pattern of lung cancer patients with low SES or from a deprived area having consistently more reduced survival than those with higher SES or from an affluent area. The differences in survival were present in both sexes (although survival tends to be higher in females) and in most countries regardless of the indicator/s used, but in general, and in comparison with other cancer types—especially those of good prognosis (Lundqvist et al. 2016; Syriopoulou et al. 2019)—the associations observed for lung cancer are rather weak. Previous research on several cancer sites and countries have also shown that cancer survival is worse for more deprived patients and patients living in more deprived areas (Fidler and Bray 2018; WHO International Agency for Research on Cancer 2019) and that that association has even been reported in countries where relatively comprehensive and universal healthcare is provided for the population (Finke et al. 2018). Most of the studies reviewed in this chapter investigated differences in long-term survival; however, comparative analyses, including both short and long-term assessments, would be more revealing in order to find explanations for inequalities. In this line, various international comparison studies have exposed that differences across countries are greatest in the short term (Holmberg et al. 2010; Rachet et al. 2010; Dalton et al. 2015).

In general, some limitations occur with studies that do not explicitly state the mechanisms through which a determined area-level exposure can influence a health outcome (WHO International Agency for Research on Cancer 2019). In this regard, other patient and community factors that emerge as possible contributors to the differences in lung cancer survival concerning SES were tumour characteristics, stage at diagnosis, cancer therapy, lifestyle factors such as the increased prevalence of smoking, comorbidity, distance and access to specialised healthcare centres, and geographical remoteness (Woods et al. 2006; Finke et al. 2018).

Overall, it seems reasonably clear that the social gap between the most and less privileged groups in lung cancer survival in Europe is, in part, mediated through the stage of disease at diagnosis and access to optimal treatment and specialised care, although the evidence is not always consistent. Patient characteristics such as nutrition, comorbidity, health-seeking behaviours (inevitably influenced by the stigma of lung cancer) and other psychosocial factors more commonly forgotten may also interact with treatment decisions and, eventually, survival. Of other potential contributing factors, the role of ethnicity, stress, religious beliefs, marital status, social support and more, has scarcely been studied. Disentangling the reasons behind social disparities in cancer survival remains a topic of active research.

Main Hypotheses for the Underlying Mechanisms

The influence of the social environment on the risk of developing and dying from cancer is a global phenomenon. However, the explanations for social differences and the mechanisms underlying the social gradient in lung cancer survival in Europe are not very well documented (WHO International Agency for Research on Cancer 2019). Mechanisms that might lead to social differences in lung cancer survival in Europe can be separated into (i) factors related to the tumour (stage at diagnosis, biological characteristics), (ii) the patient (host factors and the effect of treatment, psychosocial factors) and (iii) the healthcare system (treatment received, medical expertise, screening, geographical remoteness). These and other issues are discussed in depth in the chapters belonging to Part D in this volume.

Concluding Remarks

The information on the survival of cancer patients in a population enables the comparison of the effectiveness of health systems as well as of possible factors that are contributing to social disparities in survival. Overall, lung cancer in Europe is characterised by a consistent lower survival probability compared with other cancer sites. Despite the poor survival everywhere in Europe, there is a generalised slight increasing trend in lung cancer survival during recent years.

Furthermore, evidence shows that inequalities in lung cancer survival reveal a socioeconomic gradient across Europe. However, the significant heterogeneity of methods used to measure socioeconomic inequalities across Europe warrant precaution comparing the differences between countries. Therefore, a standardised European socioeconomic measure would be desirable to enhance comparability across countries and different levels of aggregation.

This review adds summative evidence supporting the hypothesis that more deprived lung cancer patients have lower survival in Europe. However, the effect sizes are generally smaller and not as consistent as those seen in cancers of better prognosis. Moreover, it is important to highlight that most of the studies were conducted in Northwestern European countries, and therefore further investigations in the rest of the European countries should be addressed.

Overall, the possible underlying causes of social disparities in lung cancer survival can be separated into three groups: factors relating to the tumour, the patient and the health care system. Regarding the proposed mechanisms associated with lower survival for the most deprived patients in Europe, it seems that the stage of disease, in part, mediates the survival gap. However, differences in access to optimal treatment and specialised care between socioeconomic groups have also been postulated as one of the reasons for the survival gap between the most and less deprived groups, but other potential contributing factors should also be more commonly investigated.

In line with international recommendations, priority should be given to prevention, with tobacco control policies and improvements in early cancer diagnosis and better access to first-line treatment and healthcare centres. In addition, further research on all possible social contributors to the differences in survival should be considered pressing and investigated thoroughly.

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Chapter 10
Social Disparities in Survival from Head and Neck Cancers in Europe

Victoria Sass and Sylvie Gadeyne

Introduction and Background

Head and neck cancer (HNC) is a broad classification for a variety of malignancies affecting regions of the mouth, nose, throat and sinuses. As such, there are differences in aetiology depending upon the subsite of the tumour and thus the accompanying risk factors associated with developing cancer. Prior research has demonstrated a clear link between various social disparities and the patterning of incidence (Elwood et al. 1984; Zatonski et al. 1991; Hobdell et al. 2003; Menvielle et al. 2004; Conway et al. 2008, 2010a, b; Johnson et al. 2008, 2011; Boing et al. 2011; Sharpe et al. 2012; Hwang et al. 2013; Santi et al. 2013; Everatt et al. 2014; Hoebel et al. 2018) and mortality (Hobdell et al. 2003; Menvielle et al. 2005, 2007; Hagedoorn et al. 2016; Vanthomme et al. 2017; Hoebel et al. 2018) for HNC broadly as well as individual anatomical sites. However, less research has been conducted on social disparities in HNC survival and the potential mediating factors contributing to observed disparities.

As a group, the incidence of HNC is disproportionately high in Europe (World Health Organization 2019), with the highest age-standardised rates mainly clustered in Eastern Europe, with the exception of France and Portugal. There is considerable heterogeneity between countries, with the lowest rate of 4.0 in Iceland and the highest rate of 23.7 in Hungary. These figures are largely driven by the pattern of male incidence, which makes up the lion's share of HNC diagnoses across populations. For females, the pattern is largely reversed, with the preponderance of cases being

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diagnosed in Western Europe, though the range of rates between countries is much smaller. These trends in incidence are generally mirrored in age-standardised mortality rates, with the exception of France, which has relatively lower levels of mortality despite high incidence rates. Overall, HNC is the sixth most commonly diagnosed cancer in Europe, and with 150,000 additional incident cases each year, its prevalence is increasing (European Cancer Patient Coalition 2019).

Survival from head and neck cancer in Europe reflects much of the heterogeneity found in incidence and mortality rates. In most countries studied, it appears there is both an increase in survival over the past several decades as well as an increase in incidence, though this varies by sex and type of cancer (Guizard et al. 2017; Jakobsen et al. 2018). Depending upon the anatomical site of the tumour, 5-year relative survival rates range from greater than 90% for lip cancer to approximately 25% for hypopharyngeal cancer (Eurocare 2019), which suggests the importance of looking at site-specific outcomes to gain a better understanding regarding aetiology and the different risk factors related to social status and survival. Despite the severity of this disease, there is limited public awareness about its signs and symptoms. Additionally, depending upon the stage at diagnosis, the available treatment options can have dramatic psychological and physical consequences for patients. These factors contribute to a variety of social disparities in HNC survival that go overlooked by focusing solely on rates of incidence and mortality. In order to better understand the mechanisms underlying various forms of HNC and thus the potential pathways for public policy interventions, we carried out a systematic review of the literature on the social patterning and disparities in HNC survival.

Methodology

We conducted a systematic review through Google Scholar and MedLine using a combination of terms to locate broader articles as well as more targeted research on specific tumour subsites and/or various inquiries into potential mechanisms contributing to the social disparities in HNC survival in Europe. The combination of terms used was ‘socioeconomic/social/inequ−/disparity/depriv-’ + ‘head and neck/upper aerodigestive/laryn-/pharyn-/oral/mouth/lip/nasal/salivary’ + ‘cancer/carcinoma/tumour’ + ‘survival’.

Firstly, abstracts or summary sections were read to ascertain whether an article fit certain criteria to be included in our review of the literature. These criteria included research that was conducted on a European population, was focused on HNC survival (or one of its constituent subsites), and was either explicitly investigating social disparities or included social covariates in their analyses.

Research studies that met these standards were then read in their entirety to determine whether they offered an original contribution and still met the aforementioned criteria. The citations of these articles were then used to locate additional research aligning with our original search aims. Additionally, a reverse search was conducted to locate articles that had cited those already included in our review to

guarantee inclusion of the most recent research to date. Finally, only those studies that were population-based or followed a prospective cohort were included in our review to ensure a reflection of the most methodologically rigorous evidence available. Our search resulted in 23 original studies which have been extensively summarised in Table 10.1 (Kogevinas et al. 1991; Rosso et al. 1997; Coleman et al. 1999, 2001, 2004; Edwards and Jones 1999; Paterson et al. 2002; Dikshit et al.

Table 10.1 Articles reviewed

Authors (Year) ——— Title	Setting Data source Population	Time period	Social indicator	Mediating factors ——— Controls	Cancer types	Main findings
Robertson G. et al. (2010) ——— Explaining the effects of socio-economic deprivation on survival in a national prospective cohort study of 1909 patients with head and neck cancers	Scotland Scottish Audit of Head and Neck Cancer N = 1909 total patients; 606 laryngeal patients	1999–2006	-2001 DEPCAT deprivation score	-WHO performance score -Smoking status -Alcohol status -Stage -Tumor differentiation -Cancer site ——— -Age -Sex	SITES MODELLED TOGETHER & LARYNX MODELLED SEPARATELY -Larynx -Oral -Hypopharynx and pyriform sinus -Oropharynx -Other	A clear socioeconomic gradient was found with those living in more deprived areas having worse survival as well as more advanced stage at diagnosis. When all available mediating factors were taken into account the association with deprivation lost its significance suggesting lifestyle factors, functional limitations, and stage are all potential mechanisms through which socioeconomic disparities contribute to survival disparities.
Ingarfield, K. et al (2019) ——— Determinants of Long-Term Survival in a Population-Based Cohort Study of Patients with Head and Neck Cancer from Scotland	Scotland Scottish Audit of Head and Neck Cancer N = 1820 total patients	1999–2013	-Carstairs Index of Deprivation	-WHO performance score -Smoking behavior -Alcohol consumption -Stage -Cancer site -Treatment modality ——— -Age -Sex -Geographic location of treatment	SITES MODELLED TOGETHER -Lip -Larynx -Nasal cavity -Oral cavity -Oropharynx -Hypopharynx -Other or salivary gland	1-year rates show a clear SES gradient for crude, disease-specific, and net survival however this trend is less obvious for 12-year survival, though higher rates are still found when comparing the least deprived to the most deprived quintiles. SES was not independently predictive of survival and was not included in fully adjusted models but all mediating factors and age were associated with longer term survival.
Dalton, S.O. et al. (2019) ——— Socioeconomic Inequality in Cancer Survival – Changes over Time. A Population-Based Study, Denmark, 1987–2013	Denmark Danish cancer registry N = 3928 patients	1987–2013	-Individual disposable income in year prior to diagnosis (age and gender-specific percentile)	- N/A ——— - Age - Sex	-Head and Neck	Support found for a SES gradient for head and neck cancer which was also found to be widening over time. The general survival improvements in survival over the period of study were found to be disproportionately going to the most affluent. This could be due to an increase in incidence of the oropharyngeal subtype which the authors note is more commonly found among more affluent popula-tions and has better prognosis than other head and neck cancer subtypes.

(continued)

Table 10.1 (continued)

Rachet, B. et al. (2010) ---------- Socioeconomic Inequalities in Cancer Survival in England after the NHS Cancer Plan	England National Cancer Registry N = 15,537 male laryngeal patients	1996–2007	-Ecological measure of deprivation (based upon socioeconomic characteristics of Lower Super-Output Area of patient's residence)	N/A ---------- - Age - Sex - Geographical area - Calendar period	-Larynx	There was a significant deprivation gap between 1996 and 2006, which also widened during the same time period.
Andersen Z.J. et al. (2008) ---------- Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark, 1994–2003	Denmark Danish national registers N = 3058 mouth/pharyngeal patients;1799 laryngeal patients	1994–2006	-Level of education -Disposable income -Affiliation to work market -Social class -Housing tenure -Size of dwelling -Cohabitating status -Type of district	-Charlson comorbidity index -Depression -Schizophrenia or other psychosis ---------- -Age -Sex -Period -Ethnicity	SITES MODELLED SEPARATELY - Mouth and pharynx - Larynx	Survival rates for mouth/pharyngeal were better for both sexes for the more highly educated, those working, homeowners, those living in larger homes, and those married/cohabitating, though the latter was a more pronounced effect for men. Additionally, higher income was associated with better survival for men only. Laryngeal cancer survival was associated with higher levels of education, higher income, working, homeownership, and size of dwelling for both sexes. Being married/cohabitating was associated with better survival for men only.
Sharp, L. et al. (2014) ---------- Smoking at Diagnosis Is an Independent Prognostic Factor for Cancer-Specific Survival in Head and Neck Cancer: Findings from a Large, Population-Based Study	Ireland National Cancer Registry Ireland N = 1469 oral cancer patients; 1734 pharyngeal cancer patients; 1717 laryngeal cancer patients; 732 other cancer patients	1994–2010	-Deprivation category (census-based small-area indicator using information on unemployment, social class, car ownership, type of housing tenure, and overcrowded housing)	-Smoking at diagnosis -Marital status -Morphology (i.e., squamous cell or not) -Stage -Grade Cancer-directed surgery (yes/no) -Cancer site ---------- -Age -Sex	SITES MODELLED TOGETHER -Oral cavity -Pharynx -Larynx -Other sites, including salivary gland	Smoking at diagnosis was found to significantly decrease 5-year survival (36% difference between current smokers and those who had never smoked). Deprivation was still found to be significantly associated with worse survival and being married with better survival, even after adjusting for smoking behavior. There were also findings that suggest smoking may play a differential role in survival depending upon treatment received, suggesting a possible mechanism by which smoking behavior effects the observed disparities.

Table 10.1 (continued)

van Harten, M.C. (2015) --- Determinants of Treatment Waiting Times for Head and Neck Cancer in the Netherlands and Their Relation to Survival	The Netherlands Netherlands Cancer Registry N = 13,140 total patients; 4309 oral cavity patients; 2525 oropharynx patients; 952 nasopharynx, paranasal sinus, and nasal cavity patients; 896 hypopharynx patients; 3721 larynx patients; 737 salivary glands patients	2005–2011	-Socioeconomic status (determined using validated relative scores provided by The Netherlands Institute for Social Research (SCP), based on postal code)	-Stage -Initial therapy -Institute of diagnosis and treatment -Cancer site --- -Age -Sex	SITES MODELLED TOGETHER -Oral cavity -Oropharynx -Nasopharynx/nasal sinuses -Hypopharynx -Larynx -(Malignant) salivary glands	Patients with a higher socioeconomic score had significantly better survival outcomes than those with a low score. Having a longer wait time for treatment was significantly associated with low SES, with said group experiencing a median wait time of 10% longer than those with a high SES. There was also an association found between SES and stage with those in the low SES group presenting with more advanced stages of the disease.
Coleman, M.P. et al. (1999) --- Cancer Survival Trends in England and Wales, 1971 1995: Deprivation and NHS Region	England & Wales Regional cancer registries (cover whole population since 1962) N = 32157 larynx patients; 13435 oral cavity patients; 6546 salivary gland patients; 5936 lip patients; 7292 nasal cavities and paranasal sinuses patients; 7187 hypopharynx patients; 3126 nasopharynx patients; 6001 oropharynx patients; 10481 tongue patients	1971–1995	-Carstairs Index of Deprivation	-N/A --- -Region -Calendar period of diagnosis -Age -Sex	SITES MODELLED SEPARATELY -Larynx -Oral cavity -Salivary glands -Lip -Nasal cavities and paranasal sinuses -Hypopharynx -Nasopharynx -Oropharynx -Tongue	With the exception of lip and hypopharyngeal cancers, there was a classic socioeconomic disparity between survival rates between most affluent versus most deprived for all subsites.
Coleman, M.P. et al. (2001) --- Socioeconomic Inequalities in Cancer Survival in England and Wales	England & Wales Regional cancer registries (cover whole population since 1962) N = 8671 larynx patients and 3663 oral cavity patients	1971–1995	-Carstairs Index of Deprivation	-N/A --- -Age -Sex -Administrative region of the NHS	SITES MODELLED SEPARATELY -Oral cavity -Larynx	Significant deprivation gaps were found for both subsites with oral cavity survival being 9.3% higher for the most affluent group compared to the most deprived group and similarly the survival gap advantage for laryngeal cancer being 11.6% higher for the advantaged group.

(continued)

Table 10.1 (continued)

Coleman, M.P. et al. (2004) ---------- Trends and Socioeconomic Inequalities in Cancer Survival in England and Wales up to 2001	England & Wales National Cancer Registry N = 20,112 larynx patients diagnosed 1986- 1999, 5666 men diagnosed 19961999	1986–2001	-Carstairs Index of Deprivation	-N/A ---------- -Age -Sex -Period of diagnosis	-Larynx	A deprivation gap was observed during both periods of the study (1986-1990 and 1996-1999) and a significant increase in the deprivation gap for 5-year laryngeal cancer survival rates for men was found, reaching 17% for the period 1996-1999. The increases in survival for laryngeal cancer in men over the period of study disproportionately went to the most affluent group and was therefore significantly associated with widening disparities by deprivation.
Shack, L.G. et al. (2007) ---------- Socioeconomic Inequalities in Cancer Survival in Scotland 1986–2000	Scotland Scottish Cancer Registry N = 1128 laryngeal cancer patients (diagnosed during 1996- 2000)	1986–2004	-Carstairs Index of Deprivation -Scottish indices of multiple deprivation	-N/A ---------- -Age -Sex -Calendar period	-Larynx	A significant socioeconomic gradient was found for male laryngeal cancer patients diagnosed during 1996-2000 and it had widened significantly since 1986, resulting in 10.8% higher 5-year survival rates for the most affluent group compared to the most deprived. These large socioeconomic differences witnessed for 1996-2000 were a result of a 3% widening of the deprivation gap every five years, during the period of this study.
Paterson, I.C.M. et al. (2002 ---------- Effect of Deprivation on Survival of Patients with Head and Neck Cancer: A Study of 20,131 Cases	United Kingdom Regional cancer registries (West Midlands, Trent, Wales and East Anglia) N = 20,131 patients	1981–1994	-Carstairs Index of Deprivation	-N/A ---------- -Age -Sex -Geographic region -Period	-Head and Neck	Found additional evidence of socioeconomic disparities for head and neck cancer survival but also found that deprivation's detrimental effects were confined to the first 12-18 months after diagnosis. Subsequently no association between deprivation and survival could be found.
Dalton, S.O. et al. (2008) ---------- Social Inequality in Incidence of and Survival from Cancer in a Population-Based Study in Denmark, 1994–2003: Summary of Findings	Denmark National cancer registry N = 2984 mouth and pharynx patients; 1761 larynx patients	1994–2006	-Level of education -Disposable income -Affiliation to work market -Housing tenure -Size of dwelling -Cohabitating status -Type of district	-Charlson comorbidity index -Depression -Schizophrenia or other psychosis ---------- -Sex	SITES MODELLED SEPARATELY -Mouth and pharynx -Larynx	Men were found to have significantly better survival from mouth and pharynx cancers with more education (1-year), higher disposable income (1- and 5-year), work market affiliation (1- and 5-year), homeownership (1- and 5-year), dwelling size (1- and 5-year), and cohabitation status (1- and 5-year). For women the only significant predictive socioeconomic indicator was work market affiliation (1- and 5-year). Comorbidities were significant for men for both 1- and 5-year but only for 1-year survival in women. With the exception of education, the same socioeconomic variables were significantly associated with survival for men from laryngeal cancer. Only work market affiliation (1- and 5-years) was predictive for women.

Table 10.1 (continued)

Rylands, J. et al. (2016) --- Outcomes by Area of Residence Deprivation in a Cohort of Oral Cancer Patients: Survival, Health-Related Quality of Life, and Place of Death	England Aintree University Hospital database N = 533 patients	2008–2016	-Index of Multiple Deprivation (IMD 2010)	-Quality of Life - physical function -Quality of Life - social-emotional function -Treatment type -Tumor site -Staging -Year of surgery -Use of adjuvant radiotherapy --- -Age -Sex	RETROSPECTIVE??? -Oral cavity	Nearly half the sample lived in the least deprived quartile (Q1) and there were significant differences between their 2- and 5-year survival rates when compared to the rest of the sample (Q2-Q4). This disparity held for those treated with curative intent even after adjustments fo age and stage at diagnosis. Additionally, quality of life was also found to be worse for those living in the most deprived areas even after inclusion of individual and clinical factors.
Jansen, L. et al. (2014) --- Socioeconomic Deprivation and Cancer Surviva in Germany: An Ecological Analysis in 200 Districts in Germany	Germany 10 pooled populationbased cancer registries N = 30,349 mouth/pharynx patients and 9,526 larynx patients	1997–2006	-German Index of Multiple Deprivation	-Stage --- -Age -Sex -Calendar period	SITES MODELLED SEPARATELY -Mouth and pharynx -Larynx	For patients with mouth or pharyngeal cancer there was a significant difference between 5-year relative survival between the most deprived quintile and all other quintiles. Adjustments for staging did not have an effect on short-term survival (3-month and 1-year conditional on 3-month survival continued to be significantly associated with deprivation) but did attenuate the association with longer-term survival (5-year). For cancer of the larynx living in a more deprived area was significantly associated with lower levels of survival and when adjusting for stage at diagnosis this holds for 1 year survival (close to marginal statistical significance) but not 3 month or 5 year survival.
Ali, H. et al. (2016) --- Oral Cancer Incidence and Survival Rates in the Republic of Ireland, 1994-2009	Ireland National Cancer Registry Ireland N = 2,147 oral cancer patients	1994–2012	-Marital status -Occupation status -Deprivation index (from local area socioeconomic status)	-Smoking status -Tumor site -Tumor stage --- -Age group -Sex -Year of diagnosis	SUBSITES MODELLED JOINTLY -Oral cancer -Base of the tongue -Tongue -Gum -Floor of the mouth -Palate -Unspecified mouth	A clear association was found between survival and socioeconomic status and this held even after adjusting for smoking status and tumor stage. Being married and employed were also associated with better survival. A linear relationship between cancer stage and death was observed.

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Table 10.1 (continued)

Rosso, S. et al. (1997) ---------- Social Class and Cancer Survival in Turin, Italy	Italy (Turin) Piedmontcancer registry N = 294 mouth/pharynx patients and 161 larynx patients	1991–1992	-Education	-N/A ---------- -Age -Sex -Area of birth -Housing tenure	SITES MODELLED SEPARATELY -Mouth and pharynx -Larynx	Mouth and pharyngeal cancer did not exhibit a significant socioeconomic trend despite non-significant differences between primary school and both high school and university (highest CFR was middle school). There was a significant association between education and survival from laryngeal cancer.
Kogevinas, M. et al. (1991) ---------- Socioeconomic Differences in Cancer Survival	England & Wales OPCS Longitudinal study N = 55 male larynx patients	1971–1983	-Housing tenure	-N/A ---------- -Age -Sex -Period	-Larynx	5-year suvival from laryngeal cancer was found to be significantly better for owner occupiers compared to council tenants.
Edwards, D.M. and J. Jones (1999) ---------- Incidence of and Survival from Upper Aerodigestive Tract Cancers in the U.K.: The Influence of Deprivation	United Kingdom Cancer registries (Thames and West Midlands) N = 1014 lip patients; 7292 mouth patients; 1536 salivary glands patients; 5876 other pharynx patients; 889 nasopharynx patients; 9296 larynx patients	1984–1993	-Carstairs Deprivation Index *-Marital status correlated with deprivation and less predictive so excluded from final analysis*	-"Extent of spread" index ---------- -Age group *-Ethnic category (based upon surname at birth)-not predictive, excluded from multivariate analysis* *-Sex (not predictive, exluded from multivariate analysis)*	SITES MODELLED TOGETHER & SEPARATELY -Mouth -Pharynx -Larynx	The crude and corrected survival for those living in more affluent areas was better for all cancers combined as well as by individual subsite. 5-year cause-specific survival rates were significantly better for those in the most affluent areas compared to the two most deprived. This association between deprivation and survival held even after accounting for site, extent of spread, and age.
Rachet, B. et al. (2008) ---------- Survival from Cancer of the Larynx in England and Wales up to 2001	England & Wales National Cancer Registry N = about 17,800 males (89% eligible of ~20,000 in original sample)	1986–2001	-Carstairs Deprivation Index	-N/A ---------- -Sex - Calendar period of diagnosis	-Larynx	5-year survival was significantly lower for men in the most deprived group compared to the most affluent group and it has been widening over the time periods of the study (by about 3.7% every five years). All of the improvements in survival from laryngeal cancer for men over the study period have gone to those in the most affluent group while survival rates have remained steady or declined for those in the most deprived group.

Table 10.1 (continued)

Belot, A. et al. 2018 ——————— Describing the Association between Socioeconomic Inequalities and Cancer Survival: Methodological Guidelines and Illustration with Population-Based Data	France (West France: Calvados and Manche) Cancer registries N = 4090 lip-oral cavity-pharynx patients and 1037 larynx patients	1997 – 2013	-European Deprivation Index (EDI)	-N/A ——————— -Age -Sex -Département (French administrative area) -Calendar year	SITES MODELLED SEPARATELY -Lip-oral cavity-pharynx -Larynx	For both men and women a significant difference in 5-year net survival rates for lip-oral cavity-pharyngeal cancers was found between the least and most deprived groups. A similar association was also found for men with laryngeal cancer (women not analyzed due to small sample size). Additionally, deprivation was found to account for a substantial share of the overall effect on the excess mortality hazard.
Ellis, L. et al. (2012) ——————— Trends and Inequalities in Laryngeal Cancer Survival in Men and Women: England and Wales 1991–2006	England & Wales National Cancer Registry N = 29,420 patients	1991 – 2007	-Ecological measure of deprivation (based upon socioeconomic characteristics of Lower Super-Output Area of patient's residence)	-N/A ——————— -Subsite group -Sex -Calendar period of diagnosis	SUBSITES MODELLED TOGETHER & SEPARATELY -Larynx -Glottal -Supraglottal	Survival was lower in women than in men for all laryngeal cancers and also within specific subsites, despite differential rates of diagnosis by subsite. Evidence was found to support a significant deprivation gap in laryngeal cancer survival for men at both 1- and 5-year for all subsites. No such relationship was found for women (though they also made up a significantly smaller share of the sample).
Dikshit, R. et al. (2005) ——————— Lifestyle Habits as Prognostic Factors in Survival of Laryngeal and Hypopharyngeal Cancer: A Multicentric European Study	Southeast Europe: - Switzerland - France - Italy - Spain Cancer registries N = 931 patients	1979 – 2000	-Occupation (skilled/unskilled)	-Average cigarette consumption (cigs per day) -Average alcohol consumption (g/day) -Dietary intake ——————— -Age -Tumor site	SITES MODELLED TOGETHER & SEPARATELY -Endolarynx -Epilarynx -Hypopharynx	No socioeconomic association was found with survival using a binary measure of occupational status. Cigarette smoking was found to negatively affect survival, especially for tumors in the endolarynx while alcohol was also found to worsen survival with the strongest effect for tumors of the epilarynx. Dietary factors were also associated with better survival, particularly a high consumption of poultry, vegetables, and vitamin C intake.

2005; Shack et al. 2007; Andersen et al. 2008; Dalton et al. 2008, 2019; Rachet et al. 2008, 2010; Robertson et al. 2010; Ellis et al. 2012; Jansen et al. 2014; Sharp et al. 2014; van Harten et al. 2015; Rylands et al. 2016; Ali et al. 2016; Belot et al. 2018; Ingarfield et al. 2019).

Results

As mentioned previously, head and neck cancer comprise a diversity of malignancies which the ICD-10 has classified into 18 separate diagnoses (C00-C14; C30-C32) (World Health Organization 2016). The most commonly referenced of these are the lip, oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, and the salivary glands. Cancers of the lip, nasal cavity and paranasal sinuses, and the salivary glands are relatively rare and current research suggests separate etiological mechanisms when compared to other head and neck cancers (Boing et al. 2011;

Simard et al. 2014). Laryngeal cancer was the most commonly analysed site in the articles of our review (64% of all analyses), with head and neck cancer as a whole making up 15% and mouth/pharynx and oral cavity each constituting 12% of the analyses (percentages add up to greater than 100% since multiple analyses were carried out for over a third of all included studies).

Social position was most commonly operationalised as an aerial measure of deprivation using sociodemographic variables from census data linked to the geographic residence of the patient. Quartiles or quintiles of this distribution were then used to create a categorical measure ranging from most deprived to most affluent. Of the 23 studies examined, 16 used such an ecological measure while six employed individual-level data and one used both. The most common individual-level indicators were occupational status, education and disposable income.

The overwhelming majority of articles we reviewed (22 out of 23) found a statistically significant association between social position and survival rates for head and neck cancer (Kogevinas et al. 1991; Rosso et al. 1997; Coleman et al. 1999, 2001, 2004; Edwards and Jones 1999; Paterson et al. 2002; Dikshit et al. 2005; Shack et al. 2007; Andersen et al. 2008; Dalton et al. 2008, 2019; Rachet et al. 2008, 2010; Robertson et al. 2010; Ellis et al. 2012; Jansen et al. 2014; Sharp et al. 2014; van Harten et al. 2015; Rylands et al. 2016; Ali et al. 2016; Belot et al. 2018; Ingarfield et al. 2019). For all but two of these studies, this relationship persisted even after adjustment for explanatory covariates (Kogevinas et al. 1991; Rosso et al. 1997; Coleman et al. 1999, 2001, 2004; Edwards and Jones 1999; Paterson et al. 2002; Dikshit et al. 2005; Shack et al. 2007; Andersen et al. 2008; Dalton et al. 2008, 2019; Rachet et al. 2008, 2010; Ellis et al. 2012; Jansen et al. 2014; Sharp et al. 2014; van Harten et al. 2015; Rylands et al. 2016; Ali et al. 2016; Belot et al. 2018). Calculating age- and sex-standardised survival rates as well as relative risk was the most common methodological approach, but there was more variability when it came to the choice of anatomical site(s) or their grouping and the covariates used in the analyses. Because survival from head and neck cancer and its association with social position seems largely driven by such mediating factors, a more extensive description of the potential mechanisms is presented below.

Discussion

The importance of documenting and more fully understanding the role of social position with respect to survival from head and neck cancer is clear from the current state of the literature. However, there are a number of dynamics at play—both methodologically as well as with respect to the aetiology of head and neck cancer—that complicate the narrative about how social position is related to survival from this set of diseases.

Methodologically speaking, the preponderance of studies that have thus far been carried out rely on national cancer registry datasets. These data are generally of very high quality, yet they often lack individual-level social indicators. The research that

has been able to link these data to other high-quality individual-level data sources is largely limited to a small handful of countries. Furthermore, of the 23 studies examined in this review, all examined populations in Western Europe where the incidence and mortality from head and neck cancer are much lower. Additionally, those papers that focused on populations within the United Kingdom and Denmark made use of the same country-specific datasets, thereby further limiting the diversity of samples from which to draw conclusions about social position and survival.

Etiological factors, as well as understudied mechanisms that are potentially associated with both survival and social position, provide many avenues for additional research to more clearly elucidate the ways social status is operating on survival from head and neck cancers. What follows is a brief description of the current research on some of these potential mechanisms discussed in the reviewed articles as well as other relevant literature.

Cancer Characteristics

As previously mentioned, aetiology varies depending upon cancer site, and therefore the risks associated with developing a specific type of head and neck cancer varies from site to site. Many studies focus on head and neck cancers broadly defined but doing so may obfuscate the differential risks of both incidence and survival from a specific malignancy. All but two (Paterson et al. 2002; Dalton et al. 2019) of the studies in our sample that conducted such an analysis also included information on the tumour site as a covariate, but when sample size permits, it may be more informative to run separate analyses to help tease out the most predictive factors and how they may vary between subtypes.

Relatedly, recent research has shown that Human Papilloma Virus (HPV) may be an important risk factor for certain types of head and neck cancers (Fakhry et al. 2008; Evans et al. 2013; Gatta et al. 2015). These tumours have been found to have a better prognosis and are also disproportionately diagnosed in those in higher social positions (O'Rorke et al. 2012). Numerous studies in our review found evidence for improved survivability for HNC as a whole, but widening disparities, indicating that the most, or only, improvement in survival is happening for those at the higher end of the socioeconomic gradient (Coleman et al. 2004; Shack et al. 2007; Rachet et al. 2008). The increasing incidence of HPV-related HNCs may help to explain this phenomenon, given that the disparities in survival are increasing amidst only relatively small increases in incidence. Further work should attempt to include information on HPV status to more fully account for this potential social disparity.

A number of studies have also found that those in a more disadvantaged social position tend to be diagnosed with cancers that are more advanced (Carvalho et al. 2002; Olsen et al. 2015; Auluck et al. 2016; Khalil et al. 2019). Stage at diagnosis is, therefore, an important explanatory mechanism in the association between survival and social status, but studies that account for it still find persistent social

disparities in survival. This suggests that while part of this relationship may be related to delayed access to healthcare or treatment, there are additional mechanisms contributing to the disparities we are witnessing.

Patient Characteristics

The preponderance of head and neck cancer risk has been attributed to tobacco and alcohol (ab)use (Merletti et al. 1989; Zatonski et al. 1991; Zhang et al. 2015). These behaviours have also been linked to worse survival, and there is evidence that they are disproportionately more common among those with a lower social position (Crosignani et al. 1996; Hilgert et al. 2009; Antunes et al. 2013; Eichler et al. 2016). However, similar to stage at diagnosis, some studies that have investigated the specific role of tobacco and alcohol continue to find an association with social position and survival (Sharp et al. 2014; Ali et al. 2016). Additionally, most studies on survival that include covariates related to tobacco and alcohol use a measure of historical usage, which may limit our understanding of how these substances play into survival patterns. Collecting and incorporating data on tobacco and alcohol patterns after diagnosis may also be instructive as there is emerging evidence that these substances may differentially affect both survival from specific subtypes as well as interact with different treatment protocols (Eichler et al. 2016).

Diet and physical activity have also been implicated, though to a lesser degree, in the association between social status and survival from head and neck cancer (Zatonski et al. 1991; Crosignani et al. 1996). Differences between social classes in access to a balanced diet, rich in fresh and nutritious foods, as well as the time and space to engage in regular movement may contribute to the observed social gradient. This is an understudied aspect of this relationship, and more work is needed to draw any firm conclusions.

People from more deprived backgrounds also tend to suffer from a greater number of additional health issues, and therefore accounting for comorbidities is also important for our fuller understanding of head and neck cancer survival. The two studies in our review that found the association between social status and survival attenuated by the addition of a variety of explanatory covariates found that the most predictive of those was the WHO Performance Status which is a 5-point assessment on functional limitations and quality of life (Robertson et al. 2010; Ingarfield et al. 2019). Additionally, Rylands et al. (2016) found that even after adjustments for individual and clinical factors, quality of life with respect to social-emotional functioning was significantly worse for those living in the most deprived areas. More research is needed to ascertain the pathways through which social position may be operating, but given the evidence on the connection between mental and physical health, it seems imperative to include factors associated with other ailments as well as psychological indicators.

Social/Structural Characteristics

Relatedly, the studies that have included marriage or cohabitation as a measure of social position, capturing a degree of social capital in-line with Pierre Bourdieu's articulation of the broader concept of capital, have largely found marriage to be predictive of greater survival (Dalton et al. 2008; Sharp et al. 2014; Ali et al. 2016). The social and emotional support provided by a spouse is an important factor in this relationship, and there is the additional, practical support of assisting a patient in navigating the healthcare system and treatment process. More work is needed in this area to see how a more generally defined concept of social integration and support may modify survival outcomes. This may potentially lead to beneficial policies geared towards strengthening this dimension of social disparity among those diagnosed with head and neck cancer and improve survival for the most marginalised.

Many of the studies included in this review were focused on populations for which universal health care was the standard. Even within this context, there is evidence for disparities in access to and use of medical care, both for initial diagnosis as well as for follow-up care (Teppo et al. 2003; Scott et al. 2008; Teppo and Alho 2008, 2009). The more severe the stage at diagnosis, the lower the survival for HNC, and therefore those who do not receive regular and comprehensive medical care are more likely to go undiagnosed and not receive appropriate treatment (Seoane et al. 2012). Additionally, for those who are diagnosed, the research suggests that the less affluent you are, the longer the time between diagnosis and treatment, further worsening survival prognosis. As Rosso et al. (1997) point out, there were larger survival gaps for cancers for which effective treatment was available. They argue that this suggests there remain non-financial disparities with respect to health care and treatment, and more work should examine the role of structural bias and discrimination within the healthcare system.

Lastly, cancer screening programmes show mixed efficacy for improving early detection and treatment for head and neck cancer (Netuveli et al. 2006; Gourin et al. 2009; Ford and Farah 2013; Petti and Scully 2015; Farquhar et al. 2017). This is largely due to the variability in symptomatology for different subsites of the disease and also a lack of public awareness about known signs of its presentation. It appears that regular dental visits are beneficial for early diagnosis, and therefore better survival outcomes, but access to regular dental care is also associated with social position. Additional research into screening programmes and the role of dental healthcare is therefore needed.

Conclusion

Social disparities in health outcomes are extremely important because they reflect preventable instances of disease and death. There is clear evidence that survival from head and neck cancer is associated with an individual's social status. In the

systematic review we conducted, these findings held even after adjustments for many various social indicators, also implicated in the inequalities we see. Much more work is needed, therefore, to more fully understand the ways social status is operating to disproportionately increase the risk of death from this set of diseases for those at the lower end of the social status spectrum. While there are firmly established risk factors for head and neck cancer, such as tobacco and alcohol consumption, more work should be done on the ways these and other factors directly impact survival. By taking into account these as well as less-studied factors, such as social support, health care and treatment disparities, and the efficacy of screening programmes, we may gain a clearer insight into ways to close the deprivation gap for head and neck survival.

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Chapter 11
Disparities in Cancer Survival in Adults in Europe: The CONCORD Programme

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Introduction

Wide European differences in population-based survival from cancer have been highlighted for decades (Berrino et al. 1995, 1999, 2003; Capocaccia et al. 2009; De Angelis et al. 2014; Coleman et al. 2008; Allemani et al. 2015; Allemani et al. 2018).

The term disparity indicates a difference, especially one connected with unfair treatment. When we think about international differences in cancer survival, we generally focus our attention on disparities in relation to macro-economic indicators such as the gross domestic product (GDP) or total national expenditure on health (TNEH). Socioeconomic inequalities in health outcomes within a given country are generally examined with social class, unemployment or levels of education, but disparities in cancer survival may be geographical or racial (race/ethnicity). They may also reflect differential access to screening or optimal treatment.

Estimates of cancer survival obtained from data provided by population-based cancer registries are a key measure of the overall effectiveness of the health system in managing cancer. In contrast to clinical trials, which aim to achieve the highest possible survival in a group of patients selected by age, stage and lack of comorbidity, survival estimated from real-world data, obtained from population-based cancer registries, reflects the average survival achieved by all cancer patients, and therefore the overall quality of the health system in managing cancer, from early diagnosis to treatment and final outcome (Coleman 2014; Allemani 2017).

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Population-based cancer registries routinely collect a basic data set on each person diagnosed with cancer in a population defined by residence in a country (national coverage) or a defined geographical area such as a province or state (regional coverage). The basic data set includes both patient characteristics (date of birth, sex and place of residence) and tumour characteristics (date of diagnosis; the topography, morphology and behaviour of the tumour, and the basis of diagnosis). Most cancer registries also collect information on each patient's last known vital status (alive, dead, emigrated) and the date of the last known vital status. That information is essential for the estimation of survival.

The CONCORD protocol attempted to collect information on stage at diagnosis and the first course of treatment, on a voluntary basis. Unfortunately, most cancer registries do not yet collect stage at diagnosis or socioeconomic status systematically for every registered patient. Summary measures of socioeconomic status have not always been comparable between countries either. More recently, the European Deprivation Index (EDI) has largely resolved this problem (Guillaume et al. 2016), but this new European index has not yet been sufficiently widely used over a sufficient period of time to enable international comparisons of cancer survival using the EDI as a standardised measure of socioeconomic status.

The CONCORD programme provides the most up-to-date estimates of population-based survival trends world-wide. In this chapter, we will focus on geographical differences in cancer survival in Europe and offer a few examples of differences in the distribution of stage at diagnosis and stage-specific survival, and of survival by GDP and TNEH. We also provide a summary of the availability of data on socioeconomic status in Europe.

The CONCORD programme

The first cycle of the CONCORD programme included data for about two million adult patients (15–99 years) diagnosed during 1990–1994 with a cancer of the breast (women), colon, rectum or prostate, and followed up to 1999. Data were provided by 101 cancer registries in 31 countries, of which 16 with national coverage (Coleman et al. 2008).

The CONCORD programme established world-wide surveillance of trends in cancer survival for the first time in 2015 (CONCORD-2) by analysing data for 25,676,887 patients diagnosed during the 15 years from 1995 to 2009 with one of 10 common adult cancers (stomach, colon, rectum, liver, lung, breast (women), cervix, ovary or prostate, or leukaemia), and for 75,000 children (0–14 years) with acute lymphoblastic leukaemia (Allemani et al. 2015). These cancers represented 63% of the global cancer burden in 2009. Patients were followed up to 31 December 2009. The 279 participating registries covered a total population of 896 million people, in 67 countries that were home to two-thirds (4.8 billion) of the world's population. In 40 countries, the data covered 100% of the national population.

In 2018, the third cycle of the CONCORD programme (CONCORD-3) updated the world-wide surveillance of cancer survival trends to include patients diagnosed

from 2000 to 2014, with follow-up to 31 December 2014 (Allemani et al. 2018). It included data for 18 cancers or groups of cancers that collectively represented 75% of the global cancer burden in 2014: oesophagus, stomach, colon, rectum, liver, pancreas, lung, melanoma of the skin, breast (women), cervix, ovary and prostate in adults (15–99 years), and brain tumours, lymphomas and leukaemias in both adults and children (0–14 years). Trends and international variations in cancer survival were examined. Individual patient records for over 37.5 million cancer patients were included in the analyses. These data were provided by 322 population-based cancer registries in 71 countries and territories, of which 47 provided data with 100% national population coverage.

For some cancers where adequate data were available, survival analyses by stage at diagnosis, morphology and race/ethnicity (selected countries) have been published (Di Carlo et al. 2020; Alawadhi et al. 2019; Bannon et al. 2019; Bailey et al. 2018; OECD/European Union 2020; Weir et al. 2017). Analyses of the availability and timeliness of the first course of treatment are in preparation.

The Organisation for Economic Co-operation and Development (OECD) has included survival estimates from the CONCORD programme for 48 countries in its *Health at a Glance* publications since 2017 (Organisation for Economic Co-operation and Development 2019). This provides formal recognition by an international agency of the global coverage, methodological rigour and international comparability of the CONCORD survival estimates.

In Europe, data for CONCORD-3 were provided by 157 population-based cancer registries in 31 countries, 22 of which provided data with national coverage.

Results

Age-standardised 5-year net survival was highest for melanoma of the skin (European range: 61–94%) and cancers of the prostate (68–94%) and breast (71–89%), followed by cervical cancer (54–80%), lymphoid malignancies (40–74%), and cancers of the colon (45–68%) and rectum (42–68%) (Fig. 11.1a–c). Five-year survival in some countries reached almost 60% for myeloid malignancies in adults, although the range was very wide (23–58%), but less than 50% for cancers of the ovary (28–47%) and brain (21–42%), again with a very wide European range.

Five-year survival was generally much lower for cancers of the stomach (18–38%), oesophagus (5–24%), liver (4–21%), lung (8–20%) and pancreas (4–12%).

Survival varied widely between countries. Four of the five Nordic countries (Finland, Iceland, Norway and Sweden), together with Belgium, Germany and Switzerland, showed the highest age-standardised 5-year net survival for many cancers, while survival was generally lowest among most of the Eastern European countries (Bulgaria, Poland, Romania, Slovakia and the Russian Federation).

In some Southern and Eastern European countries, 5-year survival for liver, pancreas and lung cancer was similar to or higher than in the Northern European countries, although 5-year net survival for these cancers rarely exceeds 20% anywhere. Denmark is closing the survival gap with the other Nordic countries; for patients

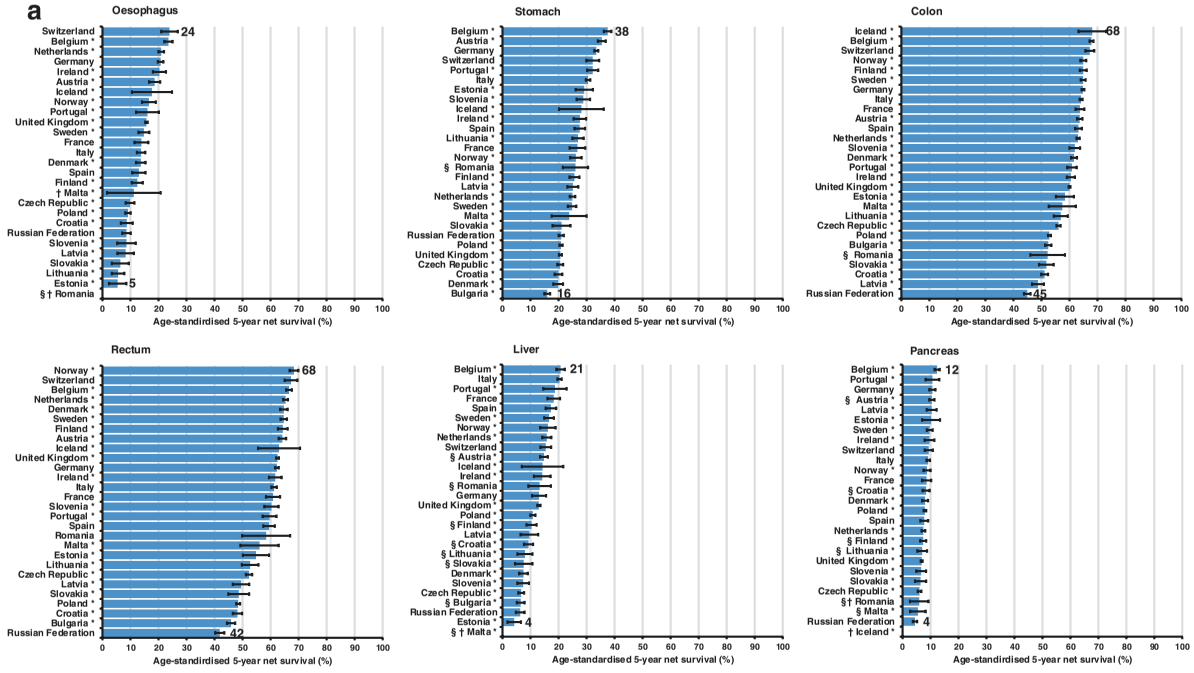

Fig. 11.1 (**a**) Age-standardised 5-year net survival (%) for adults (15–99 years) diagnosed during 2010–2014 in Europe, by country: cancers of the oesophagus, stomach, colon, rectum, liver and pancreas. (Source: Allemani et al. 2018). Footnote: survival estimates are ranked from highest to lowest. Where data were available for more than one registry in a given country, the survival estimates were derived by pooling the data for that country, but excluding data from registries for which the estimates were considered less reliable because 15% or more of patients were (**a**) lost to follow-up or censored alive within 5 years of diagnosis, or if diagnosed in 2010 or later, before 31 December 2014 or (**b**) registered only from a death certificate or at autopsy or (**c**) with incomplete dates (i.e. unknown year of birth, unknown month or year of diagnosis or unknown year of last vital status). Data with 100% coverage of the national population. [§] Estimate flagged as less reliable because the only available estimates were from a registry or registries in this category. [†] Estimate not age-standardised

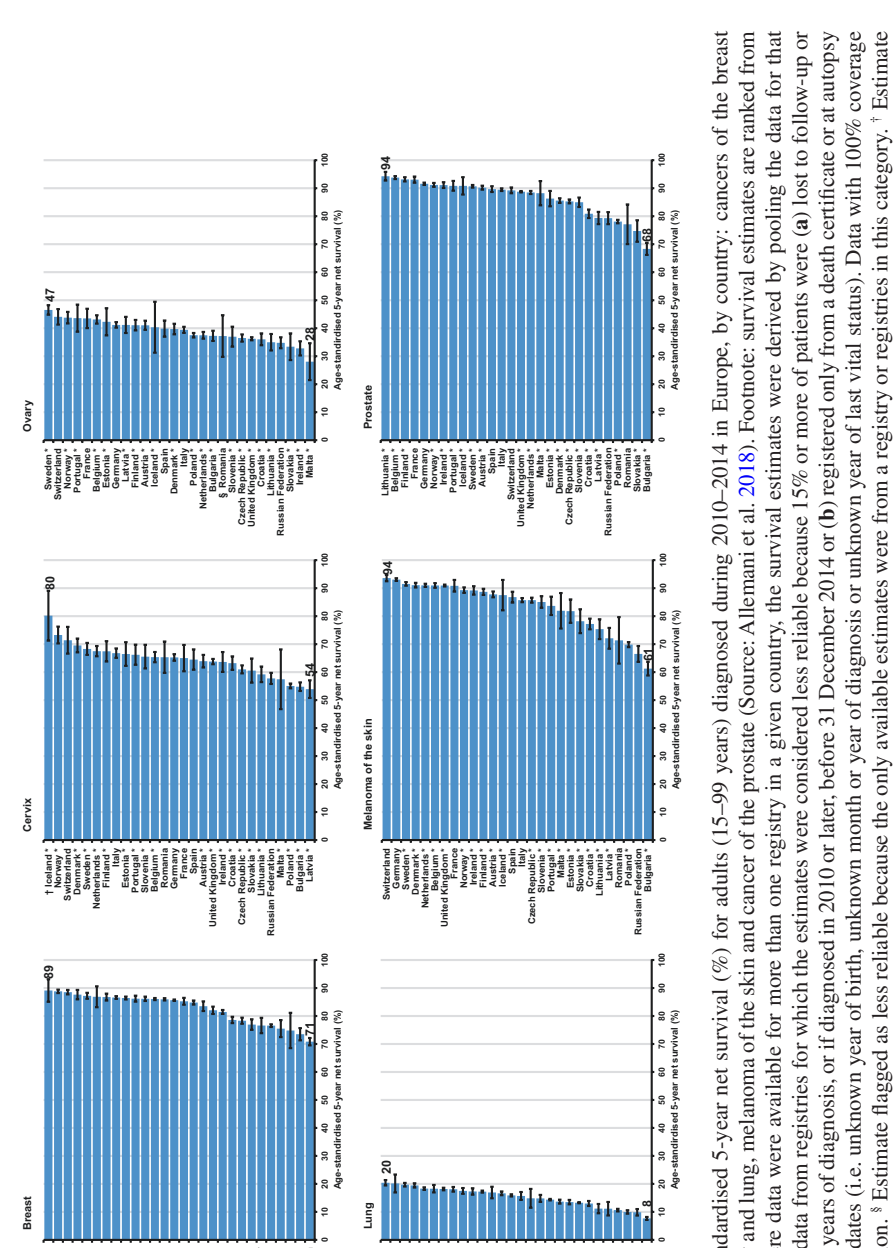

Fig. 11.1 (**b**) Age-standardised 5-year net survival (%) for adults (15–99 years) diagnosed during 2010–2014 in Europe, by country: cancers of the breast (women), cervix, ovary and lung, melanoma of the skin and cancer of the prostate (Source: Allemani et al. 2018). Footnote: survival estimates are ranked from highest to lowest. Where data were available for more than one registry in a given country, the survival estimates were derived by pooling the data for that country, but excluding data from registries for which the estimates were considered less reliable because 15% or more of patients were (**a**) lost to follow-up or censored alive within 5 years of diagnosis, or if diagnosed in 2010 or later, before 31 December 2014 or (**b**) registered only from a death certificate or at autopsy or (**c**) with incomplete dates (i.e. unknown year of birth, unknown month or year of diagnosis or unknown year of last vital status). Data with 100% coverage of the national population. § Estimate flagged as less reliable because the only available estimates were from a registry or registries in this category. † Estimate not age-standardised

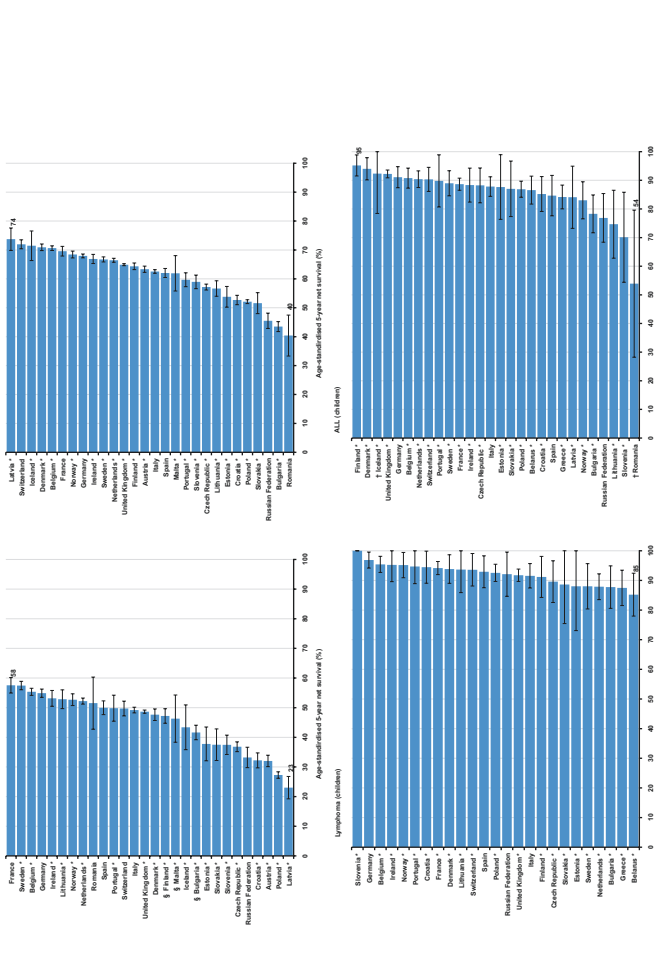

Fig. 11.1 (**c**) Age-standardised 5-year net survival (%) for patients diagnosed during 2010–2014 in Europe, by country: adults (15–99 years) diagnosed with a tumour of the brain, or a myeloid or lymphoid malignancy, and children (0–14 years) diagnosed with a tumour of the brain, or a lymphoma or acute lymphoblastic leukaemia (ALL) (Source: Allemani et al. 2018). Footnote: survival estimates are ranked from highest to lowest. Where data were available for more than one registry in a given country, the survival estimates were derived by pooling the data for that country, but excluding data from registries for which the estimates were considered less reliable because 15% or more of patients were (**a**) lost to follow-up or censored alive within 5 years of diagnosis, or if diagnosed in 2010 or later, before 31 December 2014 or (**b**) registered only from a death certificate or at autopsy or (**c**) with incomplete dates (i.e. unknown year of birth, unknown month or year of diagnosis or unknown year of last vital status). Data with 100% coverage of the national population. [§] Estimate flagged as less reliable because the only available estimates were from a registry or registries in this category. [†] Estimate not age-standardised

diagnosed during 2010–2014, 5-year survival in Denmark was among the highest in Europe for cancers of the rectum, breast, cervix and brain, and for melanoma of the skin and lymphoid malignancies.

In the United Kingdom (UK), survival for cancers of the stomach, pancreas, lung, ovary and brain was similar to that seen in some of the Eastern European countries. Five-year survival was high in the European range only for melanoma of the skin.

International variation in survival was more marked for cancers of the oesophagus, stomach, colon and rectum, and for melanoma of the skin and the lymphoid malignancies, especially for patients diagnosed during 2010–2014 (Figs. 11.1a–c and 11.2a–c).

For many cancers, survival also varies widely within countries (Fig. 11.3a–c), although the variations are less marked for cancers with the best and worst prognosis. For most cancers, regional variation in the countries of Southern and Eastern Europe (France, Italy, Poland, Spain and the Russian Federation) was wider than in countries of Central Europe (Germany and Switzerland) and the UK.

Five-year survival has increased steadily for many cancers between 2000–2004 and 2010–2014, particularly for cancers of the colon and rectum and the lymphoid malignancies (data not shown), but for some of the most common cancers, such as those of the lung, liver, pancreas and oesophagus, age-standardised 5-year net survival remains stubbornly below 20%.

OECD recently included CONCORD estimates of age-standardised 5-year net survival by stage at diagnosis for women diagnosed with breast cancer during 2010–2014 in 21 European countries in *Health at a Glance: Europe 2020* (OECD/European Union 2020) (Fig. 11.4). Across Europe as a whole, approximately 50% of women were diagnosed at an early stage and 10% at an advanced stage. Five-year survival for women diagnosed at an early or localised stage is on average 96.4% in the EU, but survival for women diagnosed at an advanced stage remains much lower, ranging between 35% and 50%.

There is a curvilinear relationship between 5-year net survival for breast cancer and the gross domestic product of each country. The relationship reaches an asymptote around a GDP of US$30,000 to US$35,000 per head of population. Above a certain level of wealth, 5-year survival levels appear to plateau. The relationship between 5-year survival and total national expenditure on health as a proportion of GDP is more linear (Verhoeven et al. 2020).

Other European Studies

Women with breast cancer with a higher socioeconomic position in Sweden have been shown to have a lower risk of death after controlling for tumour characteristics, treatment, comorbidity and lifestyle factors (relative risk [SRR] 0.82; 95% CI 0.70–0.97) (Lundqvist et al. 2016). This study suggests the need to examine further the impact of screening attendance, use of contraceptives, lifestyle and reproductive

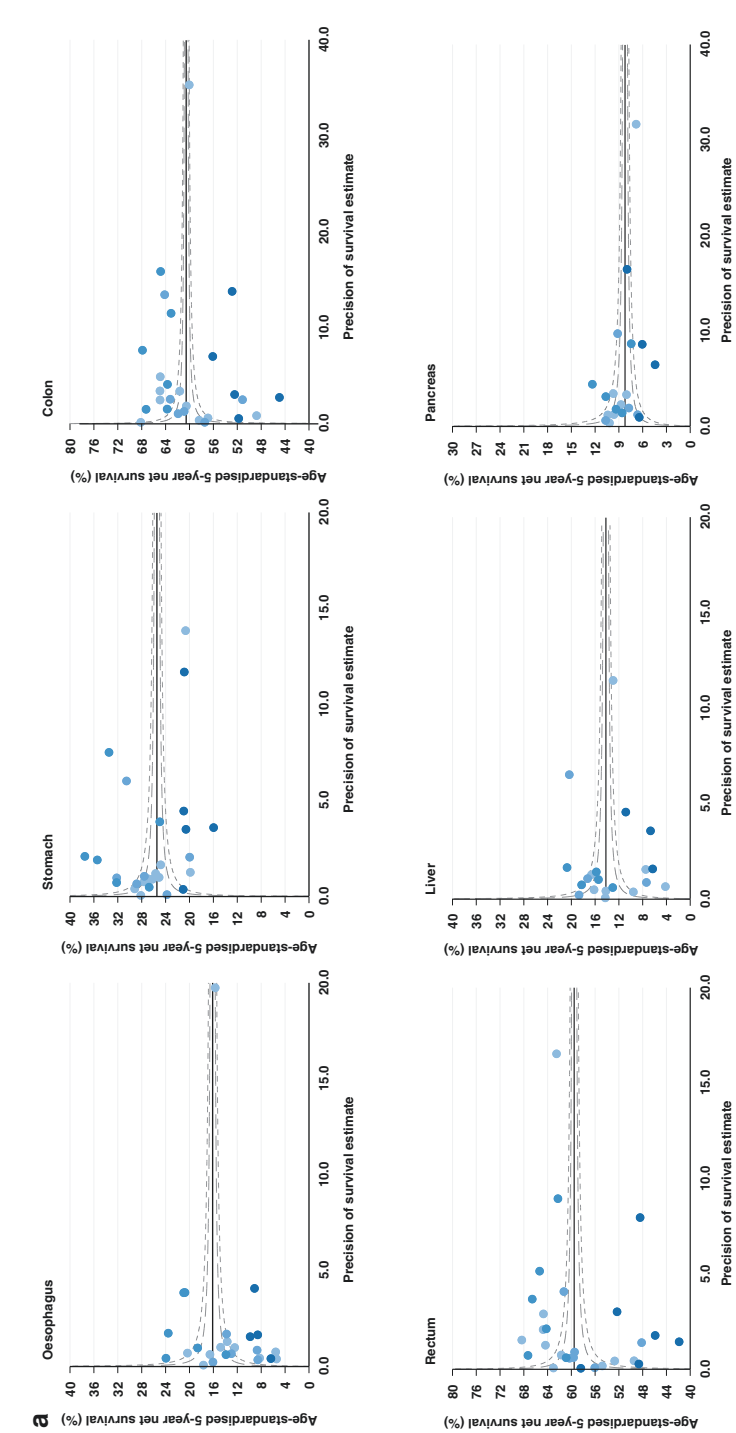

Fig. 11.2 (**a**) International variation in age-standardised 5-year net survival (%) for adults (15–99 years) diagnosed during 2010–2014, by European region: cancers of the oesophagus, stomach, colon, rectum, liver and pancreas (Source: Allemani et al. 2018). Footnote: funnel plot with each national survival estimate plotted against its statistical precision (the inverse of its variance). The target value is the pooled estimate for all participating countries in the same period. Only age-standardised estimates are included. Control limits for 95% and 99.8% are shown. The wider control limits to the left emphasise the increased variability expected between survival estimates that are less statistically precise, while the narrower limits to the right emphasise the reduced variability between more precise estimates (Quaresma et al. 2014)

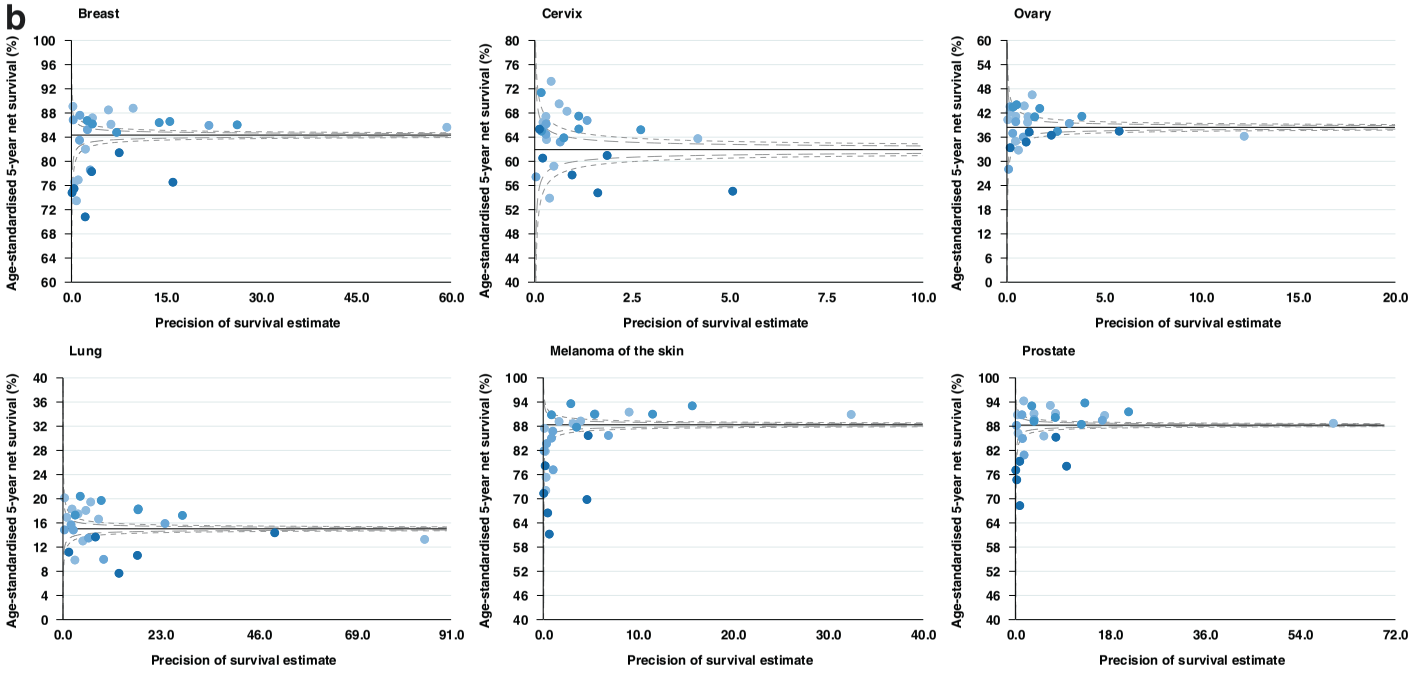

Fig. 11.2 (**b**) International variation in age-standardised 5-year net survival (%) for adults (15–99 years) diagnosed during 2010–2014, by European region: cancers of the breast (women), cervix, ovary and lung, melanoma of the skin and cancer of the prostate (Source: Allemani et al. 2018). Footnote: funnel plot with each national survival estimate plotted against its statistical precision (the inverse of its variance). The target value is the pooled estimate for all participating countries in the same period. Only age-standardised estimates are included. Control limits for 95% and 99.8% are shown. The wider control limits to the left emphasise the increased variability expected between survival estimates that are less statistically precise, while the narrower limits to the right emphasise the reduced variability between more precise estimates (Quaresma et al. 2014)

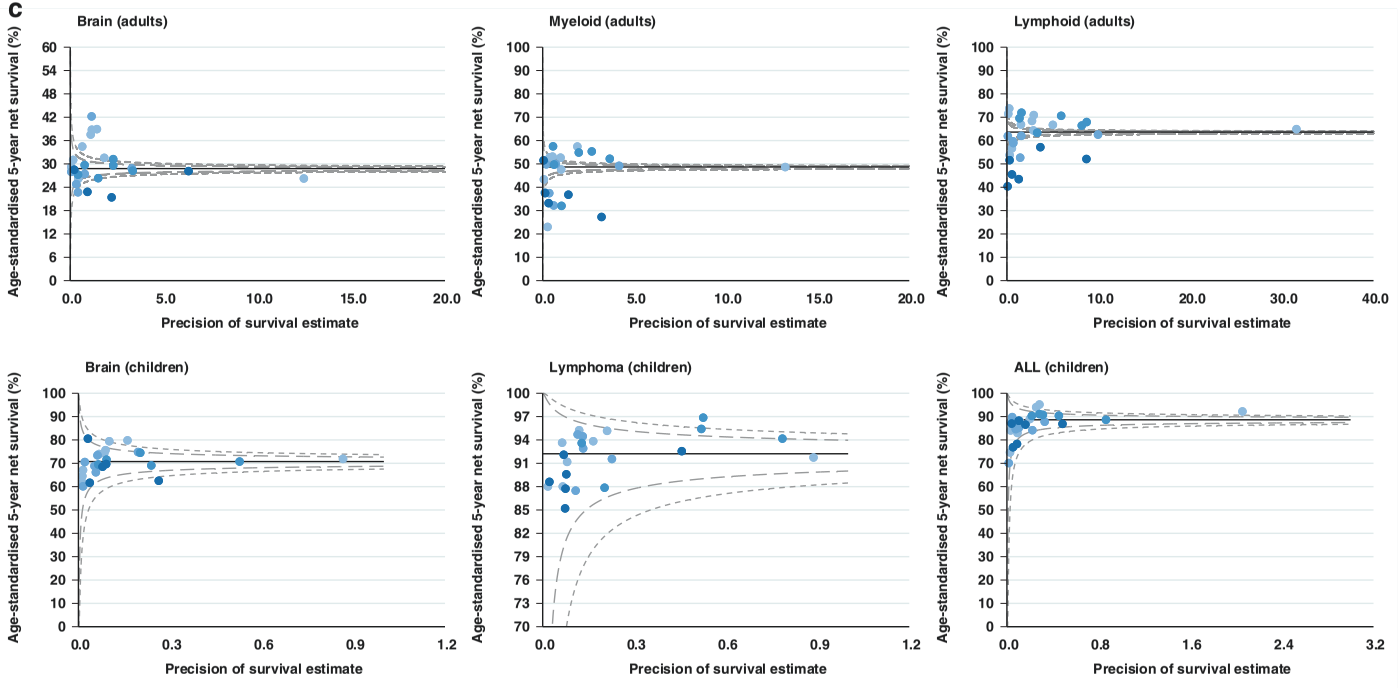

Fig. 11.2 (**c**) International variation in age-standardised 5-year net survival (%) for patients diagnosed during 2010–2014, by European region: adults (15–99 years) diagnosed with a tumour of the brain or a myeloid or lymphoid malignancy, and children (0–14 years) diagnosed with a tumour of the brain or a lymphoma or acute lymphoblastic leukaemia (ALL) (Source: Allemani et al. 2018). Footnote: funnel plot with each national survival estimate plotted against its statistical precision (the inverse of its variance). The target value is the pooled estimate for all participating countries in the same period. Only age-standardised estimates are included. Control limits for 95% and 99.8% are shown. The wider control limits to the left emphasise the increased variability expected between survival estimates that are less statistically precise, while the narrower limits to the right emphasise the reduced variability between more precise estimates (Quaresma et al. 2014)

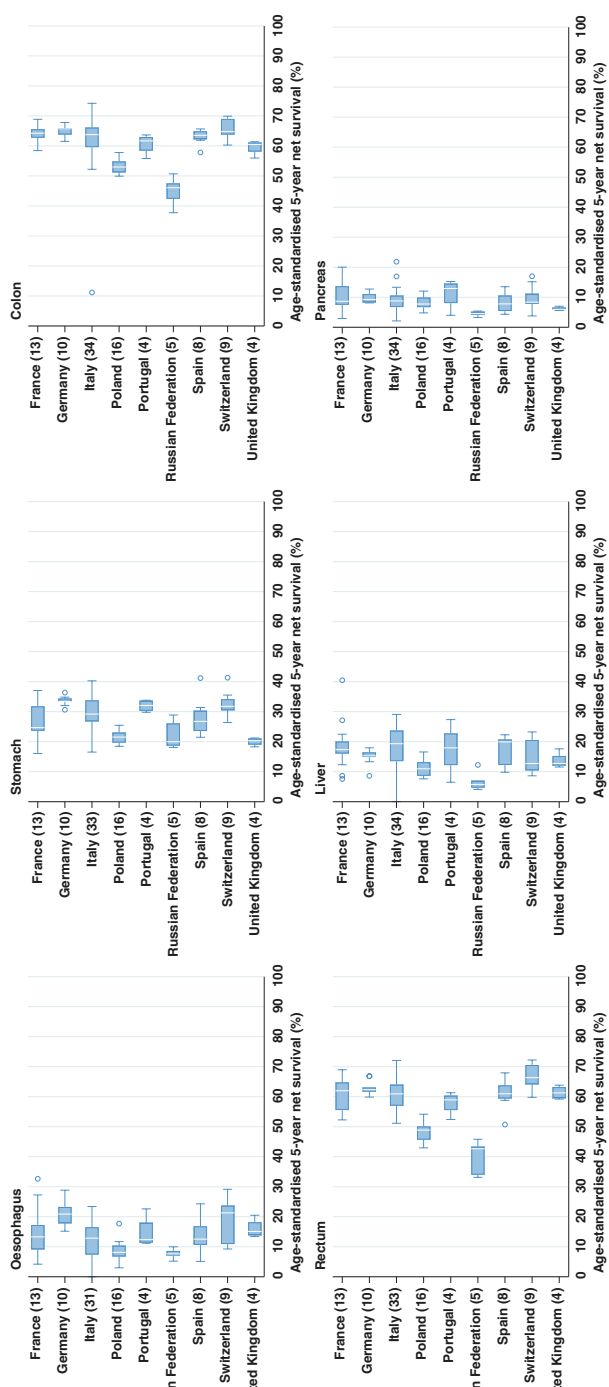

Fig. 11.3 (**a**) Regional variation in age-standardised 5-year net survival (%) in European countries with more than one participating population-based cancer registry: adults (15–99 years) diagnosed during 2010–2014 with a cancer of the oesophagus, stomach, colon, rectum, liver or pancreas (Source: Allemani et al. 2018). Footnote: Each box-plot shows the range of survival estimates among all cancer registries for which suitable estimates were obtained in each country. Survival estimates considered less reliable are not included. The vertical line inside each box represents the median survival estimate among all contributing registries (the central value in the range, or 50th centile). The box covers the interquartile range (IQR) between the lower and upper quartiles (25th and 75th centiles). Where there are only a few widely scattered estimates, the median may be close to the lower or upper quartile. The extreme limits of the box-plot are 1.5*IQR below the lower quartile and 1.5*IQR above the upper quartile. Open circles indicate 'outlier' values, outside this range

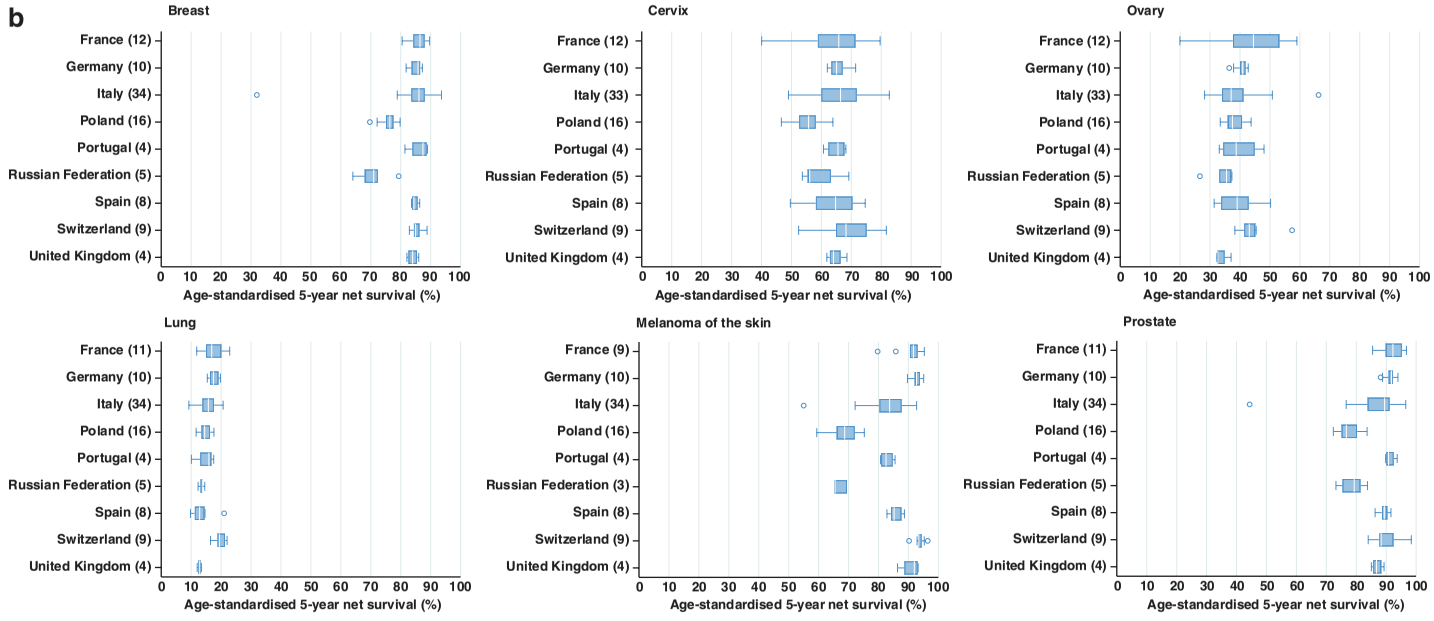

Fig. 11.3 (**b**) Regional variation in age-standardised 5-year net survival (%) in European countries with more than one participating population-based cancer registry: adults (15–99 years) diagnosed during 2010–2014 with a cancer of the breast (women), cervix, ovary or lung, melanoma of the skin or cancer of the prostate (Source: Allemani et al. 2018). Footnote: Each box-plot shows the range of survival estimates among all cancer registries for which suitable estimates were obtained in each country. Survival estimates considered less reliable are not included. The vertical line inside each box represents the median survival estimate among all contributing registries (the central value in the range, or 50th centile). The box covers the interquartile range (IQR) between the lower and upper quartiles (25th and 75th centiles). Where there are only a few widely scattered estimates, the median may be close to the lower or upper quartile. The extreme limits of the box-plot are 1.5*IQR below the lower quartile and 1.5*IQR above the upper quartile. Open circles indicate 'outlier' values, outside this range

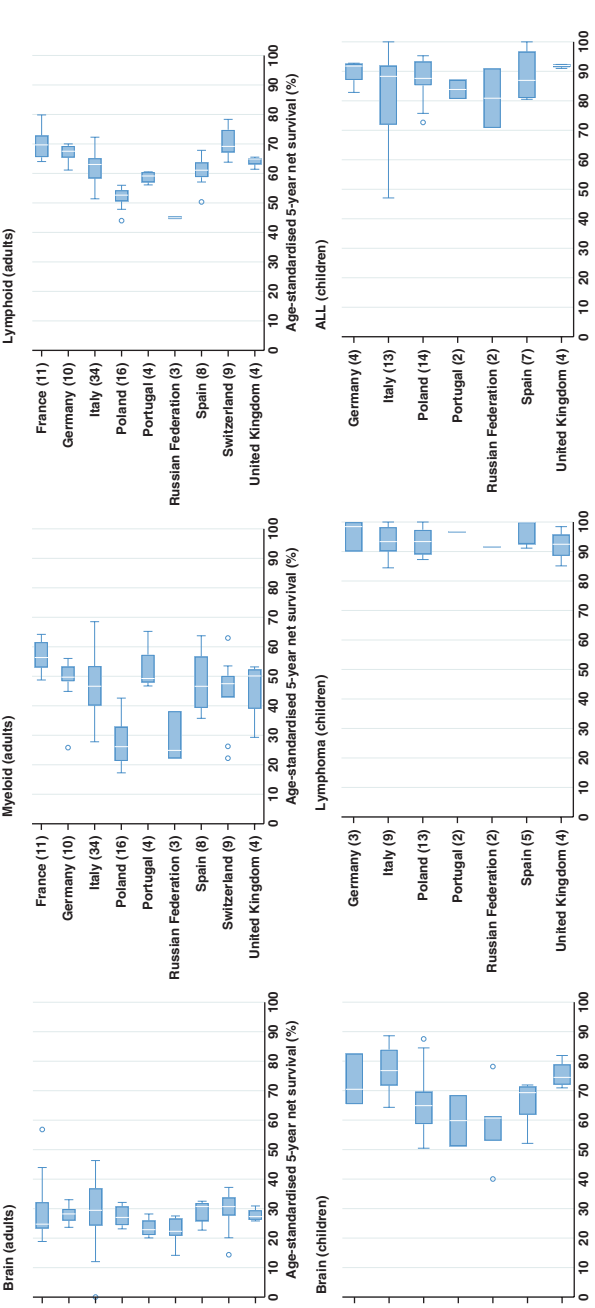

Fig. 11.3 (**c**) Regional variation in age-standardised 5-year net survival (%) in European countries with more than one participating population-based cancer registry: adults (15–99 years) diagnosed with a tumour of the brain, or myeloid or lymphoid malignancy, and children (0–14 years) diagnosed with a tumour of the brain, or lymphoma or acute lymphoblastic leukaemia (ALL) (Source: Allemani et al. 2018). Footnote: Each box-plot shows the range of survival estimates among all cancer registries for which suitable estimates were obtained in each country. Survival estimates considered less reliable are not included. The vertical line inside each box represents the median survival estimate among all contributing registries (the central value in the range, or 50th centile). The box covers the inter-quartile range (IQR) between the lower and upper quartiles (25th and 75th centiles). Where there are only a few widely scattered estimates, the median may be close to the lower or upper quartile. The extreme limits of the box-plot are 1.5*IQR below the lower quartile and 1.5*IQR above the upper quartile. Open circles indicate 'outlier' values, outside this range

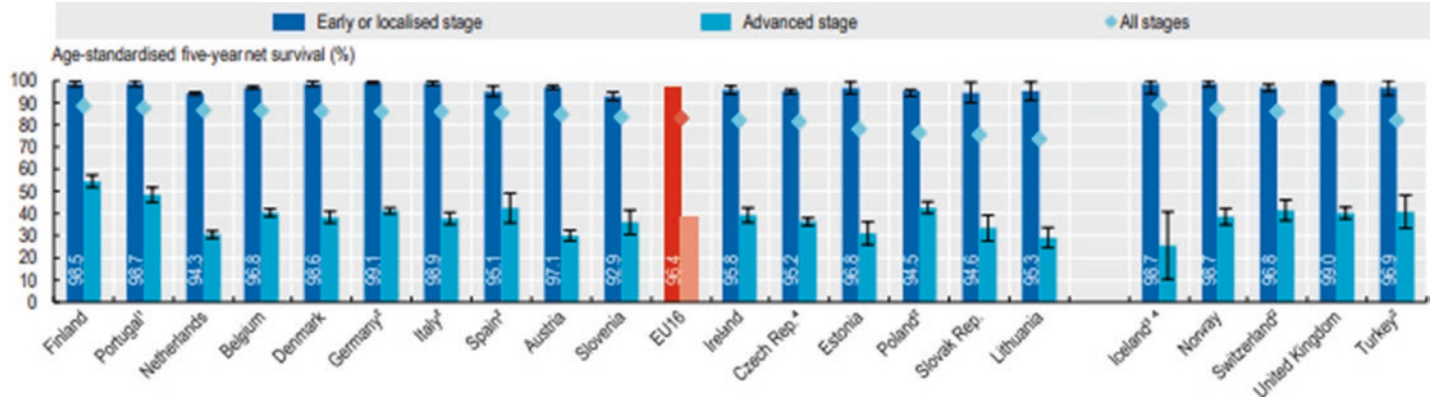

Fig. 11.4 Age-standardised 5-year net survival (%) for breast cancer, by stage at diagnosis: Europe, women diagnosed during 2010–2014. Footnote: Stage was categorised according to the seventh edition of the Tumour, Nodes, Metastasis (TNM) staging system (Sobin et al. 2009). Early or localised stage refers to tumours without lymph node involvement or metastasis (T1–3, N0, M0); 'advanced stage' to large tumours with ulceration or involvement of the chest wall, or those that had metastasised to other organs (T4, any N, M0 or M1). The EU average is unweighted. 1. Coverage is less than 100% of the national population for stage-specific survival estimates. 2. Coverage is less than 100% of the national population. 3. Survival estimates for advanced stage are not age-standardised. 4. Data for 2004–2009. Source: CONCORD programme, London School of Hygiene and Tropical Medicine. Reproduced with permission from OECD: Fig. 6.21 in (OECD/European Union 2020)

variables. Similar inequalities have been shown in England after screen-detection and the timeliness and appropriateness of treatment were taken into account (Woods et al. 2016).

A pooled analysis of 18 case-control studies has shown that women with a lower level of education who were diagnosed with ovarian cancer had more advanced disease than those with a higher level of education, after adjusting for age and race/ethnicity (odds ratio [OR] 1.15; 95% CI 1.03–1.28) (Praestegaard et al. 2016).

Similar results have been found for lung cancer, with patients from a lower socioeconomic position slightly more likely to present with later-stage disease (OR 0.92, 0.84–0.99) (Dalton et al. 2011). The more deprived patients were much less likely to receive lung cancer surgery (OR 0.61; 0.56–0.66) or chemotherapy (OR 0.80; 0.68–0.95), although no difference was seen for receipt of radiotherapy (OR 1.07; 0.87–1.32) (Forrest et al. 2013).

A recent systematic review has shown that patients with a lower socioeconomic position tend to have lower survival from colon and rectal cancers (Manser and Bauerfeind 2014). This may be due to lower compliance with screening programmes and a more advanced stage at diagnosis. Differences in access to care, compliance with treatment and the quality of treatment may also play a role. Another systematic review, carried out before the introduction of screening in the Netherlands, showed that colorectal cancer patients with a low socioeconomic position are generally less likely to receive adjuvant or neo-adjuvant treatment (Aarts et al. 2010).

A regional population-based study in England has suggested that elimination of the differences in survival from melanoma of the skin between socioeconomic groups and between men and women could reduce deaths within 5 years of diagnosis by approximately 11% (215 deaths a year) on a national scale (Rutherford et al. 2015).

Discussion

Government policy may be designed to minimise the impact of socioeconomic position on disease outcomes in several ways: first, by acting to reduce social inequality per se; then by reducing exposure to risk factors that may also be prognostic factors, such as smoking or obesity; and finally by developing policy to ensure that socioeconomic position does not influence referral for diagnosis or access to optimal treatment.

For example, socioeconomic inequalities in cancer survival in the UK were first identified 40 years ago (Silman and Evans 1981). Twenty-year trends in those socioeconomic inequalities have been documented (Coleman et al. 1999). The UK subsequently developed several strategies designed to reduce these inequalities in cancer survival (Expert Advisory Group on Cancer 1995; Department of Health 2000, 2007, 2011). Despite substantial investment in health personnel and equipment in the early 2000s, the impact of these strategies on socioeconomic inequalities in cancer survival has been disappointing (Exarchakou et al. 2018a, b; Fowler et al. 2017; Ellis et al. 2012; Rachet et al. 2010; All-Party Parliamentary Group on Breast Cancer 2010; National Cancer Intelligence Network 2010; Department of Health 2008).

As the former Chief Medical Officer of the American Cancer Society has put it: 'Equal treatment yields equal outcome among equal patients, but there is no equal treatment' (Brawley 2006). He was referring to the wide and persistent differences in lung cancer survival between blacks and whites in the United States (US), where race and ethnicity are often seen as partial surrogates for socioeconomic status, especially in access to health insurance and health care. The Veterans Health Administration, a federal system that provides health care for US military personnel and their families, has also shown that patients who receive the same treatment obtain similar outcomes, regardless of race or socioeconomic status (Akerley et al. 1993).

In the UK, extended follow-up of patients recruited to large, well-conducted, randomised controlled trials of treatment for colorectal and testicular cancers, in which there was no difference in outcome between the various arms of the trials, did not show the socioeconomic inequalities in survival seen in population-based studies that include all patients (Nur et al. 2008, 2012). These studies also suggest that, as in the US, the persistent socioeconomic inequalities in cancer survival must somehow be related to differential access to optimal treatment, whether that arises from patient delay in seeking health care, medical delay in referral, or differential navigation or access to treatment within the healthcare system (Lyratzopoulos et al. 2003, 2012, 2013, 2014).

One of the main limitations of the studies analysing socioeconomic differences is that they use various measures of socioeconomic position, often categorised differently. Education, disposable income, occupation, housing tenure and place of residence are only some of the indicators found in the literature.

A recent world-wide survey of population-based cancer registries, carried out as part of the VENUSCANCER project, funded by the European Research Council, has shown that each population-based cancer registry in Europe holds different types of socioeconomic data. In Eastern European countries, these data are not available at all, whereas in the Nordic countries, France and Slovenia, several variables are available on the socioeconomic position of all registered patients (Fig. 11.5). In Poland, data on education level are available in 3 of the 5 registries that responded.

A standardised measure to compare social inequalities in health between countries with different economies, social structures and healthcare systems is now available (Guillaume et al. 2016). The European Deprivation Index is a weighted combination of aggregated variables from each national census that are most highly correlated with a country-specific individual deprivation indicator. The EDI is now available in France, Italy, Portugal, Spain, Slovenia and England (Guillaume et al. 2016; Ribeiro et al. 2017; Zadnik et al. 2018). When it is more widely used, this new index will help overcome the absence or incomplete collection of comparable socioeconomic data for each person in routine health databases, including cancer registries.

Conclusions

Further investigation of the patient and healthcare system factors that contribute to socioeconomic inequalities in survival is needed to help develop policies and other interventions that ensure equitable access to appropriate investigation and treatment.

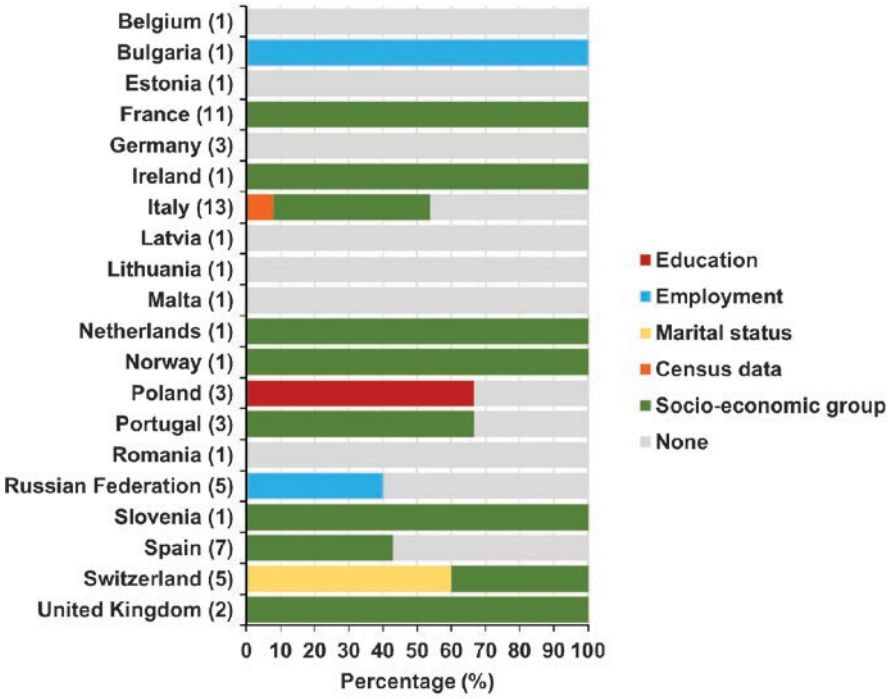

Fig. 11.5 Availability of socioeconomic data (%) in population-based cancer registries in 2019: Europe. Footnote: The number of registries replying to the survey in each country is shown in parentheses (see text). (VENUSCANCER project 2017)

The VENUSCANCER questionnaire has shown that population-based data on the socioeconomic status of patients with cancer are not yet available in many European countries, or in many other countries world-wide. More widespread and systematic collection of the data required to generate the European Deprivation Index in cancer registries in Europe would help to standardise the collection of socioeconomic information in countries where this kind of research is currently difficult or impossible.

The European Network of Cancer Registries could consider championing the idea that population-based cancer registries should systematically collect indicators of socioeconomic position for all registered patients.

Real-world, observational studies of cancer survival, using population-based data on stage at diagnosis, treatment, lifestyle and socioeconomic status, are essential if we are to quantify the extent to which differences in these factors explain the wide international variations in survival.

It is crucial for governments to recognise that population-based cancer registries are key policy instruments that can be used to evaluate both the impact of cancer prevention strategies and the effectiveness of the national health system in managing all patients who are diagnosed with cancer, regardless of their socioeconomic status.

Acknowledgements The authors would like to thank all staff members of the cancer registries participating in the CONCORD programme. Without their assiduous work, population-based research would not be possible.

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Part III
Social Disparities in Cancer Incidence and Survival — Mechanisms

Chapter 12
Overview of Main Mechanisms Involved in Social Disparities in Cancer Incidence and Prognosis

Guy Launoy, Michel P. Coleman, and Vesna Zadnik

The numerous studies on which the chapters of this book are based testify to the now widely documented reality of the link between the social environment and the incidence and lethality of cancers. As for any health event linked to the social environment, the explanatory mechanisms are complex and involve, on the one hand, proximal factors whose direct causality can be easily demonstrated, and on the other, more distal factors whose connection is more difficult to demonstrate but which in fact are its initial cause. These proximal and distal factors form the basis of a reference model on health determinants: the Dahlgren and Whitehead model (1991) (Fig. 12.1).

In this model, the proximal factors are those whose direct link with the health event can easily be demonstrated by epidemiological approaches and which correspond to individual socio-demographic (sex, age) and socioeconomic (professional activity, income, level of education) characteristics, lifestyle habits and behaviour (diet, tobacco, alcohol, sedentary lifestyle). The second group of factors are those that pertain less to the individual per se but take into account rather the family, social and community networks that determine their life in terms of family, school, neighbourhood, village, workplace, etc. These factors are subsumed by the individual's social, economic and cultural background. The social relationships that they maintain in each of these communities influence their beliefs, attitudes, behaviour and lifestyle. The third level is an intermediate level that encompasses the way in which the political framework and values of society regulate access to work,

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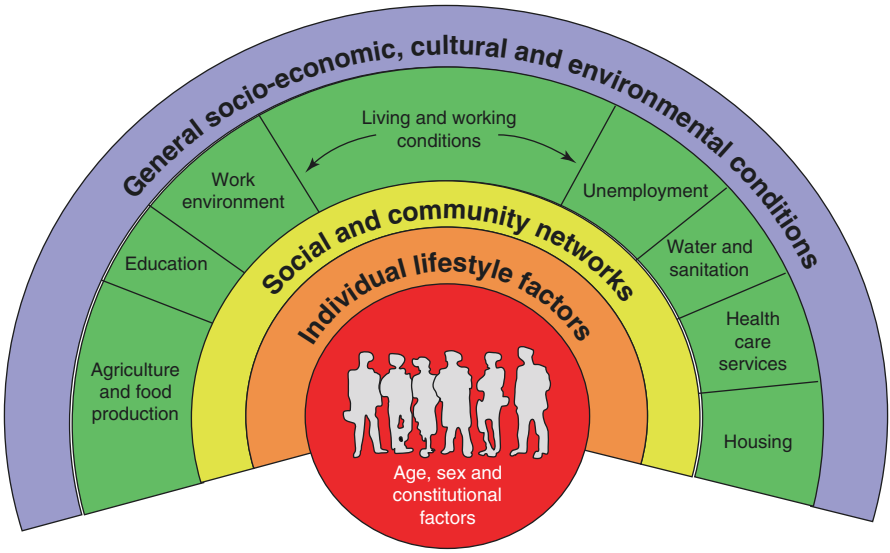

Fig. 12.1 The Dahlgren and Whitehead model (1991). (Reprinted with permission from Dahlgren and Whitehead (1991))

access to essential services and to facilities such as water, housing, health services, food, education and working conditions. Its determinants include the main systems administered by the public authorities at a national or local level: the education and childcare systems, the health and social services system, land-use planning, employment support, social solidarity programmes and other systems and schemes. Finally, the fourth level comprises the social, economic, cultural and environmental conditions in a given society, which are considered as an expression of its norms and values. Of course, these general conditions, or distal determinants, have an impact on all the other levels. In the field of cancer, they have a major impact at all stages, including prevention, screening, treatment, follow-up and social reintegration.

Two conceptual frameworks that complement this general model are particularly relevant for probing a chronic, multifactorial disease such as cancer. The life course hypothesis emphasises the role of physical and social exposures during gestation, childhood, adolescence and young adulthood in the development of diseases occurring during adult life. A new field of knowledge is taking form concerning the biological, behavioural and psychosocial processes that intervene during life and across generations to support such a hypothesis. Chapter 16 (Delpierre and Kelly-Irving) is devoted to this hypothesis. The second concept concerns the notion of 'allostatic load' (Gruenewald et al. 2012; Seeman et al. 2014). An individual's load is greater when they have little financial, social or cultural capital, and is repeatedly, even daily, placed in conditions of material, financial or cultural difficulty to meet all their needs: eating, growing crops, travelling, having a warm, comfortable, pleasant home, ensuring the future of their children, etc. This permanent state of demand ('social stress') overstretches their ability to adapt, particularly the psychological

adaptability (coping) needed to ensure the necessary balance in life. When external demand exceeds an individual's capacity to adapt, the mobilisation of mechanisms to maintain the balance can become deleterious. Indeed, a growing number of authors consider that socioeconomic disadvantage 'gets under one's skin' (Goldberg et al. 2002; Krieger 2005). These stress defence mechanisms mobilised in response to psychosocial stress, such as lasting exposure to social deprivation, are the same as those needed to cope with infectious or physical stress. Research in neuropsychology has shown that four major physiological systems are mobilised in response to stress: the central nervous system, the autonomic nervous system, the immune system and the endocrine system, particularly on the hypothalamic–pituitary–cortical–adrenal axis. The latter is involved in the release of corticotropin-releasing hormone (CRH), which is transported to the pituitary gland by the hypothalamic–pituitary system. Because CRH levels are closely correlated to many physiological effects, an allostatic load score based on the collection of approximately 20 physiological parameters has been proposed (Robertson et al. 2015; Levine et al. 2016). Several publications have confirmed the relevance of this score by highlighting its correlation with an unfavourable socioeconomic environment in cohorts of several thousand people and its association with health indicators such as overall mortality (Seeman et al. 2004, Gruenewald et al. 2012). Results validating this hypothesis are still sparse concerning cancer, and the cellular and molecular mechanisms subtending it remain to be identified (Leung and Sharp 2010; Cole et al. 2015).

Methodologically speaking, the statistical methods usually used for causality analysis, particularly in observational studies, deal relatively well with multifactoriality and confounding but have difficulty in taking the notion of mediation and causal pathways into account. For this reason, more and more epidemiologists are turning to new methods of causal analysis. Graphical representation approaches allow heuristic views of the hypothesis on causal relationships between proximal and distal factors and health events. In the case of multifactorial events, directed acyclic graphs are used to identify possible confounding sources. Path analysis and structural equation models may be used to quantify direct and life course epidemiology (Dumas et al. 2014).

The application of this general model enriched with these concepts and new analytical methods is all the more useful in understanding the mechanisms underlying social inequalities in cancerology if we consider the risk of getting cancer (measured by incidence) and the risk of dying from it (measured by lethality/survival) in a differentiated manner. Indeed, the social determination of the risk of getting or dying from cancer is expressed in quite different ways in terms of both outcomes and mechanisms. As documented in the following chapters of this book, the social determination of the risk of having cancer varies greatly in its intensity and nature according to cancer location, some cancers being more frequent in the most disadvantaged (lung, head and neck) and others being more frequent in the most advantaged (ovary, melanoma and prostate), whereas the social determination of the risk of dying from cancer is clear: whatever the location, the poorest always have the worst survival. Even if the magnitude of the social gradient of survival may vary from one location to another, no study has even found that, for a given location,

survival is better for the most underprivileged in society. Finally, the impact of social inequalities on the incidence of cancer and on survival varies greatly from one location to another. In a recent study based on data from the FRANCIM network of French cancer registries, Bryère et al. (2019) identified three different patterns. The first comprises cancer sites with higher incidence and lethality among the deprived and for which social inequalities in mortality are mainly due to social inequalities in incidence. This mainly concerns tobacco-related cancers and both tobacco- and alcohol-related cancers such as head and neck, lung and digestive cancers such as oesophageal and stomach cancer in both sexes and liver cancer in females. This group consists mainly of men. From a public health point of view, the major contribution of excess death in the deprived in this group is due to the excess incidence of lung cancer and head and neck cancer in men. The second pattern includes cancer sites where the contribution of the excess incidence and the excess lethality are comparable. This concerns the bladder in both sexes, the liver in males, and the lip–mouth–pharynx and cervix in females. The third pattern, i.e. reduced incidence and excess lethality in the deprived, concerns breast cancer and colorectal cancer, for which screening is organised throughout Europe, and prostate cancer, for which screening is widespread in some countries as France despite the lack of evidence of its benefit. For these cancer sites, both the reduced incidence and the excess lethality can be partly explained by the lower participation in screening among the deprived reported in numerous papers. In summary, social inequalities are major for preventable or detectable screenable cancers, and most of the excess mortality is due to the excess incidence of tobacco-dependent cancers and the excess lethality of screenable cancers.

Regarding incidence, the following chapters of this book show that the main proximal factors are behavioural, occupational and environmental. Bryère et al. (Chap. 13) underline how many studies have demonstrated the social gradient in tobacco consumption, body mass index, physical activity, and fruit and vegetable consumption. These behaviours are particularly important in the most lethal and socially differentiated forms of cancer, i.e. lung and upper aerodigestive tract cancer. Menvielle et al. (Chap. 14) describe how the contribution of occupational exposures is more difficult to establish, often for methodological reasons. In men, it appears to contribute as much as tobacco, while too few studies have been conducted in women to draw conclusions. Occupational exposure is typically a proximal factor in the social differentiation of incidence, the magnitude of which depends directly on less proximal factors, such as the measures taken by employers to protect workers and the legal requirements to which they must adhere. Finally, Ribeiro et al. (Chap. 15) draw attention to the fact that many environmental exposures such as air pollution and water contamination are also socially determined. Again, the impact of the social determination of these proximal risk factors depends directly on the regulations in force.

Our understanding of the social determination of incidence is lacking the most in cancers whose incidence is highest in the most advantaged social groups. Screening is more frequent in these groups, and thus the inevitable over-diagnosis associated

with it probably explains part of the over-incidence observed for prostate cancer and, to a lesser extent, breast cancer. As discussed in several chapters of this book, the proximal determinants should not be investigated individually but should be seen as the most proximal mediators of the causal chains linking social determinants together. For example, while lack of financial resources is not a direct risk factor for cancer, it may prevent people from having a healthy diet rich in fruit and vegetables, i.e. a protective factor against the risk of cancer. Similarly, having received fewer years of schooling reduces the likelihood of having knowledge of the biological or physiological mechanisms that would allow one to correctly understand the benefits of prevention or to correctly interpret the initial symptoms of the disease. Another example is unemployment: it does not directly cause cancer but may trigger anxiety, which in turn can lead to smoking. Furthermore, its effect on cancer incidence will differ from country to country according to the way in which the social protection system manages this risk.

Regarding survival, the mechanisms that require further research are certainly related more to the organisation of care than regarding the incidence of cancer. Precise analysis of the medical history of cancers, how they are discovered and how they are treated is very useful because it makes it possible to identify the tipping points, those crucial moments in the history of the disease that lead to the greatest social inequalities. As Grosclaude and Zadnik (Chap. 2) clearly show, data from cancer registries are highly contributive in this field, as in many others, because they are reliable, accurate and above all representative of the whole population and its social diversity. Numerous studies have shown that, all clinical parameters being equal, curative treatments are less often proposed or less often administered in disadvantaged patients, whether surgical, medical or radiological in nature. Treatments that require frequent round trips to and from hospital do not have the same chance of success in all social groups. Care pathways are also determined by the patient's social environment. Many studies have found that attendance at consultations in specialised centres is directly dependent on the proximity of the patient's home. A constant finding is the diversity of the ways in which social inequalities are created throughout the patient's care pathway, from the diagnosis of cancer to the conditions for their reintegration. However, given the fundamental prognostic value of the spread of the disease at the moment it is discovered, the circumstances of its discovery and whether it was revealed or not by screening play a very important role in the social gradient of the survival of cancer patients. Guillaume (Chap. 17) clearly shows how numerous studies document social inequalities in participation in breast or colon–rectum cancer screening in the various European countries, and how its organisation does not guarantee on its own that screening reduces social inequalities, and how it can sometimes even aggravate it if the organisation is not designed from the outset to reduce social inequalities.

In their expression, evaluation and mechanisms, social inequalities are inseparable from territorial inequalities in cancer survival. Independently of the social composition of neighbourhoods and municipalities, the geographical distance (network distance) to the supply of care has been found by many authors to be an

independent prognostic factor, a finding not limited just to cancer. As Dejardin shows (Chap. 19), the impact on health status of the distance one lives and works from care resources is highly dependent on the way in which care is organised in the country concerned.

Among the socially determined prognostic factors, comorbidities play a special role. As Fowler demonstrates (Chap. 18), their existence complicates the interpretation of results. Indeed, without the availability of socially stratified overall mortality data tables, it is very difficult to know whether the observed social gradient in survival—even when net survival modelisation is used—is due or not to the socially differentiated management of patients or to comorbidities that are also socially determined.

Finally, although the underlying mechanisms concerning the modalities of care have received the most attention for explaining social gradient in survival, a few authors have explored the allostatic load hypothesis, suggesting the direct prognostic effect of a stressful social environment. As for incidence, the demonstration of the cellular and biological mechanisms of this hypothesis is a major issue in understanding the social inequalities in the survival of cancer patients (Vineis et al. 2020).

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Chapter 13
Behavioural Factors in the Social Gradients in Cancer Incidence

Joséphine Bryère and Gwenn Menvielle

Large social disparities have been observed in cancer incidence (Chap. 5), the relationship between socioeconomic position and the risk of developing cancer being not necessarily unidirectional. For most of the cancer sites, the risk is higher among the most deprived (head and neck, lung, oesophagus, cervix, liver, stomach), while for some, cancer is more frequent in the least deprived (breast, prostate, skin).

Cancer is a multifactorial disease. The risk factors could be behavioural, environmental or genetic, according to the International Agency for Research on Cancer (IARC) monographs that identify factors that can increase the risk of human cancers (Pearce et al. 2015). They classify the potential risk factors into four categories ranging from carcinogenic to humans (group 1) to probably not carcinogenic to humans (group 4). The level of evidence for carcinogenicity is considered high if the risk factors are classified in group 1 or in group 2A by IARC. Group 1 consists of factors for which there is convincing evidence that the agent causes cancer, with epidemiological studies showing the development of cancer in exposed humans. Group 2 consists of factors for which there is limited evidence that the agent causes cancer in humans and sufficient evidence that the agent causes cancer in animals. For nutritional risk factors, the classification comes from the World Cancer Research Fund (WCRF), which classifies the risk factors into the following groups: 'convincing', 'probable', 'limited-suggestive', 'substantial effect on risk unlikely' and 'limited – no conclusion' (WCRF and AICR 2007).

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Based on these classifications, in 2019, the following behavioural risk factors for cancer were classified as carcinogenic (group 1 or 2A for IARC, 'convincing', 'probable' and 'limited-suggestive' for WCRF): tobacco smoking, overweight and obesity, poor diet (a deficit in intake of fruit and vegetables, red and processed meat, deficit in intake of dietary fibre), alcohol consumption, infections, sedentary behaviour (insufficient physical activity), postmenopausal hormone use and insufficient breastfeeding (Pearce et al. 2015; WCRF and AICR 2007).

Most of these behavioural factors are known to be socially stratified, meaning that they are distributed differentially according to the social position of individuals, which makes these factors real potential candidates for explaining the strong social inequalities in the incidence of cancers.

In this chapter, we will address the issue of the contribution of behavioural factors in the social gradient for cancer. We will first list the set of socially determined behaviours that constitute known risk factors for cancers and then explore the contribution of the different behavioural risk factors to the social gradient in cancer incidence.

Behavioural Factors Associated with Cancer Incidence

In 2014, it was estimated that 42% of all incident cancer cases in adults aged 30 years and older in the United States were attributable to behavioural factors (Islami et al. 2018). Because these factors are mostly modifiable and their impact on cancer is major, they represent a real potential for reducing the burden of cancer in Europe and worldwide.

Tobacco smoking is a well-known risk factor for many cancers. Since 1986, studies established the causal association between cigarette smoking and cancer of the lung, oral cavity, pharynx, oesophagus, pancreas, urinary bladder and renal pelvis and more recently for cancer of the nasal cavities and paranasal sinuses, nasopharynx, stomach, liver, kidney, uterine cervix and myeloid leukaemia (Sasco et al. 2004). It has been estimated that tobacco smoking was responsible for approximately 15–20% of the total number of cancer cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011). This percentage is higher in men than in women. The difference between men and women is quite large in the United Kingdom (23.0% and 15.6%, respectively, in 2010 (Parkin et al. 2011); 17.7% and 12.4%, respectively, in 2015 (Brown et al. 2018)), but it is even stronger in France (28.5% and 9.3%, respectively, in 2015 (IARC 2018)). These figures very likely reflect the diffusion of the smoking epidemic over time in the different European countries.

There are many prospective epidemiological studies which have demonstrated a direct association between overweight and obesity, and cancer. The IARC and the WCRF showed that common cancers in obese people were predominantly endometrial, oesophageal adenocarcinoma, colorectal, postmenopausal breast, prostate and renal cancers. Less common malignancies associated with obesity are malignant melanoma and thyroid cancers, as well as leukaemia, non-Hodgkin's lymphoma

and multiple myeloma (De Pergola and Silvestris 2013). Obesity is thought to be responsible for approximately 6% of the total number of cancer cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011), with an attributable fraction slightly higher in women (7%).

Diet is also an important component of cancer risk and is estimated to be responsible for approximately 5% to 9% of the total number of cancer cases, with no difference between men and women. Results concerning diet differ according to the studies and the countries. By looking in more details at the constituents of diet, insufficient intake of fibre is involved in colorectal and breast cancers and has been estimated to be responsible for 1.5% to 3% of the total number of cancer cases. A deficit in intake of fruit and vegetables is involved in oral cavity, pharynx, larynx, oesophagus, stomach and lung cancer and is thought to be responsible for 2% to 4.5% of the total number of cancer cases. Finally, excess red and preserved meat consumption is associated with an increased risk of colorectal and pancreatic cancer and is thought to be responsible for 1% to 2.5% of the total number of cancer cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011).

The carcinogenesis of alcohol has been demonstrated by several studies, including some carried out by IARC, even when consumed at medium or low volumes (Cao et al. 2015; Bagnardi et al. 2015). The first published exploratory study on the carcinogenesis effect of alcohol dates back to the beginning of the twentieth century, when an excessive mortality from cancer due to alcohol consumption was reported (Newshome 1903). Alcohol consumption is involved in cancers of the oral cavity and pharynx, oesophagus, colon–rectum, liver, larynx and breast, and is responsible for approximately 3% to 8% of the total number of cancer cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011), with no differences between men and women. By contrast, substantial differences are reported between countries, with a population attributable fraction of 3% to 4% in the United Kingdom and 8% in France.

Among the 11 infectious agents classified as well established carcinogenic agents in human beings by IARC (Plummer et al. 2016), six are included in European studies. The five others will not be presented in this chapter: *Opisthorchis viverrini*, *Clonorchis sinensis* and *Schistosoma Hæmatobium* are excluded because they only exist in Asia or Africa, human T-lymphotropic virus type 1 for lack of data in Europe and HIV because it is recognised that it is associated with an increased risk of cancer only in the presence of a co-infectious agent whose carcinogenicity is increased by causing immunosuppression (only other infectious agents identified as carcinogens, and potentially diagnosed in HIV patients, are studied). The infectious agents considered in this chapter are: *Helicobacter pylori*, hepatitis B virus, hepatitis C virus, human papillomavirus, Epstein–Barr virus and human herpes virus. Globally, infections are involved in cancers of the oral cavity and pharynx, stomach, liver, larynx and cervix and are thought to be responsible for about 3% to 4% of the total number of cancer case cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011), with no differences between men and women.

Insufficient physical activity is well known to increase the risk of colon, breast and endometrial cancers (WCRF and AICR 2007). More recently (without IARC

classification to date), it has been demonstrated that insufficient physical activity might also be associated with increased risk for ten other cancers: oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, myeloid leukaemia, myeloma, head and neck, rectum and bladder (Moore et al. 2016). Just considering the well-known sites, insufficient physical activity is thought to be responsible for approximately 1% of the total number of cancer cases (IARC 2018; Brown et al. 2018; Parkin et al. 2011), with no differences between men and women.

Postmenopausal hormones have been classified as carcinogenic by IARC. They are associated with breast, endometrial and ovary cancers. Since 2003 and the publication of the negative effects of these treatments on women's health (Beral 2003; Rossouw et al. 2002), the use of postmenopausal hormones has dropped sharply. However, they can be prescribed to a woman experiencing functional disorders related to menopause that alter her quality of life. The dose should be as low as possible and the duration of the treatment as short as possible. Postmenopausal hormones could be responsible for 1% to 2% of the total number in cancer cases in women (IARC 2018, Brown et al. 2018, Parkin et al. 2011).

Insufficient breastfeeding is involved in breast cancer: the longer women breastfeed, the more they are protected against breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2002). It has been estimated that insufficient breastfeeding could be responsible for 1% to 2% of the total number of cancer cases in women (IARC 2018, Brown et al. 2018, Parkin et al. 2011).

Figures 13.1 and 13.2 show the proportions of behavioural factors in the total number of cancer cases observed in the United Kingdom in 2010 (Parkin et al.

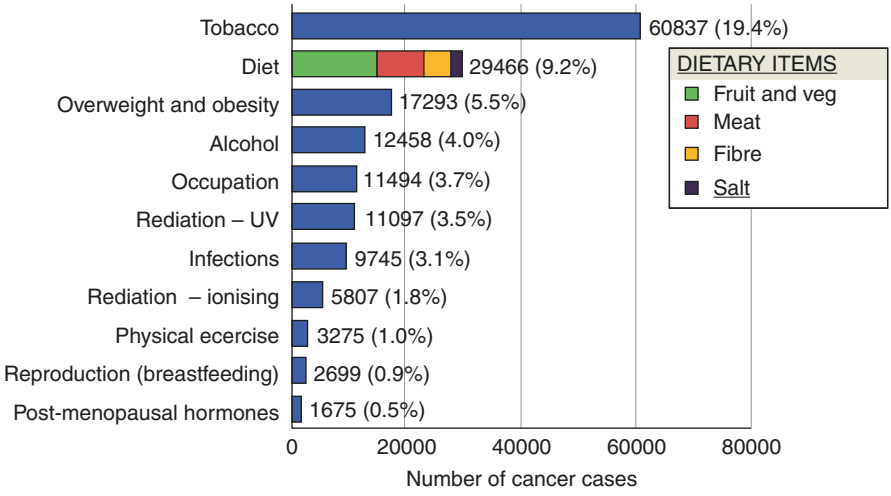

Fig. 13.1 Number and percentage of cancer cases in the United Kingdom attributable to different exposures in 2010 (Reprinted with permission from Springer Nature: on behalf of Cancer Research UK: Nature. Parkin et al. (2011). https://doi.org/10.1038/bjc.2011.489, licensed under the terms of the Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License, http://creativecommons.org/licenses/by-nc-sa/3.0/)

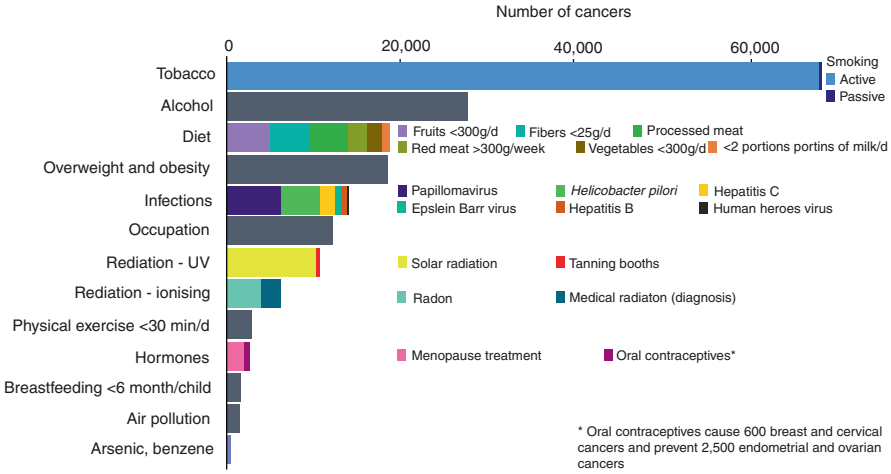

Fig. 13.2 Number of attributable cancer cases related to lifestyle and the environment in France in 2015 among adults aged 30 and over (Marant-Micallef Sante Publique France 2018, translated by the authors)

2011) and in France in 2015 (Marant-Micallef et al. 2018). The results are almost similar except for alcohol, for which the attributable fraction is much higher in France than in the United Kingdom.

Contribution of Behavioural Factors on Social Disparities in Cancer Incidence

Socially Stratified Behavioural Risk Factors

Behavioural risk factors for cancer are, for the most part, socially stratified. They can be over-represented in deprived or in affluent individuals. The majority of studies investigating this issue were initially interested in the relationship between the prevalence of the considered behavioural risk factors and people's socioeconomic position, measured at the individual level (with indicators such as level of education, level of income and occupational class).

Tobacco is the leading behavioural risk factor for cancer, is involved in almost a fifth of the total number of cancer cases and is strongly socially stratified. A French study, published in 2007 (Baumann et al. 2007), observed a strong association between deprivation (measured at the individual level by a cumulative score integrating low educational level, manual worker, living alone, non-western European nationality, low income and non-home ownership) and tobacco use, with an odds ratio of 2.62 (95% CI: 1.98–3.46) in men and 2.06 (95% CI: 1.48–2.86) in women for the most deprived compared to the least deprived. A review published in 2012

(Hiscock et al. 2012) reported that smoking prevalence was generally higher among deprived people and that quitting attempts were less likely to be successful in deprived people. Finally, a study examining the changes over time in educational disparities in smoking in France, Germany and the United States (Pampel et al. 2015) reported a strengthening of educational disparities across birth cohorts for both men and women in France and the United States and for women in Germany. The results were less consistent for men in Germany. Overall, this study predicted a worsening of educational disparities in smoking for the coming years.

With over 1 billion adults worldwide estimated to be overweight and at least 300 million obese, and given the major consequences of overweight and obesity on health and specifically on cancer incidence as seen in the previous section, the socioeconomic gradient in obesity has been studied in many countries. A recent study evaluated the educational disparities in obesity and overweight in 11 OECD countries (Devaux and Sassi 2013). Among the countries included, the highest inequalities in the prevalence of obesity and overweight were observed in European countries. Absolute inequalities were largest in Hungary and Spain with a difference of 11.6% and 10.0% in obesity rates in men, and 18.3% and 18.9% in women, respectively, across the education spectrum. In all countries, these inequalities were always larger among women than among men. Relative inequalities were largest in France and Sweden, with poorly educated men 3.2 and 2.8 times more likely, respectively, to be obese compared to men with the highest education (18 times for women in Spain). Similar results were also observed by Mackenbach et al. in 2008 (Mackenbach et al. 2008) and by Roskam et al. in 2010 (Roksam et al. 2010), with greater inequalities among women than among men, especially in the countries of southern Europe (Italy, Spain, France and Portugal).

Individual social gradients in diet habits are poorly documented in the literature, where some have only looked at social inequalities in the consumption of fruits and vegetables. A Finnish study (Lallukka et al. 2010) observed that higher income was similarly associated with higher fruit and vegetable consumption among those with low, intermediate and high education.

The direction of the social gradient for alcohol consumption is unclear. Some studies (Baumann et al. 2007) reported that increased individual levels of deprivation were associated with a greater likelihood of alcohol abuse, but others (Pena et al. 2017) showed, on the contrary, that lower socioeconomic position was associated with higher abstinence rates and that heavy volume drinking was more prevalent in people with high socioeconomic position. These contradictory results may, in part, come from the differences in the consumption profiles studied (binge drinking, low or high volumes, occasional or frequent). However, a greater risk of harm in individuals with a low socioeconomic position compared with those of higher position is always observed. That is why this has given rise to a paradox, named the alcohol harm paradox (Bellis et al. 2015; Katikireddi et al. 2017), whereby deprived populations that apparently have the same, or a lower, level of alcohol consumption, suffer from greater alcohol-related harm than more affluent populations.

The current literature is well documented concerning the social gradient in rates of different infections involved in cancer risk: *Helicobacter pylori* (Dowd et al.

2009), hepatitis B virus (Dowd et al. 2009; Meffre et al. 2010), hepatitis C virus (Meffre et al. 2010), human papillomavirus (Kahn et al. 2007), Epstein-Barr virus (Stowe et al. 2010) and human herpesvirus (Dowd et al. 2009; Stowe et al. 2010). Dowd et al. reported that parental education was significantly associated with the likelihood of infection for *Helicobacter pylori*, herpesvirus and hepatitis B virus. They also found that after controlling for parental education and race/ethnicity, increased family income was associated with lower odds of infection for herpesvirus. Meffre et al. examined the social factors of the prevalence of hepatitis B and hepatitis C viruses and reported that low socioeconomic position (measured at the individual level) was associated with a higher prevalence of hepatitis B and hepatitis C viruses. Kahn et al. focused on the sociodemographic factors associated with human papillomavirus infection. They observed that women living below the poverty line were more likely to be positive for human papillomavirus. Moreover, among women living above the poverty line, high income was significantly associated with a reduced risk of being infected by human papillomavirus. Finally, Stowe et al. reported that great reactivation of Epstein-Barr virus and herpesvirus were observed in the least educated population.

A paper published in 2006 (McNeill et al. 2006) reviewed studies focusing on the influence of different aspects of the socioeconomic position on physical activity. It has been observed that individuals at the highest levels of income, education or job were more likely to engage in physical activity than those at lower levels. A European study (Demarest et al. 2014) analysed the association between educational level and non-activity during leisure time on a European scale. Almost everywhere in Europe, a low level of leisure-time physical activity was more pronounced in lower educated than in higher educated subjects. The educational inequalities of presenting a low level of leisure-time physical activity were more pronounced in men than in women, but no considerable difference between countries emerged.

The studies examining the social gradient in postmenopausal hormone replacement therapies are rare, not recent and give contradictory results. One study (Topo et al. 1999) found that hormone therapy use was significantly more common among women with longer education than among other women but another (Olesen et al. 2005) reported no substantial socioeconomic gradient.

The social gradient of breastfeeding, on the contrary, has been widely studied in the literature over the years and in many countries. An article published in the Lancet in 2016 (Victora et al. 2016) studied the epidemiology, the mechanisms and the lifelong effects on women's health of breastfeeding. This review of studies from high-income countries showed that high-income and best-educated women breastfed more commonly than those in low-income groups or with fewer or formal education.

More recent research now integrates the social environment into its full contextual dimension using aggregated indices quantifying the level of deprivation of living areas. Some studies even assess the relative contribution of the socioeconomic position measured at the individual level and of the socioeconomic position measured at the environmental level on the prevalence of several behavioural risk factors.

After having shown the social stratification of tobacco smoking, at the individual social level on one hand (Baumann et al. 2007) and at the aggregated social level on the other hand (Lakshman et al. 2011), more recent studies have analysed the social stratification of smoking in its entire individual and aggregated social dimensions but with various results. One study conducted in the United Kingdom (Morris et al. 2018) reported a positive association between neighbourhood deprivation and smoking behaviour at age 17. Children born into more socioeconomically deprived neighbourhoods were up to twice more likely to become smokers than those born into less deprived neighbourhoods. There was suggestive evidence that those born into the most deprived neighbourhoods were also more likely to be heavier smokers, with a 25% higher cigarette consumption than among those born into the least deprived neighbourhoods. These associations were largely a function of family socioeconomic position and parental smoking behaviour. The authors concluded that adolescent smoking behaviours were due to compositional effects rather than to direct contextual neighbourhood effects. In other words, it was not the deprived neighbourhoods themselves that give rise to deleterious smoking behaviours, but the composition of people residing within them. On the contrary, another study conducted in the United States (Mathur et al. 2013) examined smoking from age 12 to 18 years. They reported that individual socioeconomic position affected smoking behaviour differentially, depending on the neighbourhood socioeconomic context. They showed that among higher socioeconomic position neighbourhood people, the level of smoking increased more with age among the lower individual socioeconomic position group than among the higher individual socioeconomic position group. In addition, among the lower neighbourhood socioeconomic position people, the level of smoking increased more with age among the lower individual socioeconomic position group than among the higher individual socioeconomic position group.

Concerning diet, ecological approaches have been conducted in different countries (Ball et al. 2015) and have reported increased odds of greater fruit intake in higher socioeconomic position neighbourhoods. A couple of studies (Lakshman et al. 2011; Shohaimi et al. 2004) investigated the independent association between individual and area-based socioeconomic position measures and fruit and vegetable consumption. These two studies conducted in the United Kingdom concluded to an independent effect of neighbourhood deprivation on fruit and vegetable consumption, after adjusting for individual socioeconomic position. Shohaimi et al. found that having a manual occupation, having no educational qualifications and living in a deprived area all independently predicted significantly lower consumption of fruit and vegetables. The effect of residential area deprivation was more pronounced in those in manual occupations and with no educational qualifications.

For alcohol, explanations have been proposed to explain the higher levels of alcohol-related harm experienced in lower socioeconomic position groups, whatever the direction of the relationship between socioeconomic position and alcohol consumption (Bellis et al. 2015), as mentioned previously. The hypothesis is that the social characteristics of the neighbourhoods may have an effect on alcohol

consumption independently of the individual socioeconomic position. However, this hypothesis has not been studied yet for alcohol consumption.

The study analysing the relationship between individual level socioeconomic position and physical activity (McNeill et al. 2006) also examined the association between social environment characteristics and physical activity. They identified five modifiable dimensions of the social environment (social support and social network; socioeconomic position and income inequality; racial discrimination; social cohesion and social capital; and neighbourhood factors), and then specified and summarised the mechanisms by which these dimensions influence physical activity. They reported that an unequal distribution of physical activity resources in rich and poor neighbourhoods is likely to influence opportunities for physical activity. The lack of availability and accessibility of health and municipal services such as recreational facilities limit opportunities for physical activity. Community support services, such as reduced daily school physical education, act as barriers to physical activity. They concluded that physical activity was determined not only by individual-level factors but also by social environment characteristics.

To the best of our knowledge, analyses including contextual measures of socioeconomic position do not exist to date for the other behavioural risk factors. In addition, whereas the prevalence of many behaviours and their social stratification are likely to differ across European countries, we often lack data across the whole of Europe.

Quantification of the Cases Attributable to Behavioural Risk Factors in Social inequalities in Cancer Incidence

According to the literature, the majority of behavioural risk factors for cancer are socially stratified. This suggests that behavioural risk factors strongly contribute to social inequalities in cancer incidence. A large number of studies have compared the magnitude of socioeconomic inequalities in cancer incidence in models without and with adjustment for the behavioural risk factors. These studies provide information on the contribution of these risk factors to excess risk in deprived individuals due to the higher exposure to behavioural risk factors in these groups but usually do not quantify the burden of those risk factors on the number of excess cancer cases in deprived individuals (Robert et al. 2004; Ekberg-Aronsson et al. 2006; Webster et al. 2008; Conway et al. 2010; Boing et al. 2011; Kim et al. 2010; Doubeni et al. 2012). One possibility to quantify this burden is to use an 'attributable risk' approach.

Population attributable risk approaches have been used to assess the weight of various behavioural risk factors in cancer incidence in the general population in a couple of countries (IARC 2018; Wang et al. 2010; Martel et al. 2012). However, studies specifically using this approach in the context of social epidemiology are rare in the literature, almost non-existent; one French study (Menvielle et al. 2018)

nevertheless proposed a methodology aiming to measure the part of inequalities in cancer incidence in France induced by smoking and estimated the potential reduction in cancer burden if inequalities in smoking were to be eliminated. One European project also developed a method to estimate the potential impact of changes in the social distribution of risk factors on socioeconomic inequalities in mortality (Mackenbach et al. 2008).

Combining the approach developed in the French study and the European project, we will detail a methodology population risk approach to assess the weight of any risk factor in social inequalities in cancer in the general population.

The first step of the methodology is to assess the population attributable fraction (PAF) (Levin 1956; Rockhill et al. 1998) of the cancer burden attributable to the considered risk factor according to socioeconomic position. The PAF assesses the proportion of cancer cases that could be avoided if exposure was modified according to an alternative scenario, often the removal of the exposures, and therefore compares the current situation to one alternative, often hypothetical, situation or scenario.

Let's consider a risk factor with k categories of exposure, $i = 1 \ldots k$. The PAF can be computed with the following formula:

$$\mathrm{PAF} = \frac{\sum_{i=1}^{k} p_i RR_i - \sum_{i=1}^{k} p_i' RR_i}{\sum_{i=1}^{k} p_i RR_i}$$

where p_i is the proportion of the population exposed at the i^{th} exposure category, p_i' is the proportion of the population exposed at the i^{th} exposure category in the alternative scenario and RR_i is the relative risk of the i^{th} exposure category on cancer risk. For each cancer site we are interested in, the PAF needs to be calculated by socioeconomic position but also, if possible, by age group and sex.

Several alternative scenarios could be of interest, taking into account the specificities of each risk factors, including:

(i) No one is exposed to the risk factor in each socioeconomic group.
(ii) The whole population is exposed to the risk factor as the least deprived.
(iii) The whole population is exposed to the risk factor as in a reference population.

The hypothetical scenario (i) provides an estimate of the maximal reduction in cancer cases that would be observed if the risk factor could be totally eliminated. The scenarios (i) and (iii) may imply changes in the distribution of the behavioural risk factor in all socioeconomic position groups compared to scenario (ii) where the risk factor distribution does not change among the least deprived. Social inequalities in exposure may still be present in scenarios (i) and (iii). However, in scenario (iii), social inequalities in exposure correspond to an observed situation, and therefore it is a more realistic and possible to achieve scenario.

For smoking, the method developed by Peto and Lopez can be used to compute the PAF, but then the alternative scenario is always the situation without smokers.

Other alternative scenarios can still be considered, but it necessitates more calculations (Menvielle et al. 2018).

The second step of the methodology quantifies the contribution of the considered risk factors to socioeconomic inequalities in cancer incidence at the national level. There are several possibilities to assess this burden:

- To compute the PAF by socioeconomic group using one alternative scenario. Using the PAF, the number of cancer cases attributable to the risk factor by socioeconomic position can also be computed. By doing so, we estimate the proportion of cancer cases and the number of cancer cases that would be avoided by socioeconomic group if social inequalities in exposure were to be modified according to the alternative scenario considered.
- To assess the change in absolute or relative social inequalities in cancer incidence. Using the PAF and the corresponding number of cancer cases, we compute the new number of cancer cases and the new cancer incidence rate by socioeconomic group that would be observed in the alternative scenario. Then, absolute and relative inequalities in cancer incidence can be assessed in this alternative situation and compared with the current situation.
- To assess the number of excess cancer cases that would be avoided in the whole population if social inequalities in exposure were to be modified according to the alternative scenario considered. To compute this figure, we need to assess the total number of excess cancer cases due to low socioeconomic position in the observed situation. To do so, we assume that the whole population has the same incidence rates as the least deprived, we compute the corresponding number of cancer cases that would be observed by socioeconomic group and we deduce the number of excess cancer cases in each socioeconomic group in the observed situation. The number of cancer cases that could be prevented if inequalities in the studied risk factors were to be modified could then be estimated by comparing the number of excess cancer cases in each socioeconomic group in the observed situation with the number of excess cancer cases in each socioeconomic group in the alternative situation.

This methodology has strengths. It can combine data from different sources. It can also address scenarios and compare the current situation to one or several hypothetical situations. The main difficulty in implementing this method concerns the availability of data. Indeed, as for studies evaluating the attributable fraction of different risk factors in the general population (IARC 2018; Brown et al. 2018; Parkin et al. 2011), the proportion of exposed individuals, as well as cancer incidence, must be known in the general population, but moreover, for each social stratum and with the same socioeconomic indicator in the cancer incidence and in the risk factor exposure data source. Such data sources are rare, which certainly explains why this approach has been hardly used. In addition, the RRs of the risk factor exposure on cancer risk should come from high-quality data. Ideally, the RRs should differ by socioeconomic group. Indeed, an increasing number of studies suggested that socioeconomic factors may be embodied and associated with different levels of epigenetic markers that in turn may be associated with a high risk of diseases (Castagné

et al. 2016; Kelly-Irving et al. 2013). However, in 2020, no good high quality exists for RRs of the risk factor exposure on cancer risk by socioeconomic groups.

The French study focusing on smoking (Menvielle et al. 2018) reported that if inequalities in smoking were eliminated, the excess cancer cases in the whole population would be reduced by 27.5% (accounting for 2388 cancer cases) in men and 43.4% (accounting for 1187 cancer cases) in women. The proportion would not differ by sex in the age group 60–74 (approx. 30%) but would be much higher in women than in men in the age group 30–59 (48.1% vs. 26.3%).

The European study quantified the potential reduction of social inequalities in cancer mortality associated with obesity and smoking in 21 European countries. If educational disparities in BMI were to be eliminated, 1% to 2% of colorectal cancer deaths in women and 1% to 3.5% in men, 1% to 1.5% breast cancer deaths, 1% to 5% kidney cancer deaths in men and 6% to 11% in women would be avoided among people with up to lower secondary education (Hoffman et al. 2015). If educational disparities in smoking were to be eliminated, on average, in Europe, 17.3% of lung cancer deaths in men with up to lower secondary education would be avoided and 10.1% in women with up to lower secondary education, ranging from 2% in Italy to 30% in the United Kingdom in men and from 1% in Italy and 33% in Scotland in women (Kulik et al. 2013).

Conclusion

Because approximately 40% of all incident cancer cases in adults aged 30 years and older are attributable to behavioural risk factors and because there is strong evidence that these behavioural risk factors are over represented in deprived populations, they represent the main opportunity to reduce social inequalities in cancer incidence in Europe.

A large quantification, updated over time, of the burden of these risk factors on social inequalities in cancer incidence is currently lacking but would guide public policies in their intention to tackle social inequalities in cancer. The existence of a tool, such as an aggregated index of social deprivation, in each deprivation country, with the possibility to link it to data sources including information on risk factor exposure, would be a unique opportunity to assess this burden and should be promoted.

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Chapter 14
Occupational Factors in the Social Gradients in Cancer Incidence

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As presented in Chap. 5, large social inequalities in cancer incidence are observed for several cancer sites. Chapter 16 elaborates on the theoretical framework explaining the origins of these inequalities. In addition to the behavioural factors discussed in Chap. 13, exposure to occupational carcinogens also contributes to these inequalities.

Compared to other proximal risk factors, occupational exposures present several distinct characteristics. First, they are closely related to the nature of the job and are therefore largely involuntary. In addition, the workers are often not aware of the specific carcinogens that they might be exposed to at work (e.g. crystalline silica or beryllium). If they happen to know, they will be unable to specify to which level they were exposed. Consequently, the assessment of occupational exposures is complex.

Occupational exposures are closely tied to people's socioeconomic position. Indeed, occupational exposures to carcinogens are more frequently observed among manual (blue-collar) workers, which ultimately lead to social inequalities in cancer risk and burden.

Table 14.1 illustrates variations in nationwide prevalence of exposure to four major lung cancer carcinogens by industry sectors in countries (combined) in the European Union (Driscoll et al. 2005). It clearly shows that exposure to, for example, asbestos is much larger among those working in the mining and construction

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Table 14.1 Percentage of workers exposed to major lung carcinogens by industry (work) sectors in the European Union (1990–1993) (Driscoll et al. 2005)

	Agriculture	Mining	Construction	Services	Finances
Asbestos	1.248	10.248	5.203	0.284	0.016
Chromium	0.000	0.346	0.237	0.225	0.000
Nickel	0.000	2.025	0.047	0.043	0.000
Silica	0.372	23.049	18.860	0.061	0.002

Table 14.2 Percentage of people working in the private sector exposed to at least one chemical carcinogen by occupational class and year, France (2003, 2010, 2017) (Memmi et al. 2019, translated by the authors)

	Professionals and managers	Technicians and associate professionals	Office clerks	Sales and service workers	Skilled manual workers	Unskilled manual workers
2003	3.3	10.9	1.2	5.1	31.0	23.3
2010	2.0	6.1	1.0	2.8	24.7	15.4
2017	1.9	5.9	0.7	4.2	30.0	13.6

sectors, while the exposure is lower among those working in the agriculture sector, and negligible among those working in the services or finances sectors.

Table 14.1 suggests that exposure to the main occupational carcinogens is distributed unequally across occupational groups, manual workers being over-represented in the mining, construction and agriculture sectors and under-represented in the services and finances sectors. This unequal distribution is clearly shown in Table 14.2. In France, exposure to chemical carcinogens has decreased over time but is much more prevalent among manual workers, in particular skilled manual workers, and is lowest among professionals and managers, as well as among office clerks.

In this chapter, we will discuss how occupational exposures can contribute to the social gradient in cancer incidence. We will first review the occupational exposures that are associated with cancer incidence. We will then present the main findings from the literature dealing with the role of occupational exposures in social inequalities in cancer incidence before mentioning several avenues for future research in this field.

Cancers Related to Occupational Exposures

The history of cancer and occupational exposure is an old one, dating back to 1775 when Percival Pott, an English surgeon, reported for the first time the link between scrotal cancer and soot, which was highly prevalent among chimney sweeps (Pott 1775). He also noted the terrible life conditions that the patients experienced since early childhood, making him a pioneer in occupational epidemiology and also in social epidemiology, with the introduction of the life course concept. The report has increased awareness of the disease and its cause, and some decades later, it initiated

regulatory changes to protect chimney sweeps and other workers in close contact with coal tar, including coal tar pitch (Brown and Thornton 1957). A century later, a substantial decrease in scrotal cancer incidence was reported, which was partly related to improved regulatory measures protecting workers, and partly due to changes related to industrialisation and housing structure, i.e. heating systems. Today, coal tar is a well-known carcinogen (IARC 1985) and has been linked to cancers of the skin, lung and bladder.

Many further stories can be found throughout history, probably not as well known, but nonetheless important in initiating studies leading to research on the carcinogenicity of certain chemicals, changes in the workplace and legal frameworks to protecting workers. In 2017, among agents classified by the International Agency for Research on Cancer (IARC) in group 1 (defined as causally linked to cancer through human, animal and experimental studies), there were 59 occupational settings: 47 individual substances, mixtures or types of radiation and 12 occupations, industries or processes. These have been associated with 23 cancer types with cancers of the lung, skin, bone, bladder and nasal cavity and paranasal sinuses as the most common cancers associated with occupational carcinogens (Loomis et al. 2018).

Various studies have reported on the association between occupational risk factors and cancers ((Cogliano et al. 2011), see also the part on the "Role of Occupational Exposures in Social Inequalities in Cancer Incidence" of this chapter), yet few have estimated the impact on cancer burden (population attributable fraction or PAF), especially on the overall cancer burden in populations. One reason for this is the lack of data on exposure to these agents or under-reporting of these agents at population levels, with the exceptions of a few job exposure matrices (JEMs) that have been developed in a few high-income countries such as Australia, Finland, France, the United Kingdom and the United States (Kauppinen et al. 1998; Pannett et al. 1985; Sieber Jr. et al. 1991; Fevotte et al. 2011). JEM is a method used to estimate occupational exposures by matching combinations of occupation and industry sector with the level of exposure to certain agents present at the occupational setting (dust, fumes, etc.) (Kauppinen and Partanen 1988). This lack of data has driven large international exposure information systems also known as the Internal Information Systems on Occupational Exposure to Carcinogens (CAREX: Carcinogen Exposure). One of the first international collaborations reporting PAF across regions was made possible due to this common data collection framework. For example, the burden of lung cancer due to 13 occupational carcinogens in four European regions in 2016 was estimated using the CAREX database (Table 14.3). A marked difference in the proportion of cancers related to occupational exposures across European regions was seen with large PAF of lung cancer deaths in Northwestern Europe as compared to Eastern Europe, 31% vs. 9%, respectively (Collaborators GBDRF 2017). This can mainly be attributed to asbestos, linked to the high historical use of asbestos in Northwestern Europe, which were also early adopters of the national asbestos ban (Kameda et al. 2014).

A few countries have also estimated PAF, often requested by national health and safety agencies, in which national data with a comprehensive set of carcinogens

Table 14.3 Population attributable fraction (PAF) of lung cancer deaths attributable to 13 occupational carcinogens by European regions 2016

Regions	PAF
Eastern Europe	9.4%
Central-southern Europe	12.5%
Northwestern Europe	30.8%

Adapted from GBD 2016 Risk Factors Collaborators (2017). https://doi.org/10.1016/S0140-6736(17)32366-8, licensed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/)

Table 14.4 Major studies assessing the contribution of occupational exposure on national cancer burden (PAF, %) by sex and country

Country	Author, date	# of occupational carcinogens and cancers	PAF (%) Men	PAF (%) Women
Finland	Nurminen and Karjalainen 2001 (17)	>40/26	14	2
United States	Steenland et al. 2003 (16)	>40/9	4	1
Australia	Fritschi and Driscoll 2006 (18)	>40/26	11	2
The United Kingdom	Rushton et al. 2012 (19)	>40/24	8	2
France	Marant Micallef et al. 2018 (20)	>40/23	6	1
Canada	Labreche et al. 2019 (21)	31/24	3.9–4.2[a]	

[a]*No point estimate and not reported separately by sex*

were used to assess the overall impact of occupational carcinogens on the national burden of cancer. Results in a few European countries and several highly industrialised countries are shown in Table 14.4. Overall, 3% to 14% and 1% to 2% of all new cancer cases among men and women, respectively, were attributable to occupational exposures. Observed differences can partly be linked to differences in methodologies used and in the numbers of included carcinogens, for example, exclusion of radiation in the United States (Steenland et al. 2003). Nonetheless, the international variations could also be caused by true differences in exposure linked to major industrial or occupational activities within certain geographic regions. Where longitudinal assessments have been performed, a declining burden of cancers linked to occupational exposures was evident, which is likely due to improved working conditions and worker protection (Kameda et al. 2014) as well as changes in the composition of the main industry sectors. As such, we expected a decrease in incidence in some cancer types, for example, mesothelioma linked to asbestos, in particular in highly developed countries, that does not preclude newfound cancer cases related to more recent occupational carcinogens.

One of the largest causes of occupational-related cancers is asbestos, which is strongly linked to mesothelioma and other cancers of the lung, larynx and ovary. This is followed by chromium IV, nickel and silica, as well as painters, which is an occupational group exposed to several carcinogenic agents (Loomis et al. 2018; Marant Micallef et al. 2018). Because inhalation is the main exposure route of many carcinogens at the workplace, occupational-related cancers are often diagnosed along the respiratory pathway. As such, part of the inequalities in occupational-related cancers could largely be prevented through improved workplace protection, including setting standards and exposure limits alongside continuous monitoring.

Finally, there are marked differences in occupational-related cancers by sex, due to variations in job types between men and women. In general, a larger proportion of cancers due to occupational carcinogens are observed in men (see Table 14.4). In addition, differences are also seen in the types of major carcinogens that impact occupational-related cancers. For example, formaldehyde, a common carcinogen in the health sectors, contributed to 5% of cancers in women and only 4% in men, while for most other carcinogens, the reverse is reported. Figure 14.1 shows the proportion of various carcinogens that contributed to cancers caused by occupational exposures in France in 2015. All carcinogens found at occupational settings classified in group 1 and group 2a by the IARC Monographs are included in this assessment (causally linked to cancer in humans (group 1), and probably carcinogenic to humans (group 2a)). Asbestos contributed to almost half of all cancers attributable to occupational carcinogens in men, while in women, shift work

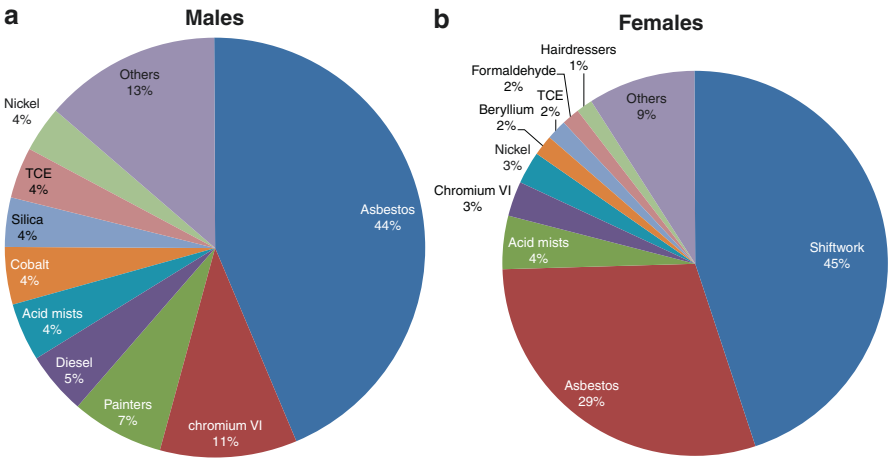

Fig. 14.1 Contribution of various occupational carcinogens to cancers caused by occupational carcinogens in France in 2015 by sex. (Source: Marant Micallef et al. 2019)

contributed to 45%, followed by asbestos, which contributed 29% to the total cancers caused by occupational carcinogens (Marant Micallef et al. 2019).

Role of Occupational Exposures in Social Inequalities in Cancer Incidence

The first and most comprehensive attempt to globally assess the burden of occupational exposures in inequalities in cancer incidence was published in 1997 (Boffetta et al. 1997). At that time, no study had directly investigated to what extent occupational exposures accounted for the association between people's socioeconomic position and their risk of developing cancer. Boffetta et al. used an indirect method to estimate the per cent excess risk attributable to occupational exposures among manual workers compared to non-manual workers. The estimation is based on cancer mortality data from 1971 in England and Wales. For all cancers combined, 32% of the excess risk among manual workers compared to non-manual workers was attributable to occupational exposures. Several groups of cancers were investigated, namely respiratory (larynx, lung and nose), bladder, liver, prostate and skin (non-melanoma). The per cent excess risk among manual workers compared to non-manual workers attributable to occupational exposures ranged from 5% for laryngeal cancer and 9% for prostate cancer to 48% for lung cancer, 52% for bladder and 100% for cancer of the nasal sinuses.

Since 1997, several studies have explored the mechanisms of social inequalities in cancer incidence and specifically investigated the role of occupational exposures. A large body of this literature deals with respiratory cancers (mostly lung and head and neck) in men, which are also cancer sites with large social inequalities in cancer incidence and for which occupational exposures account for a substantial number of cancer cases (high PAF). Therefore, occupational exposures are not only likely to substantially contribute to the excess risk of respiratory cancers among people with a low socioeconomic position but also to account for a non-negligible number of cancer cases in this group.

Most (Conway et al. 2007, 2010, 2014; Boing et al. 2011; Menvielle et al. 2004, 2009, 2016, 2018; van Loon et al. 1995; Louwman et al. 2004; Schmeisser et al. 2010; Hovanec et al. 2018; Santi et al. 2014; Behrens et al. 2016) but not (Nkosi et al. 2012) all studies investigating the mechanisms of social inequalities in respiratory cancers incidence reported that inequalities remained after accounting for differences between social groups in the two main risk factors, namely tobacco and alcohol consumption. Collecting the history of alcohol and tobacco consumption is challenging because of changes over the life course in the quantity and the type of products consumed, and residual confounding is therefore always an issue. However, most studies investigating the mechanisms of social inequalities in the incidence of respiratory cancers devoted special efforts to measuring and modelling lifetime tobacco and alcohol consumption (Boing et al. 2011; Menvielle et al. 2004, 2009,

2016, 2018; Hovanec et al. 2018; Santi et al. 2014; Behrens et al. 2016), yet the remaining inequalities after accounting for alcohol and tobacco consumption were often quite large (approx. 50% of all inequalities), making it unlikely that residual confounding due to imprecise measurement of alcohol and tobacco consumption is the only explanation for the remaining social inequalities in cancer incidence.

The main studies exploring the role of occupational exposures in respiratory cancers incidence are summarised in Table 14.5. It shows characteristics of the study, in particular regarding the measure of occupational exposures, the magnitude of social inequalities remaining after adjustment for the main behavioural risk factors (tobacco and alcohol consumption) and the percentage decrease in excess risk after adjustment for occupational exposures. For the sake of consistency, this percentage has been systematically computed by authors. However, this value should be interpreted in relation to the magnitude of social inequalities adjusted for tobacco and alcohol consumption.

Almost all studies were conducted among men. The few studies that included women did not report a role of occupational exposures in social inequalities either in lung or in head and neck cancers incidence (Menvielle et al. 2018; Hovanec et al. 2018). This is certainly related to the much lower proportion of cancers due to occupational carcinogens in women than in men. Among men, one study investigating all smoking-related and alcohol-related cancers together observed a substantial decrease in social inequalities when accounting for occupational exposures to asbestos (Melchior et al. 2005). Among studies investigating lung cancer specifically, a couple of studies reported a small role for occupational exposures in social inequalities in cancer incidence (decrease in excess risk when adjusting for occupational exposures <10%) (Hovanec et al. 2018; Behrens et al. 2016; van Loon et al. 1997), whereas others did report a substantial decrease (>10%) in social inequalities when adjusting for occupational exposures (Menvielle et al. 2010, 2016). Three studies have investigated head and neck cancers; two observed a very large effect (decrease in excess risk when adjusting for occupational exposures around 50%) of occupational exposures on social inequalities in cancer incidence (Menvielle et al. 2004; Santi et al. 2014), whereas the other found a smaller yet substantial effect (decrease around 15%). (Menvielle et al. 2018).

In the studies summarised in Table 14.5, several methods are used for the assessment of occupational exposures. In some studies, exposures are assessed based on a list of occupations considered as exposing workers to carcinogens, which quantifies occupational exposures in a somewhat crude manner, for example, exposed/not exposed. Other studies assessed occupational exposures using JEMs, which provide more detailed quantitative information such as the intensity or the probability of exposure. The literature suggests that the more precise the measure of occupational exposures, the higher the contribution of occupational exposures to social inequalities in cancer incidence. Indeed, the per cent excess risk among lower social groups compared to higher social groups explained by occupational exposures is lower when occupational exposures are directly derived from occupations (Hovanec et al.

Table 14.5 Summary of the major studies exploring the role of occupational exposures in respiratory cancer incidence

Respiratory cancers	Study characteristics and main results	
Melchior, 2005 (Melchior et al. 2005)	Smoking and alcohol-related cancers[1] – Men – Cohort study – 14,853 subjects, including 107 cancer cases	
Carcinogens	Asbestos	
Measure of occupational exposures	Sum over all jobs of the product of the exposure intensity (from a JEM) and duration Exposed to a level higher than 5.75 fibres/cm^3/year (yes/no)	
Estimate after adjustment for tobacco and alcohol	Clerks vs. manager: $HR_{adj\ for\ tobacco}$ = 2.39 (1.10-5.19); $HR_{adj\ for\ alcohol}$ = 2.47 (1.13-5.38) Manual worker vs. manager: $HR_{adj\ for\ tobacco}$ = 1.96 (1.04-3.71); $HR_{adj\ for\ alcohol}$ = 1.72 (0.90-3.28)	
% excess risk additionally explained by occupational exposures	Clerks vs. manager[2]: 31.7% for the $HR_{adj\ for\ tobacco}$; 35.4% for the $HR_{adj\ for\ alcohol}$ Manual worker vs. manager[2]: 43.8% for the $HR_{adj\ for\ tobacco}$; 25.0% for the $HR_{adj\ for\ alcohol}$	
Lung cancer		
Van Loon, 1997(van Loon et al. 1997)	Lung cancer – Men – Case-cohort study – 1245 cohort members, including 470 lung cancers	
Carcinogens	Asbestos, paint dust, PAH and welding fumes	
Measure of occupational exposures	Continuous variable equal to the sum over all jobs of the product of the exposure probability (assigned by an expert) and duration	
Estimate after adjustment for tobacco	Tertiary vs. primary education RR = 0.37 (0.17–0.82)	Senior high school vs. primary education RR = 1.12 (0.48–2.58)
% excess risk additionally explained by occupational exposures	Tertiary vs. primary education: 6.3%	Senior high school vs. primary education: The excess risk increased
Menvielle, 2010 (Menvielle et al. 2010)	Lung cancer – Men – Cohort study – 88,265 subjects, including 703 cancer cases	
Carcinogens	Asbestos, heavy metals, environmental tobacco smoke, PAH and silica	
Measure of occupational exposures	A list of occupations exposed to each carcinogen developed by experts Sum of reported jobs included in the list as a categorical variable (0, 1, 2, 3+)	
Estimate after adjustment for tobacco	All men: Up to primary education vs. tertiary education HR = 1.60 (1.25–2.05) Born before 1941: Up to primary education vs. tertiary education HR = 1.78 (1.33–2.37) Born after 1941: Up to primary education vs. tertiary education HR = 1.13 (0.70–1.82)	
% excess risk additionally explained by occupational exposures	All men: Up to primary education vs. tertiary education: 11.7% Born before 1941: Up to primary education vs. tertiary education: 46.2% Born after 1941: Up to primary education vs. tertiary education: 11.5%	

Table 14.5 (continued)

Respiratory cancers	Study characteristics and main results	
Behrens, 2016 (Behrens et al. 2016)	Lung cancer – Men – Case-control study – 11,433 cases and 14,147 controls	
Carcinogens	None specific	
Measure of occupational exposures	Ever worked in a job from list A[3] (yes/no)	
Estimate after adjustment for tobacco	Medium vs. high social prestige OR = 1.39 (1.29–1.50)	Low vs. high social prestige OR = 1.74 (1.61–1.87)
% excess risk additionally explained by occupational exposures	Medium vs. high social prestige: 5.1%	Low vs. high social prestige: 8.1%
Menvielle, 2016 (Menvielle et al. 2016)	Lung cancer – Men – Case control study – 2074 cases & 2720 controls	
Carcinogens	Asbestos, silica and diesel motor exhaust	
Measure of occupational exposures	Asbestos and silica: Sum over all jobs of the product of the exposure intensity, probability, frequency (from a JEM) and duration Combined exposure to asbestos and silica as a 3-category variable Diesel motor exhaust: Self-reported exposure (ever/never)	
Estimate after adjustment for tobacco	Not provided, mediation analyses were performed using marginal structural models	
% excess risk additionally explained by occupational exposures	Primary vs. tertiary education: 17% Vocational secondary vs. tertiary education: 23%	
Menvielle, 2018 (Menvielle et al. 2018)	Lung cancer – Men & women – Case-control study – 2019 cases & 2676 controls in men; 558 cases & 715 controls in women	
Carcinogens	Asbestos, silica and diesel motor exhaust	
Measure of occupational exposures	Asbestos and silica: Sum over all jobs of the product of the exposure intensity, probability, frequency (from a JEM) and duration Diesel motor exhaust: Self-reported exposure	
	Men	Women
	Asbestos and silica: Restricted cubic splines Diesel motor exhaust: Ever/never	Asbestos: Ever/never Diesel motor exhaust: Ever/never
Estimate after adjustment for tobacco	Occupational prestige trajectory Low to very low vs. stable high OR = 3.05 (2.13–4.38) Stable low vs. stable high OR = 2.67 (2.07–3.46)	Occupational prestige trajectory Low to very low vs. stable high OR = 2.09 (1.51–3.33) Low to middle vs. stable high OR = 1.39 (0.87–2.21)
% excess risk additionally explained by occupational exposures	Low to very low vs. stable high: 19.0% Stable low vs. stable high: 32.3%	Low to very low vs. stable high: 0% Low to middle: 0%
Hovanec, 2018 (Hovanec et al. 2018)	Lung cancer – Men & women – Case-control study – 13,772 cases & 16,480 controls in men; 3249 cases & 4405 controls in women	
Carcinogens	None specific	

(continued)

Table 14.5 (continued)

Respiratory cancers	Study characteristics and main results	
Measure of occupational exposures	Ever worked in a job from list A[3] (yes/no)	
	Men	Women
Estimate after adjustment for tobacco and alcohol	3rd vs. 1st quarter of occupational status OR = 1.80 (1.60–2.02) 4th vs. 1st quarter of occupational status OR = 1.84 (1.61–2.09)	3rd vs. 1st quarter of occupational status OR = 1.28 (1.00–1.63) 4th vs. 1st quarter of occupational status OR = 1.54 (1.20–1.98)
% excess risk additionally explained by occupational exposures	3rd vs. 1st quarter of occupational status: 7.5% 4th vs. 1st quarter of occupational status: 8.3%	3rd vs. 1st quarter of occupational status: 3.6% 4th vs. 1 quarter of occupational status: 3.7%
Head and neck cancers		
Menvielle, 2004 (Menvielle et al. 2004)	Laryngeal and hypopharyngeal cancer – Men – Case-control study – 504 cases and 242 controls	
Carcinogens	Asbestos, coal dust and formaldehyde	
Measure of occupational exposures	Asbestos and coal dust: Ever/never exposed (from a JEM) Formaldehyde: Probability of exposure (from a JEM) (in 3 categories)	
Estimate after adjustment for tobacco and alcohol	Intermediate vs. high education OR = 1.30 (0.70–2.41) Low vs. high education OR = 1.63 (0.90–2.98)	Ever manual worker vs. never OR = 1.91 (1.23–2.95)
% excess risk additionally explained by occupational exposures	Intermediate vs. high education: 77% Low vs. high education: 46%	Ever manual worker vs. never: 42%
Santi, 2014 (Santi et al. 2014)	Laryngeal cancer - Men – Case-control study – 208 cases & 702 controls	
Carcinogens	Smoke, dust, gases and vapours	
Measure of occupational exposures	Occupational burden to four carcinogens using a four category variable (from a JEM) Average of all indices weighted by years on the job	
Estimate after adjustment for tobacco and alcohol	<10 vs. >10 years of education OR = 2.9 (1.4–6.2)	10 vs. >10 years of education OR = 1.6 (0.7–3.8)
% excess risk additionally explained by occupational exposures	<10 vs. >10 years of education: 54.1%	10 vs. >10 years of education: 37.5%
Menvielle, 2018 (Menvielle et al. 2018)	Head and neck cancers – Men & women – Case-control study – 1793 cases & 2676 controls in men; 305 cases & 715 controls in women	
Carcinogens	Asbestos	
Measure of occupational exposures	Sum over all jobs of the product of the exposure intensity, probability, frequency (from a JEM) and duration	

Table 14.5 (continued)

Respiratory cancers	Study characteristics and main results	
	Men	Women
Estimate after adjustment for tobacco and alcohol	Occupational prestige trajectory Low to very low vs. stable high OR = 4.52 (3.09–6.62) Stable low vs. stable high OR = 3.58 (2.67–4.79)	Occupational prestige trajectory Low to very low vs. stable high OR = 2.12 (1.15–3.92) Low to middle vs. stable high OR = 1.62 (0.87–3.00)
% excess risk additionally explained by occupational exposures	Low to very low vs. stable high: 7.7% Stable low vs. stable high: 14.0%	Low to very low vs. stable high: 3.6% Low to middle vs. stable high: 4.8%

1: includes head and neck, oesophagus, pancreas, larynx, lung and urinary tract cancers
2: also adjusted for marital status, body mass index, fruits and vegetables consumption, family history of lung and oral cancer
3: list A = list of jobs with potential exposure to any lung cancer carcinogen (Ahrens and Merletti 1998)
PAH polycyclic aromatic hydrocarbons, *JEM* job exposure matrix

2018; Behrens et al. 2016; Menvielle et al. 2010), than when more detailed indices of exposures are obtained from a JEM (Menvielle et al. 2016, 2018; Santi et al. 2014).

The level of occupational exposures among workers has tended to decrease over time in developed countries, with the introduction of new regulations (e.g. the EU banned asbestos in 2005) and the development of better protection equipment at workplaces. Consequently, it may be that the burden of occupational exposures on social inequalities in cancer incidence has decreased in recent years and will decrease further. This is suggested by a study that compared the role of occupational exposures in social inequalities in lung cancer incidence in different birth cohorts and found that occupational exposures seemed to contribute to social inequalities mostly in older cohorts (Menvielle et al. 2010).

Occupational exposures to carcinogens are concentrated in manual jobs. Therefore, the contribution of occupational exposures to cancer incidence is sometimes limited to the lowest social groups. Indeed, several studies have found that occupational exposures did not contribute or only marginally contributed to the higher lung cancer risk observed among men with non-vocational secondary education than among men with tertiary education (Menvielle et al. 2010).

The available literature mostly included occupational exposures to chemical or physical agents. One study nevertheless developed several indices of occupational exposures and distinguished between a physically demanding job (exposed to ergonomic stress or environmental pollution) and a psychosocially demanding job. The results showed that psychosocial factors did not contribute to social inequalities in laryngeal cancer incidence (Santi et al. 2014).

Some studies specifically compared the proportion of social inequalities in cancer incidence explained by behavioural risk factors (tobacco and alcohol consumption) to that explained by occupational exposures. Interestingly, they reported that

the percentage explained by occupational exposures was close to the proportion explained by tobacco and alcohol consumption, in particular among people with the lowest socioeconomic position. A study found that the proportion of the excess risk of laryngeal cancer among less educated men (less than 10 years of education) compared to more educated men (11 or more years of education) was 26.1% for smoking, 2.7% for alcohol and 25.4% for occupational exposures Santi et al. 2014). Another study reported that among men with primary education (compared to men with tertiary education), 22% of the excess lung cancer risk was due to differences in smoking and 17% to differences in occupational exposures. The percentages among men with vocational secondary education were 28% and 23%, respectively (Menvielle et al. 2016). Although based on a limited number of studies, this suggests a major role of occupational exposures in cancer excess risk, in particular among men with a low socioeconomic position.

Conclusion and Future Studies

Studies in occupational epidemiology have substantially improved our knowledge and evidence, both on the role of occupational exposures on cancer risk and burden and on social inequalities in cancer. Although the burden of occupational exposures on social inequalities in cancer has been little investigated compared to that of behavioural factors, the literature suggests a non-negligible role of occupational exposures for respiratory cancers among men.

The available literature nevertheless reveals several gaps. Existing studies focus on respiratory cancers that show large social inequalities and large PAFs related to occupational exposures. However, occupational exposures are likely to play a role in social inequalities for other cancers, although it may be more modest. Studies investigating other cancer sites would therefore be needed to expand our knowledge on the burden of occupational exposures on social inequalities in cancer incidence.

The current literature is likely to under-estimate the burden of occupational exposures on social inequalities in cancer due to incomplete identification of all carcinogens and imprecise measurements of known occupational carcinogens. The literature shows that the role of occupational exposures in social inequalities in cancer incidence tends to be higher when the measure of occupational exposures is more precise (Menvielle et al. 2004, 2016, 2018; Santi et al. 2014; Melchior et al. 2005). Today, despite major advances in protecting workers from known carcinogens, we see a growing number of chemicals registered for use in various industrial sectors leading to an ever-increasing challenge to ensure that social inequalities in cancer related to occupational exposures can be eliminated, or at least reduced. In order to avoid under-estimation of the burden of occupational exposures in cancer incidence and in social inequalities in cancer incidence, there is therefore a need for occupational epidemiological studies to investigate cancer risk in relation to exposure to these factors and for refining tools for surveillance of workers' exposure to occupational carcinogens.

Although no study has investigated this issue so far, assessing the role of occupational exposures in social inequalities in cancer is challenging for cancer types for which incidence rates are higher among people with higher socioeconomic position. For example, shift work has been found to be associated with a higher risk of breast and prostate cancers and is currently classified as a probable human carcinogen by the IARC Monographs (group 2a). Contrary to most cancers, breast or prostate cancer incidence is higher among people with a higher socioeconomic position (Bryère et al. 2016). Therefore, people with the highest incidence rates are not those who are the most exposed to shift work.

Constraint in the number of research studies that can be done and funded to examine the impact of chemicals on cancer poses specific issues in this area, especially for workers in industries that are highly exposed to them. In addition, we cannot rule out that in developed countries, studies are imperfectly capturing exposed workers. Notably, jobs exposing workers to high levels of carcinogens are increasingly concentrated among people with more precarious jobs, who are more difficult to include in epidemiological studies. Further, as a country's economy evolves, there is the danger of transferring certain 'dangerous occupations' and therefore higher cancer risk to countries with lower resources. Some industrial processes (mining, textiles, etc.) are already increasingly concentrated in lower-income countries. However, high-quality data in these countries are often lacking, highlighting the importance of the continuous collection of internationally comparable data, including level of exposure (Rushton 2017), to ensure that the protection of workers from occupational cancer risks remains high in the global health agenda.

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Chapter 15
Environmental Determinants of the Social Gradient in Cancer Incidence

Ana Isabel Ribeiro and Daniela Fecht

Introduction

Does the context in which individuals live, work and recreate affect their health? This question has received growing attention over the past decades. A substantial evidence base has started to accumulate, suggesting possible explanations for the socioeconomic gradient in cancer incidence such as differential exposure and susceptibility to environmental factors across different population groups. This chapter outlines the concept of environmental determinants and highlights the current

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evidence base linking environmental factors to cancer risk. In doing so, issues around the quantification of environmental determinants are identified. Furthermore, two interconnected conceptual frameworks—the environmental justice framework and the deprivation amplification model—are presented as opportunities to connect the dots that bridge social inequalities in cancer incidence and the environment.

Defining Environmental Determinants

The term environmental determinants refers to features of both physical and socioeconomic environments where people live, work and recreate. The physical environment comprises: (i) bio-geophysical exposures to physical (e.g. ionising radiation), chemical (e.g. air pollution) and biological (e.g. plants) agents external to the human body (Porta 2008); and (ii) exposures to the built, man-made environment including features such as parks, recreation facilities, services, and transportation systems. The social environment, on the other hand, refers to a wide range of aspects relating to the social dimension, including neighbourhood-level socioeconomic deprivation, social capital, social norms, presence of crime and safety, among others. Although these factors tend to be conceptualised as unique entities and investigated in isolation, in reality, they are interconnected and interrelated with features from both the physical and social environment acting synergistically and interactively in shaping an individual's health.

Environmental Determinants and Cancer Incidence: An Overview

Environmental determinants of cancer risk for which there is strong or, at least moderate, epidemiological evidence are air pollution, ionizing radiation, water contamination and neighbourhood socioeconomic deprivation. Many other environmental determinants could be potentially implicated in cancer development but are currently understudied. Empirical evidence is starting to emerge for some of these understudied environmental factors such as traffic-related noise and green space, though evidence on their carcinogenic effect is not sufficient. These factors are interconnected and act synergistically and interactively in cancer causation, but such synergies remain understudied as well. This chapter, therefore, treats them as separate factors.

Air Pollution

Air pollution is a pervasive pollutant which affects a large proportion of the world population (Vineis and Fecht 2018) and is consequently the leading environmental public health concern. Road traffic is the largest source of air pollution in developed

countries, in particular in cities. There is strong evidence from both experimental and epidemiological studies that link traffic-related air pollutants, such as particulate matter (PM) and nitrogen dioxide (NO_2), to cancer. Lung cancer has the most robust association with prolonged exposure to air pollution (Hamra et al. 2014). Evidence is strongest for PM exposure which has been consistently linked to both lung cancer incidence and mortality, especially for adenocarcinomas (Raaschou-Nielsen et al. 2013). Vineis and colleagues estimated that 7% of lung cancers in European never smokers and ex-smokers are attributable to high levels of NO_2 and proximity to heavy traffic roads (Vineis et al. 2007). There is also a growing body of evidence that air pollution is linked to an increased risk of cancer in other tissues, such as the breast, hematopoietic tissues and the urinary tract (Fajersztajn et al. 2013; Kim et al. 2018). How air pollution increases cancer risk is not fully understood yet, but two mechanisms have been proposed: DNA damage due to oxidative stress, and inflammation (Kim et al. 2018). Given the large and consistent body of evidence on the topic, ambient air pollution has been recently classified as lung carcinogens by the International Agency for Research on Cancer of the World Health Organization (Loomis et al. 2013).

Radon

The International Agency for Research on Cancer of the World Health Organization has categorized radon, a radioactive gas, as a known carcinogenic substance causing lung cancer. Naturally occurring radon is the major source of human exposure to ionizing radiation. Radon is produced by the decay of uranium (and, to a lesser degree, thorium) in the Earth's crust and can accumulate in significant concentrations in enclosed spaces such as houses. If inhaled, the solid particles produced by radon decay—namely, isotopes of polonium—can be deposited on the surface of the lung and expose the lung to carcinogenic α-particles (Darby et al. 2005). Though cigarette smoking is the main cause of lung cancer, radon exposure is the second most common cause and the predominant risk factor for lung cancer in never-smokers (Organization WH 2009). There is also a strong interaction effect between radon exposure and smoking in the determination of lung cancer so that the combined exposure of radon and smoking creates a greater risk of lung cancer than exposure to either factor in isolation (Méndez et al. 2011). A pooled analysis of 13 case-control studies of residential radon and lung cancer found appreciable hazards from residential radon, indicating that residential radon is responsible for approximately 2% of all deaths from lung cancer in Europe (Darby et al. 2005). Radon levels are generally low but, depending on the underlying geology and rock type, can vary significantly. In areas where radon concentrations are above the recommended action level, regular surveillance and measurement of radon concentrations in homes are recommended. If appropriate, building work on homes can reduce radon exposure.

Ultraviolet (UV) Radiation

Ultraviolet (UV) radiation is another important source of ionizing radiation. The main environmental source of UV radiation is the sun. Solar UV radiation is composed of UVA (wavelength 320–400 nm) and, to a smaller extent, UVB (wavelength 280–320 nm) and UVC (wavelength 100–280 nm). UVB is implicated in both protective and harmful health effects, UVC has the highest energy but is largely filtered out by the atmosphere, and UVA has the lowest amount of energy. Exposure to UVB is the most important environmental risk factor in the development of skin cancer (Reichrath 2006). To avoid skin cancer, sun protection is recommended. Lack of UVB exposure, however, can result in vitamin D deficiency, as most humans obtain 80–90% of their vitamin D requirement from sunlight. Vitamin D is essential for bone health, and its deficiency has been linked with many diseases, including various cancers (Reichrath 2006).

Water Contamination

An adequate supply of safe drinking water is one of the major prerequisites for a healthy life. All water contains natural contaminants, particularly inorganic contaminants that arise from the geological strata through which the water flows and, to a varying extent, anthropogenic pollution by both microorganisms and chemicals (Fawell and Nieuwenhuijsen 2003). While arsenic, fluoride, aluminium, nitrate levels and microbial contamination are of particular concern in the developing world, the main drinking water contaminants of health concern in developed countries are those arising from disinfection-by-products (DBP) and from nitrate contamination of private wells in rural areas. Regarding the effects of DBPs, two meta-analyses of empirical studies revealed a clear link between DBPs and cancer (Morris et al. 1992; Villanueva et al. 2003), although recent meta-analyses suggest that the evidence for a relationship with cancer is weak (Costet et al. 2011; Rahman et al. 2010). The link between cancer and nitrate is less conclusive. While empirical studies have reported elevated risks of bladder and gastric cancer due to drinking-water nitrate exposure (Barry et al. 2020; Sandor et al. 2001), a meta-analysis from 2012 suggested that there was not sufficient evidence that nitrate in drinking water is associated with increased risks for bladder cancer (Wang et al. 2012).

Neighbourhood Socioeconomic Environment

An increasing number of studies have shown that residing in deprived neighbourhoods is associated with an increased risk of death and ill health, regardless of personal socioeconomic conditions. In other words, two individuals with similar

socioeconomic characteristics (e.g. income, education, occupation) could be expected to have different health outcomes if residing in areas with different level of socioeconomic deprivation. This social miasma, embodied in the concept of neighbourhood socioeconomic deprivation, can result from multiple mechanisms (Ribeiro 2018). Living in an area characterised by high unemployment, low social class, etc., is hypothesised to adversely affect health because wealthy neighbourhoods tend to attract beneficial facilities and ward off toxic and harmful exposures such as air pollution, waste dumps or industries, which are often disproportionally concentrated in deprived areas (the so-called environmental injustice or differential exposure, discussed later in this chapter). Furthermore, the socioeconomic structure of neighbourhoods also influences behaviours, aspirations and social norms shared by residents. Epidemiological studies evaluating the detrimental effect of socioeconomic deprivation on cancer risk suggest that individuals residing in more deprived areas are at higher risk of developing cancer, particularly lung cancer (Sanderson et al. 2018; Hystad et al. 2013) and head and neck cancer (Bryere et al. 2017). However, this association seems to vary according to cancer type. For instance, higher incidence rates of prostate cancer (Meijer et al. 2013; Hastert et al. 2015) and melanoma (Clarke et al. 2017) were observed in most advantaged neighbourhoods, which can be related to increased screening and better access to healthcare in these geographical settings (Clarke et al. 2017).

Green Space

Green, natural environments[1] may influence cancer risk through several pathways. Green space has been shown to ameliorate adverse environmental exposures (e.g. air pollution, noise and extreme temperatures), increase physical activity, promote social interactions and reduce psychological stress (Hartig et al. 2014). Evidence exists indicating lower all-cause mortality among people residing in greener spaces, and it is, therefore, plausible that residential green space might decrease the risk of some cancer types. Indeed, evidence on the topic is growing, and a few studies found a protective effect of residential green space in relation to cancer in general and specific cancer types, such as lung cancer (Richardson and Mitchell 2010), mouth and throat cancer (Datzmann et al. 2018) and non-melanoma skin cancer (Datzmann et al. 2018), in particular. Contrastingly, in Australia, neighbourhood green space was associated with higher odds of having skin cancer due to increased sunlight exposure during the time spent in green space (Astell-Burt et al. 2014).

[1] Any vegetated space can be described as green space, ranging in size and quality from small areas included around housing complexes and around roads, to parks, cemeteries, forests and the open countryside.

Noise

Noise is a low-level but pervasive environmental stressor produced mostly by traffic-related sources such as aircraft, road traffic, and railways and industrial sources. Noise exposure has been linked to both psychosocial responses (e.g. annoyance, sleep disturbance) and physical responses (e.g. hearing loss, increased blood pressure, hormonal changes). Although investigation connecting cancer and noise exposure is at an early stage and evidence should be interpreted with caution, a few studies conducted in Europe found that residential road traffic, aircraft and railway noise increases the risk of breast (Andersen et al. 2018; Sørensen et al. 2014; Hansen 2017) and colon cancer (Roswall et al. 2017), possibly caused by sleep disturbances, stress and compromised circadian functioning.

Measuring Environmental Determinants and Their Health Effects: Basic Principals and Challenges

Every epidemiological study has methodological challenges related to either measuring or modelling relevant health determinants. Studies on environmental health determinants, however, have the additional challenge of establishing and defining the space in which exposure occurs. Space refers to the geographical locations where individuals live, work, move and recreate through their life and daily routines. Activity space refers to the sum of locations visited by the individual throughout the day. Capturing these different locations and their corresponding environmental characteristics is highly complex, and exposure assessment must rely on proxies of exposure. Most studies use simplistic, in some cases over-simplistic, definitions of space, often reflecting the residential neighbourhood in which individuals live. The use of residential neighbourhoods instead of activity spaces to define exposures is due to the lack of information on individuals' activity patterns; the place of residence is often the only information available to researchers. Depending on the study focus, residential neighbourhoods are conceptualised in different ways. Some studies make use of pre-defined administrative or census boundaries in which individuals live. Others use a distance-based proxy of space. Here, based on their residential address, individuals are matched to a bounded area (so-called buffers), defined by a pre-set distance either in a straight line or based on distance via the road network. Exposure assessments of residential neighbourhoods are commonly conducted by overlaying the neighbourhood boundaries with maps of environmental determinates such as air pollution or green space maps and assigning exposure values based on spatial aggregation.

The so-called Uncertain Geographic Context Problem (UGCoP) refers to the artificial geographic delineation of neighbourhoods which might not directly correspond to an individual's true geographic sphere of influence. This could lead to inferential errors when analysing the impact of spatially highly variable

environmental determinists on cancer risk. There is no direct way to overcome this problem, but acknowledging the spatial and temporal variability in exposure in defining areal units and providing indicators of uncertainty will help when interpreting study results. Quantification of uncertainty can be aided by using mobile tracking technology (such as GPS devices or mobile phones) to establish individuals' true sphere of influence, which could be potentially extrapolated to larger groups of individuals or populations.

Exposure assessment methods can be divided into (i) direct assessment of an individual's personal exposure or (ii) indirect assessment using exposure proxies for a large number of individuals or groups of people. Personal exposure assessment requires tracking individual's locations and using individual wearable/portable sensors to capture their exposure to environmental conditions as they move in space and time. This exposure assessment method has been frequently employed, for example, to capture daily exposure to air pollutants for small numbers of study participants (Liang et al. 2019). Although this type of exposure measurement is highly accurate, it is only feasible for a limited number of individuals because it is very time and cost intensive, potentially invasive and is only able to capture current exposure.

From a public health perspective, it is essential to assess both long-term (e.g. annual average) and short-term (e.g. daily average) environmental exposure for the entire population of an area, region or country. Large-scale epidemiological studies, such as the European Study of Cohorts for Air Pollution Effects (ESCAPE)[4] which studied long-term effects of ambient air pollution on lung cancer incidence in 36 areas across Europe, rely on indirect exposure assessment proxies. Indirect exposure assessment methods use either measured or modelled levels of environmental concentrations and assign these to an individual's place of residence, either the exact address or the residential neighbourhood. The ESCAPE study, for example, used a combination of air pollution measurements (from routine monitoring networks and bespoke measurement campaigns), together with contextual geospatial information as input in land use regression models (Hoek et al. 2008).

Air pollution is an example of an environmental health determinant which varies greatly over small distances, and the careful consideration of areal units to assign exposure is essential to avoid exposure misclassification. Other determinants are less sensitive. Neighbourhood-level deprivation, for example, is, as the name indicates, assessed at the neighbourhood level. It is typically measured using a multivariate index reflecting different dimensions of deprivation such as education, occupational and housing. Deprivation indices are further discussed in Chap. 3.

In identifying a link between environmental determinants and cancer risk, challenges also arise from the fact that some health determinants act at different levels, typically the individual level and the neighbourhood level. One example is socioeconomic deprivation, where both individual-level (e.g. annual income) and area-level (e.g. neighbourhood-level derivation) characteristics act in synergy (see deprivation amplification model later in the chapter). This hierarchical data structure (individuals residing in neighbourhoods) and subsequent non-independence between observations have to be taken into account in statistical analyses. Multilevel

modelling (sometimes coupled with spatial correlation structure) is the most widely used approach.

In addition to socioeconomic deprivation, statistical models must be adjusted for other important risk factors because there is a non-random selection of the individuals into neighbourhoods. Models, therefore, should account for self-selection; i.e. the fact that individuals choose a certain neighbourhood not at-random but based on their preference, financial means and other more difficult to capture decision processes such as family ties and cultural connections. The result is self-selection bias because the selection mechanism into neighbourhoods is not independent of the outcome studied. Various techniques have been proposed to address this issue in order to separate the true effect of environmental determinants from that of residential self-selection, one of the most widely used being propensity score matching (Nasri et al. 2018).

Mechanisms Connecting Environmental Determinants and the Social Gradient in Cancer

Conceptually, there are two interrelated mechanisms that might explain the relationship of environmental determinants and the social gradient in cancer risk: environmental factors linked to cancer are unevenly distributed across socioeconomic groups (differential exposure) and/or the effect of environmental factors causing cancer differs across socioeconomic groups (differential susceptibility) (Diderichsen et al. 2018).

Differential Exposure

The degradation of the environment and adverse environmental exposures are not evenly distributed across space, and there is mounting and consistent evidence that vulnerable and disadvantaged groups and ethnic minorities tend to face higher exposures to environmental hazards (Vineis and Fecht 2018). These patterns first became apparent during the 1980s, when the environmental justice movement was born in the United States, before being developed further by researchers in Europe in the mid-1990s and early 2000s[41]. The spatial coincidence of socioeconomic characteristics and environmental quality might explain part of the socioeconomic inequalities observed in cancer incidence and mortality. Several European studies have observed clear trends in socioeconomic inequalities related to traffic-related air pollutants, such as particulate matter and nitrogen oxides (Fairburn et al. 2019; Padilla et al. 2014; Fecht et al. 2015), which are well-known risk factors for cancer. Some of these studies also suggest that, although globally deprived communities tend to be exposed to higher levels of traffic-related air pollutants, the magnitude of

these disparities vary between cities (Padilla et al. 2014) and countries (Fecht et al. 2015). This variability might aid our understanding of the likely underlying factors driving the differences in socioeconomic gradients in cancer incidence between countries. In England, for instance, communities with a high percentage of ethnic minorities have on average 10 μg/m^3 higher nitrogen dioxide levels compared to those with a predominately white population, while in the Netherlands, such differences are less than 4 μg/m^3 [43]. Exposure to air pollution is just one of many examples. There is a strong body of evidence showing that deprived communities are disproportionally burdened by adverse environmental exposures, for example, a higher density of industrial and waste management facilities (Pasetto et al. 2019) in their communities. Deprived communities are also less likely to have access to health-promoting features such as green and blue spaces (Hoffimann et al. 2017; Schüle et al. 2019). Efforts to describe the magnitude of the combined exposure impact have led to the development of a multivariable index of environmental deprivation combining, for example, information on air pollution, green space and proximity of industrial sources. Application of this index in countries such as the United Kingdom, New Zealand and Portugal has shown that areas with the worst overall environmental quality were those with the highest levels of socioeconomic deprivation, which also happened to have higher levels of cancer incidence and mortality (Ribeiro et al. 2015; Pearce et al. 2011; Richardson et al. 2013).

Differential Susceptibility

Differential susceptibility to the adverse health effects associated with environmental exposure arises from the double jeopardy of socioeconomic deprived individuals residing in areas with poor environmental quality, which might result in a cumulative detrimental influence on health. This concept strongly ties in with the framework developed to conceptualise how place-based features affect public health: the 'deprivation amplification model' (Macintyre 2007). According to the 'deprivation amplification model', socioeconomic deprived individuals have an increased health risk due to their personal circumstances, including a lack of resources (e.g. access to services including healthcare and education) and lifelong behavioural choices, which combined with exposure to poor environmental quality and environmental hazards may amplify their already elevated risk of disease. On the other hand, the least deprived individuals, which due to circumstances have lower rates of disease, are less affected by environmental determinants.

This differential susceptibility to the environment between most and least deprived individuals may constitute an important contributor to socioeconomic disparities in cancer, although research on the topic is limited and does not focus on cancer explicitly. Allostatic load (biological dysregulation, discussed in Chap. 19), a potential precursor of cancer, has been shown to be elevated in deprived neighbourhoods, probably due to increased pollution levels and lack of resources and services. This effect, however, was only significant among individuals of low

socioeconomic position, possibly due to their increased susceptibility to environmental factors (Ribeiro et al. 2019). Forastiere et al. observed a positive association of mortality with air pollution in people of low social position while an opposite trend was observed for individuals of high social position. They hypothesised that these contrasting trends are a result of the differential burden of underlying chronic health conditions conferring a greater susceptibility to the most disadvantaged people (Forastiere et al. 2007). The existence of differential susceptibility is critical for designing and implementing policies to tackle socioeconomic inequalities in cancer risk and supports the need for policies oriented towards high-risk and susceptible communities.

Conclusion

Empirical evidence is beginning to emerge on the impacts of environmental determinants on cancer incidence and mortality. The evidence so far highlights the fact that the places were individuals live, work and recreate may influence their risk of developing cancer over their lifetime. This evidence, coupled with the knowledge of differential environmental exposure and susceptibility depending on personal socioeconomic factors, further indicates that a substantial share of the socioeconomic gradient in cancer incidence could be attributed to environmental factors. Although substantial epidemiological evidence already exists showing a carcinogenic effect of air and water contamination as well as of ionizing radiation, literature on the effects of nature and built environment is still in its infancy, calling for further investigations on the topic. Research into environmental determinants on cancer risk is also challenged by a number of methodological issues related to exposure assessment and causal inference, which should be addressed in future research.

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Chapter 16
Life Course Approach, Embodiment and Cancer

Cyrille Delpierre and Michelle Kelly-Irving

Social Inequalities in Health and Embodiment

Socioeconomic position (SEP), often measured in epidemiology using occupation, education or income, plays an important role in the construction of health states and leads to a social gradient in health. An established body of research, particularly in the field of life course epidemiology using cohort data, shows the influence of the socioeconomic environment, from childhood to adulthood, on health. This association between SEP and health remains persistent after taking into account the classic lifestyle risk factors in adulthood. Recent work done within a European consortium project named Lifepath, showed a strong association between adult SEP and all-cause, cardiovascular and cancer mortality after adjusting for smoking, alcohol consumption, physical activity, obesity, diabetes and hypertension (Stringhini et al. 2017). In a systematic review, the median contribution of health behaviours to social inequalities in mortality was approximately 25–30% (Petrovic et al. 2018). Furthermore, childhood SEP is associated with a higher all-cause mortality, as well as cause-specific mortality such as cardiovascular deaths, and this association was observed after adjusting for socioeconomic factors and health behaviours during adulthood (Galobardes et al. 2004).

Many pathological processes, including cancers and cardiovascular conditions, are affected by classic risk factors such as tobacco, alcohol, BMI and physical activity. However, the evidence above suggests that other mechanisms beyond these may

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be involved in constructing the social gradient in health. The relationship between socially structures exposures and our adaptive biological functioning is therefore an important domain of enquiry for understanding the social gradient in health. The idea that the social environment may have a direct biological effect that may partly explain the social gradient in health has emerged in recent years. This hypothesis refers to the concept of embodiment, the way in which human environments (physical, chemical and social) get under the skin, eliciting a response from our bodies. Krieger describes embodiment as 'the way we incorporate, like any living organism, literally, biologically, the world in which we live, including our societal and ecological circumstances' (Krieger 2005). Embodiment refers to the fact that each human being is both a social and biological living being that incorporates the world in which he or she lives throughout life. The daily interactions between individuals and their surroundings occur via a complex network of processes, including social, economic, psychological and cultural factors that ultimately lead to modifications of a biological nature. In a previous work, we have further expanded on this definition as follows: 'Embodiment is therefore a dynamic set of social and biological processes and interactions between individuals within a population and their environments over time. It is a dynamic that is socially stratified representing the past environmental landscape and an ongoing response to the present environment. Humans thus come to physically represent their past environments in their present state through a constant process of change' (Kelly-Irving and Delpierre 2017).

Schematically, the social environment may influence biological functioning and health through two major types of mechanisms that interact over the life course and are deeply intertwined: (i) through 'exogenous' exposures involving external molecules from the body that impact biology. These exposures include chemical and physical exposures, such as air pollution, pesticides, viral exposures and occupational exposures to carcinogens, as well as behavioural exposures, such as tobacco, alcohol and food; (ii) through endogenous 'exposures' involving subjective interpretation and 'internal' molecules from the body mainly linked to stress perception and stress response systems. These exposures include social relationships, isolation, occupational constraints, life stress events and adverse childhood experiences (Kelly-Irving and Delpierre 2017).

One main issue is to identify what these potential mechanisms could be. The life course approach provides a relevant conceptual and methodological framework within which to examine the mechanisms involved in social-to-biological dynamic processes (Kuh and Ben-Shlomo 2005). The framework emerged from a convergence of research findings across disciplines (Kelly-Irving et al. 2015). In the 1990s, Barker, among others, showed that intrauterine growth retardation was associated with an increased risk of cardiovascular and metabolic diseases in adulthood, introducing the concept of foetal origin of disease (which became known as DOHaD: Developmental Origins of Health and Disease) (Barker 1990). This concept, widely demonstrated both epidemiologically and biologically in animal models, is based on the fact that environmental conditions during specific, sensitive windows of development can have long-term biological effects. However, work has shown that

an upwards social trajectory is associated with better health rather than remaining in an unfavourable social group throughout life, suggesting that there are factors that can improve the health of people born into a less advantaged social environment. Although some periods of life are more sensitive than others to environmentally induced variations due to greater plasticity and developmental kinetics, the phenomenon of biological embedding is not limited to the early years of life but is an ongoing process throughout life.

Consequently, a disadvantaged socioeconomic environment may be implicated in the development of future diseases through embodiment by modifying certain biological processes, in particular those involved in the stress response system, especially when exposures occur early in life. Studies have identified the importance of early life experiences to people's health across the life course. Epidemiological studies have described a strong graded relationship between adverse childhood experiences (ACE), defined as intra-familial events or conditions in the child's immediate environment causing chronic stress responses (Kelly-Irving and Delpierre 2019), and the leading causes of death, including from cancer, as the main risk factors that contribute to these causes of morbidity and mortality (Felitti et al. 1998) and risk factors of the leading causes of death (Felitti et al. 2019). This relationship between ACE and a large variety of health outcomes, including cancer, has been confirmed in a systematic review and meta-analysis (Hughes et al. 2017). Other stressful exposures, such as social isolation, loneliness and stress at work, have also been shown as independently associated with health, notably cardiovascular health (Kivimaki and Steptoe 2018; Steptoe and Kivimaki 2013). Evidence from epidemiological research suggests an influence of chronic stress exposure on health that is supported by biological evidence. Increasingly, research stemming from physiological and biomolecular studies has established how exposure to chronic stress leads to changes in the development of the nervous, endocrine and immune systems (Anda et al. 2006; Lupien et al. 2009; Steptoe and Kivimaki 2013). Some of the biological mechanisms include epigenetic changes, such as the DNA methylation, of genes involved in the stress response system. This includes genes which regulate the hypothalamic–pituitary–adrenal (HPA) axis that controls many fundamental bodily processes such as the immune and metabolic system. The disruption or deregulation of the HPA axis is an upstream factor in many chronic diseases. The DNA methylation of these genes may be an upstream determinant of many chronic diseases, including cancer (Argentieri et al. 2017). Findings from animal models have shown how early life events such as maternal separation modify the DNA methylation profile of some genes involved in stress response and inflammation (Provencal et al. 2012; Weaver et al. 2004). In humans, a recent systematic review done in March 2017 identified 17 articles looking at the association between early-life socioeconomic position and adult DNA methylation (Maddock et al. 2018). Evidence for the impact of SEP on DNA methylation was inconclusive, mainly because of a heterogeneity in the methodologies used and the limited sample size. However, the influence of early life stress such as ACE on the epigenome is clearer (Provencal and Binder 2015). All of these results suggest that

exposure to chronic stress, especially when it occurs early in life, may be associated with an acceleration of normal ageing processes (Marioni et al. 2015; Shonkoff et al. 2009).

Embodiment and Allostatic Load

If embodiment refers to the notion, shared by all living beings, of adaptation to one's environment, including the social environment, this phenomenon may partly explain the social gradient in health observed for the vast majority of chronic diseases. A key issue is to measure the physiological reality or the expression of this embodiment in humans. Our environment is highly variable, requiring a constant response from our physiological systems. This adaptation through change is crucial for survival and defines allostasis (Sterling and Eyer 1988). Three main systems, the nervous, endocrine and inflammatory/immune systems, are involved in the allostasis process, and all of them experience a maturation phase from the pre/postnatal period to adulthood (Adkins et al. 2004; Gogtay et al. 2004). Chronic exposure to stressors and inter-individual differences in stress susceptibility are both associated with prolonged activation of these allostatic systems. In the long term, this can lead to allostatic overload with potentially harmful consequences in terms of health. The allostatic load concept is defined by McEwen as follows: 'The strain on the body produced by repeated ups and downs of physiologic response, as well as by the elevated activity of physiologic systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease. We define this state of the organism as allostatic load' (McEwen and Stellar 1993). Allostatic load (AL) refers to the idea of an overall physiological wear and tear resulting from adaptation to the environment via the stress. It is the price paid by the organism over time to adapt to the demands of the environment.

In practice, AL is measured by using a composite score that represents multiple physiological systems to capture overall physiological wear-and-tear. The MacArthur Study of Successful Aging was the first to propose a score of AL (Seeman et al. 1997). The criteria for selecting the biological parameters included in the composite measure were that they should reflect the activity of the corticotropic axis or be influenced by the increased activity of glucocorticoids, corresponding to: systolic and diastolic blood pressure, high-density lipoprotein (HDL) and total cholesterol levels, waist-to-hip ratio, blood level of total glued haemoglobin, serum dehydroepiandrosterone (DHEA-S), urinary levels of cortisol, adrenaline and norepinephrine. Each biomarker was then dichotomised into high and low risk in each sex. The high-risk quartile was the top quartile of all biomarkers, except for those for which a low level conferred an increased risk of poor health outcomes (e.g. HDL). Some variants of AL scores can be found in the literature, but the most commonly used markers are associated with cardiovascular and metabolic disease, activity of the hypothalamic–pituitary–adrenal axis (HPA), sympathetic nervous system and inflammatory system.

Social Determinants and Allostatic Load

Any measure of embodiment capturing social-to-biological processes would need to be: (a) socially patterned and (b) a determinant of future health outcomes. As such, AL is a good candidate for capturing part of the embodiment process.

Studies on the relationship between social determinants and AL describe a social gradient of AL, building up from childhood and throughout life (Christensen et al. 2018a; Gruenewald et al. 2012; Gustafsson et al. 2011; Gustafsson et al. 2012; Merkin et al. 2014; Robertson et al. 2014). The more disadvantaged the SEP, the higher the AL score. This link seems to be mainly mediated by material factors (income, wealth) and health behaviours (smoking) (Robertson et al. 2015). Over the life course, education seems to be of particular significance as a mediator of the relationship between childhood SEP and AL (Christensen et al. 2018b; Graves and Nowakowski 2017).

A graded relationship is also observed between ACE and AL (Danese and McEwen 2012; Danese et al. 2009; Shonkoff and Garner 2012). In studies aimed at clarifying the causal chains linking the early psychosocial and economic environment and AL at age 44, using one of the rare birth cohorts that have collected such variables, the National Child Development Study (NCDS Cohort) that included more than 17,000 British people born in 1958 and interviewed at regular intervals from birth to the age of 50, we found an independent positive association between ACE and AL at age 44, measured as described above, as well as a negative independent association between early SEP (mother's education, father's occupation) and AL. This relationship between adverse environment and high AL was mediated by health behaviours (smoking and, to a lesser extent, BMI) and low SEP in adulthood (especially education), but these factors were not sufficient to explain the overall relationship observed (Barboza Solis et al. 2016a; Barboza Solis et al. 2015). ACE was associated with SEP, suggesting that SEP may also influence AL through psychosocial stress exposures.

Moreover, AL is also associated with other important factors of social stratification such as gender or 'race' (Rodriguez et al. 2019), suggesting that future work will have to better characterise the causal chains that can link social environment, in its multiple dimensions, and AL.

Allostatic Load and Health Status

AL has been identified in various contexts as a determinant of all-cause mortality (Duru et al. 2012; Gruenewald et al. 2006; Hwang et al. 2014; Karlamangla et al. 2006; Seeman et al. 2004b; Seeman et al. 2001) as well as morbidity such as in cardiovascular disease, cognitive and physical performance (Seeman et al. 2001) and subjective health (Barboza Solis et al. 2016b; Hu et al. 2007). Consistent with the concept of an overall physiological effect, AL has been identified as a better

predictor of mortality than each of the individual biomarkers making up the composite score examined separately or other composite scores such as metabolic syndrome (Castagne et al. 2018; Robertson et al. 2017; Seeman et al. 2001; Seeman et al. 1997).

There are few data available to analyse the relationship between SEP over the life course, AL and subsequent health within the same data set. However, some of these studies have highlighted the mediating role played by AL in the relationship between SEP and health (Kim et al. 2018; Seeman et al. 2004a). Using NCDS data, we have highlighted the relationship between childhood SEP and AL, that this relationship was mediated by educational, material and health behaviour pathways and that AL was a predictor of subjective health and all-cause premature mortality over an 11-year period. We have also shown that AL was a better predictor than each of its components, although the inflammatory system also appears to be particularly important (Barboza Solis et al. 2016a; Barboza Solis et al. 2015; Castagne et al. 2018).

Embodiment, Allostatic Load and Cancer

The life course approach has been widely used to explore many chronic diseases, but cancers have often been overlooked. However, as an integrative approach, the life course approach could facilitate the understanding of a complex set of diseases such as cancers, which are characterised by a long latency period involving various types of exposures. We detailed in a previous work why it could be particularly relevant to study cancer as a set of pathologies which may represent life course processes and the embodiment dynamic expressed as a disease (Kelly-Irving and Delpierre 2017). First, cancer is one of the leading causes of death worldwide and plays a major role regarding social inequalities in mortality. Second, social inequalities in the burden of cancer are the result of socially stratified access to care once cancer has been diagnosed, where access to care and management (screening, treatment and surveillance) impact cancer survival, as well as the long term consequence of socially stratified exposures to cancer risk factors, mainly exogenous exposures such as chemical, physical exposures and behaviours (tobacco and alcohol consumption, physical activity, food intake). It is now well established that these determinants are not sufficient to explain social inequalities in cancer incidence, which therefore remain poorly understood and complex. Third, cancers are an interesting set of pathologies which not only have a common root in the immune/inflammatory system but also consist of a number of different aetiological processes and biological mechanisms. The immune/inflammatory system is sensitive to environmental challenges soliciting the stress response system, making cancer a potentially particularly relevant disease model for studying how social factors become biological via a life course approach.

In fact, there is increasing evidence for the role of chronic stress in cancer development and progression (Antoni et al. 2006; Kelly-Irving et al. 2013b; Lutgendorf

et al. 2010). Experimental analyses in vivo animal models have shown that chronic stress can accelerate the progression of various cancer, such as breast, prostate, ovarian carcinomas, neuroblastomas, malignant melanomas, pancreatic carcinoma and some haematopoietic cancers such as leukaemia (Cole et al. 2015). Most of these biological changes were prevented by beta-adrenergic (ADR) inhibitors, providing a link between stress-induced adrenergic axis stimulation and modulation of the antitumour immune response (Thaker et al. 2006). The sympathetic nervous system signalling may thus potentially exert clinically significant effects on tumour biology. Previous clinical studies have shown that the use of beta-blockers may favourably influence the survival of ovarian cancers (Watkins et al. 2015) and, more recently, pancreatic carcinomas (Udumyan et al. 2017). Previous human studies have described that chronic exposure to adverse social environments (poverty, isolation, combat and demanding or uncontrollable jobs) is associated with common changes in circulating immune cells gene regulation (so-called conserved transcription response to adversity, CTRA) (Cole 2013, 2014). Studies of what Cole et al. calls 'human social genomics' are now increasing and are clarifying which specific types of human genes are subject to social regulation and mapping the social signal transduction pathways that mediate these effects (Cole 2014).

The epidemiological literature on the link between stress and cancer is sparse and generally inconclusive because the results are contradictory. For example, a systematic review of studies on the association between stressful life events and breast cancer incidence did not support an overall association (Duijts et al. 2003), but a more recent systematic review found that stressful life events increased the risk of breast cancer (Bahri et al. 2019). This may be due to the nature of the stress considered (acute versus chronic), its timing (early versus adult), its measurement (retrospective versus prospective) and the study design (cohort versus case-control studies). Keinan-Boker et al. observed a higher risk of all-site cancer among Israeli Jews who were potentially exposed to the Holocaust than those who were not in a large cohort (more than 4,900,000 person-years). The risk of cancer was the highest for those who were born between 1940–1945 and thus exposed to the Holocaust between 0 to 5 years (Keinan-Boker et al. 2009), suggesting a stronger effect of early life stress. In fact, some studies using prospective data have suggested that the origins of adult cancer may have their roots in the early life environment, where adverse childhood experiences are linked to cancer development along complex life course pathways (behaviours, adult SEP) that do not totally explain the association (Kelly-Irving et al. 2013a). This result was reinforced in a systemic review that highlighted, from the 12 articles identified as analysing the associations between ACEs and adult cancer incidence, that ACEs were associated with an increased risk of cancer in adulthood (Holman et al. 2016). Regarding potential mechanisms linking ACE and cancer risk, ACE has been found as associated with the presence of the main known cancer risk factors in adulthood (Ports et al. 2019). Moreover, among the very few studies that analyse the link between AL and cancer risk, an association has been found between AL and cancer risk, notably breast cancer in black women (Parente et al. 2013); AL being associated with a higher risk of poorer tumour differentiation and large tumour size in these women (Xing et al. 2020).

Overall, these findings suggest that cancer risk may be determined, in part, by exposure to stressful conditions and events early in life. However, important issues need to be addressed to develop this research in the field of cancer.

A Promising Approach for Cancer Aetiology, but with Important Issues to Address

Research on the influence of stress on cancer development needs to be reinforced, which will require some improvements. Available results from animal models show clearly how chronic stress exposures are able to modify biological functioning, including systems involved in cancer development. Epidemiological results are inconclusive for stressful life events but suggest that there may be a link with early chronic exposures to stress and cancer risk. Future research will need to clearly define what type of stress is being measured and will need to use appropriate datasets. It seems clear that the prospective measurement of stress exposure should be preferred. However, this type of measurement remains truly exceptional in medical records and remains infrequent in cancer cohorts, which largely concentrate the collection of data on classic risk factors such as behaviours or occupational exposures to a lesser extent.

There is growing evidence to suggest that many chronic diseases, such as metabolic diseases such as obesity, diabetes and vascular diseases, or Alzheimer's disease/dementia and cancers, are interrelated. Barabasi et al. use the term 'human disease network' to explain this biological network reality, which manifests itself through molecular and genetic links between clinically very different pathologies (Barabasi et al. 2011). Many biological processes are shared between various pathologies, as well as many risk factors, with many pathologies thus sharing common roots. There is thus a biological plausibility behind the associations observed between these diseases, illustrating the notion of common roots, common soil for many chronic diseases. As a proxy for global wear and tear resulting from adaptation to the environment, AL may be a relevant concept and tool for studying embodiment processes. However, studies looking at the association between AL and cancer risk remain extremely rare and need to be more deeply developed.

The measure of embodiment is also a major issue. A systematic review aimed at providing a comprehensive overview of the way AL is built and its association with SEP has shown that although there is an overall negative association between SEP and AL, where social deprivation is related to increased physiological wear-and-tear, there is no standard method of calculating AL scores, an inconsistency in biomarkers used to operationalise AL and a lack of fidelity to its original conception (Johnson et al. 2017). Some other biomarkers may be potential candidates to measure physiological wear and tear. It is then legitimate to question the differences or complementarities existing between AL and other markers such as markers of ageing (Belsky et al. 2015; Johnson 2006) or cumulative biological risk (Karimi et al. 2019; Seeman et al. 2010). Some of these other biomarkers have been shown as

associated with chronic stress exposures as well as with cancer development and may constitute better markers of embodiment in the cancer field: this is the case for epigenetic pathways such as DNA methylation of HPA axis genes involved in glucocorticoid regulation (Argentieri et al. 2017) or epigenetic clocks (Horvath 2013; Levine et al. 2018) or telomere length (Price et al. 2013). Some works aim to compare some of these biomarkers in their capability to link SEP and health, such as for epigenetic clocks and AL (Mccrory et al. 2019). Such work needs to be deeply developed in the cancer field.

Developing a life course approach to studying cancer remains challenging. The research discussed here highlights questions of timing (especially early childhood) and causes (early psychosocial stress) other than those targeted by conventional prevention interventions and multiple mechanisms (behavioural, chemical, physical, psychosocial, biological). A major challenge is to clarify the nature of the multiple exposures associated with SEP and how they interact to influence the risk of cancer occurrence. SEP is a proxy for various exposures, and social variables are not interchangeable and do not measure the same aspects of social life. Conducting such work requires the availability of longitudinal data, over long periods of time, including a large array of variables, including not only the psychosocial and economic environment but also biological data, even though such cohorts or databases remain rare, particularly in France.

This approach re-examines the notion of causality by insisting on the notion of chains of causality, causes of causes. In this way, 'a cause' is the name attributed to any one point in a chain of causes upon which it may be possible to intervene. The contribution of this approach to the understanding of many chronic pathologies is notable. In the field of cancer, its use constitutes a paradigm shift by framing the development of cancers as the result of a chain of psychosocial, behavioural and biological causes from the beginning of life. However, the mainstream approach to cancer risk factors remains focused on proximal risk factors.

Conclusion

In this chapter, we first briefly summarised the concept of embodiment and specifically the way the social becomes biological; and second, we provided a short discussion of how and why this concept may be particularly relevant to cancer research. We highlighted how differential biological embodiment according to social groups in response to socially differentiated environments could partly explain the social gradient in health, and particularly cancer incidence. We also highlighted the evidence existing from animal and human studies on the influence of chronic stress over the life course on cancer risk. We pointed out the relative paucity of this literature in the cancer field.

The need for a scientific shift where we place biological mechanisms in their social contexts is fundamental to better understand cancer development over a long period of time. This would affect how we think about diseases and go about

studying them, enabling us to address real primary prevention. This shift needs to come from researchers and physicians—not the general public, which is already receptive to thinking about cancers as a product of life course processes and an embodiment dynamic. The increase of immunotherapy in the cancer field, by underlying the role of the immune system in cancer development and then the importance of the environment/immune system interaction, may be an opportunity to help bring about this shift. This will require expanding our investment in longitudinal studies, such as cohorts and panel studies, collecting data of a biomedical, biological, chemical and psychosocial nature. With this type of data, plausible hypotheses on the pathways between the social and the biological can be tested, and most importantly, links can be made between life course research and complex real-life interventions to not only improve health and reduce social inequalities in cancer but also in health more broadly.

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Chapter 17
Role of Screening in the Social Gradient for Survival of Cancer Patients in Europe

Elodie Guillaume

European Cancer Statistics and Recommendations

Cancer remains a major public health concern in the European Union (EU) and represents the second leading cause of death in EU countries after circulatory diseases. In 2018, there were just over 3.9 million estimated new cases of cancer. The most common cancer types were female breast cancer (523,000 cases, 13.4% of all cancer cases), followed by colorectal cancer (500,000, 12.8%) (Ferlay et al. 2018). Overall, approximately 95,300 people died of breast cancer in 2015, and the vast majority (94,300) were women. The standardised death rate was 32.7 per 100,000 inhabitants for women. Concerning colorectal cancer, 154,000 people died, and the standardised death rate was 30.4 per 100,000 inhabitants (Ponti et al. 2017).

However, the incidence and mortality of these cancer localisations vary greatly. The estimated incidence rate of breast cancer varies from 60 to 155 per 100,000, with an elevated incidence in Western European countries. For colorectal cancer, a fivefold variation in the incidence rates has been observed, with the highest rates in Central Europe. Across Europe, geographical patterns of mortality partially follow incidence (Ferlay et al. 2018). Thus, in 2015, the highest standardised death rate for breast cancer among women was recorded in Croatia (43.1 per 100,000 inhabitants), followed by Slovakia and Hungary, while the lowest rate was in Spain (23.4 per 100,000 inhabitants). For colorectal cancer, the highest standardised death rate was recorded in Hungary (54.1 per 100,000 inhabitants), followed by Croatia and Slovakia. Austria, Greece, Finland and Cyprus were the only member states to record standardised death rates for colorectal cancer that were below 25.0 per 100,000 inhabitants (Ponti et al. 2017).

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These rates were recorded despite the recommendations of the European Union Council in 2003 (European Council 2003), which proposed the implementation of organised, population-based screening programmes and made clear recommendations on organised screening for breast and colorectal cancer. The member states were to implement programmes in a well-organised manner, with quality assurance at all levels and taking into account the potential needs of specific socioeconomic groups (Ponti et al. 2017). The target populations recommended for breast and colorectal cancer screening were individuals aged 50–69 years and 50–74 years, respectively (Basu et al. 2018). A pre-established but modifiable appointment for mammography screening with double reading in an accredited centre was considered crucial for breast cancer, while mailing of the faecal occult blood test (FOBT) kit for colorectal cancer screening to the home address were considered the most effective strategies to ensure high participation. Moreover, the recommendations underlined the need for a centralised data system to ensure that all individuals targeted by the programme were invited by means of a call/recall system (Vale et al. 2019). Nevertheless, differences in health and economic policy imply disparities between the member states in terms of the status of implementation and the extent to which screening programmes are organised.

Screening Organisation in European Countries

For breast and colorectal cancer, a state of screening implementation in the EU-28 was compiled, and the information is summarised in Table 17.1.

Table 17.1 Type of screening test used and age of targeted population for breast and colorectal cancer screening in the EU-27 and UK (Basu et al. 2018; Deandrea et al. 2016; Altobelli et al. 2019; Senore et al. 2019)

EU-28	Type of BC screening programme[a]	Test[b]	Age	Type of CRCC screening programme[a]	Test[c]	Age
Austria	PB (national)	M	45–69	NPB	FIT – TC	>50
Belgium	PB (regional)	M + MMU	50–69	PB (regional)	gFOBT-FIT	50–74
Bulgaria	Pilot	MMU	NR	NPB	FIT	NR
Croatia	PB (national)	M	50–69	PB (national)	gFOBT	50–74
Cyprus	PB (national)	M	50–69	PB (national)	gFOBT	>50
Czech Republic	PB (national)	M	>45	NPB	FIT – TC/ gFOBT	50–54
Denmark	PB (national)	M	50–69	PB (national)	FIT/gFOBT	50–74
Estonia	PB (national)	M + MMU	50–62	PB (national)	FOBT	50–74
Finland	PB (national)	M	50–69	PB (national)	gFOBT	50–69
France	PB (national)	M + CBE + MMU	50–74	PB (national)	FIT	50–74
Germany	PB (national)	M	50–69	NPB	gFOBT-TC	50–54
Greece	NPB	MMU	NR	NPB	gFOBT-TC	50–70
Hungary	PB (national)	M	45–65	PB (national)	FIT	50–70

Table 17.1 (continued)

EU-28	Type of BC screening programme[a]	Test[b]	Age	Type of CRCC screening programme[a]	Test[c]	Age
Ireland	PB (national)	M + MMU	50–64	PB (national)	FIT	55–74
Italy	PB (national)	MMU	50–74	PB (national)	FIT-FS	50–70
Latvia	PB (national)	M + MMU	50–69	NPB	gFOBT	>50
Lithuania	PB (national)	M	50–69	NPB	FIT	50–74
Luxembourg	PB (national)	M	50–69	NPB	FIT	55–74
Malta	PB (national)	M	50–60	PB (national)	FIT	60–64
The Netherlands	PB (national)	M + MMU	50–75	PB (national)	FIT	55–75
Poland	PB (national)	M	50–69	PB (national)	TC	50–66
Portugal	PB (regional)	M + MMU	45–69	PB (regional)	FOBT	50–70
Romania	PB (regional)	M	50–69	NR	NR	NR
Slovakia	NPB	NR	NR	NPB	TC	>50
Slovenia	PB (national)	M + MMU	50–69	PB (national)	FIT	50–69
Spain	PB (regional)	M	45–69	PB (national)	FIT	50–69
Sweden	PB (national)	M	40–74	PB (regional)	gFOBT	60–69
United Kingdom	PB (national)	M	50–70	PB (national)	FIT	50–74

[a]*PB* Population-Based/*NPB* Non-Population-Based
[b]*M* Mammography/*MMU* Mobile Mammography Unit/*CBE* Clinical Breast Examination
[c]*FIT* Faecal Immunochemical Test/*gFOBT* guaiac Faecal Occult Blood Tests/*FOBT* Faecal Occult Blood Tests/*TC* Colonoscopy/*FS* Flexible Colonoscopy

Breast Cancer Screening

Reports on the status of European breast screening programmes (Deandrea et al. 2016; Basu et al. 2018) have shown that a national or regional programme with national coordination is implemented in nearly all countries. Bulgaria was piloting a programme, and no evidence of population-based programmes was found for Greece and Slovakia. Population-based cancer screening programmes were considered, meaning that the eligible target population in areas served by the programmes were identified and invited to each round of screening.

The screening method used most often is mammography alone, except in France, where mammography is combined with a clinical breast examination. Mammography includes radiological imaging of the breast with two views. The sensitivity of imaging is thus increased by 20%, with the greatest incremental benefit for the detection of small cancers in women with dense breast tissue (Hakama et al. 2008). The resulting images are usually read by two radiologists independently in separate sessions. A target age wider than the recommended age of 50 to 69 years (European Commission 2013) has been adopted by several countries: Austria, Czech Republic, France, Hungary, Italy (some regions), the Netherlands, Portugal and Sweden. The screening interval is 2 years in all countries except Malta and the United Kingdom

(UK), where the interval is 3 years (Basu et al. 2018). Among members using a population-based programme, some use mobile mammography units as a complement modality at the national or regional level: Belgium, Estonia, France, Ireland, Italy, Latvia, the Netherlands, Portugal and Slovenia (Guillaume et al. 2017b). The screening tests are provided free of charge in all countries, but women have to pay for the diagnostic tests in Belgium, Cyprus and France (Table 17.1).

As mentioned above, screening programmes are not implemented at the national level in all countries. Combined with other country-specific contextual factors, adherence to screening programmes varies considerably between countries and few attain the recommended participation rate of 70%. According to Eurostat, screening rates were below 50% in seven countries, with a low of 0.2% in Romania (2015 data). The lowest screening rates were recorded among those members that joined the European Union in 2004 or more recently, and in countries such as France, Germany (2015 data), Italy, Luxembourg and Greece, which had relatively low screening rates (within the range of 50–60%). In several Northern European countries, including Denmark, Finland and Sweden (2014 data), and in Portugal (2014 data), a rate of approximately 80% has been achieved (Ponti et al. 2017).

In addition to the development of population-based screening programmes, opportunistic screening may occur where a woman participates as a result of a recommendation made by a healthcare practitioner or of their own choice. Such screening is often performed in women outside the recommended screening age group.

Colorectal Cancer Screening

In contrast to the relatively standardised breast cancer screening programmes across Europe, colorectal cancer screening differs not only between countries but also between regions within countries according to their resources, infrastructure and health data management (Altobelli et al. 2014). To attempt to synthesise this information is somewhat hazardous, especially because screening is currently being implemented in some countries. Recent reviews (Navarro et al. 2017; Altobelli et al. 2019; Senore et al. 2019) have shown that in 2016, population-based colorectal cancer screening programmes were being or had been rolled out in 18 countries at the national or regional level. Other members are currently planning population-based colorectal cancer screening programmes (Basu et al. 2018).

Programmes are the most often based on periodic faecal occult blood tests (FOBTs), followed by colonoscopy when the results are positive in persons aged 50–74 years. All include a call/recall system, ensuring active invitation of the target population. The most widely used FOBT is based on a biochemical test (guaiac test, gFOBT) reacting to haemoglobin in stool. gFOBT involves dietary restrictions before testing to reduce false positives and several samples. It is progressively being replaced by a faecal immunochemical test (FIT) based on human haemoglobin antibodies. No special diet is required for this test, only one sample is needed in most

screening programmes, and the results are read automatically (Altobelli et al. 2014). This test has replaced the gFOBT in screening programmes in the UK since 2014 and in France since 2015, and it is currently used in at least 16 countries. Three countries offer endoscopy screening: flexible sigmoidoscopy (FS) in a region in Italy, and colonoscopy (TC) in Poland and Slovakia (Table 17.1).

The recommended target age of 50–74 years was adopted by the programmes in Belgium (Wallonian-Brussels region), Croatia, Czech Republic, Denmark, Estonia, France, Germany, Lithuania and the UK. The screening interval for programmes based on gFOBT or FIT is 2 years in all countries, except Austria, which implements yearly screening. For countries organising screening with colonoscopy at the regional level, screening is offered with a 10-year interval in Austria, Czech Republic and Germany and with a 5-year interval in Greece. The screening tests are administered free of charges in all countries. Diagnostic investigations, mainly by colonoscopy for positive tests, are free in all countries, except Finland, France, The Netherlands and Sweden (Basu et al. 2018).

The European Council report sets a 65% participation rate as desirable for the defined target population, but few countries reach this goal. The rate is higher in countries adopting FIT, ranging from 22.8% to 71.3%, than in those using gFOBT, ranging from 4.5% to 66.6%. For example, in the Southern Basque country, a very high participation rate of 75% is achieved, and 92% of all patients with a positive test also receive a colonoscopy. The Netherlands has the highest participation rate at 68.2%. There is also a positive correlation with participation in breast cancer screening in the same areas (Senore et al. 2019). Concerning colonoscopy as a screening test or after a positive FOBT, adhesion depends on the capacity to perform colonoscopy, with a more than threefold variation in endoscopy resources across European countries.

Disparities in Screening Programmes in European Countries

Several factors at both individual and contextual level affect breast cancer and colorectal cancer screening participation. At the individual level, there are different variables: socio-demographic characteristics such as gender, age, ethnicity, marital status, smoking status, level of education and household income. There are also factors such as healthcare utilisation, and health behavioural and psychological factors such as beliefs and attitudes towards participation. At the contextual level, the variables include health system characteristics, invitation strategies and social, cultural and environmental factors (Damiani et al. 2015; Wools et al. 2016).

Regarding colorectal cancer screening, most studies have found that women are less likely to participate than men, although this depends on the test proposed and varies across countries. For both breast and colorectal screening, being younger than 60–65 years, not having a spouse, having low household income and low education level have all been reported by several studies as a significant barrier in

adherence to screenings, as is having no health insurance coverage. People living in rural areas and having less contact with healthcare providers also have lower participation rates. Negative perceptions of screening tests include embarrassment, being afraid of pain during breast screening, the perception that 'screening is not necessary', and lack of knowledge regarding the usefulness of screening. On the other hand, having a healthy lifestyle (no smoking, doing sport) and self-efficacy are both facilitators of participation (Ouédraogo et al. 2015; Plourde et al. 2016; Wools et al. 2016).

The implementation of population-based programmes, which are available in many European countries, increases the overall participation in screening. They are implemented by ignoring the principle of proportionate universalism. As people with a high socioeconomic level adhere more to screening, inequalities in cancer screening participation related to socioeconomic status remain (Smith et al. 2019), despite the recommendation to take the needs of particularly deprived socioeconomic groups into account.

Socioeconomic inequalities may be assessed by using individual variables such as income, level of education and an ecological index measured at area level such as the European Deprivation Index (EDI). The EDI is based on the concept of deprivation and considers needs that are unmet owing to a lack of resources of all kinds, not just financial ones (Guillaume et al. 2016). The association between low socioeconomic status or deprivation and low participation in breast and colorectal cancer screening is now well established. A recent review by Smith et al. and other studies have shown evidence of a negative association between area-level socioeconomic deprivation and breast cancer screening participation in Europe (Sandoval et al. 2017; Relecom et al. 2018; Smith et al. 2019). For colorectal cancer screening, the association has also been demonstrated between low socioeconomic status (low income, unemployment, low education and area of residence) and low screening participation (Pornet et al. 2010; Altobelli et al. 2014; Hurtado et al. 2015; Larsen et al. 2017).

Impact of Inequalities in Participation

Randomised controlled trials and observational studies have consistently shown that systematic screening at the population level through quality-assured population-based programmes can reduce breast and colorectal cancer mortality. Mammography screening programmes in Europe have led to a 25–30% breast cancer mortality reduction in women between 50 and 74 years (Peintinger 2019). CRC screening based on stool testing (FOBTs) with gFOBTs has led to a 15–33% reduction in CRC mortality, but with more contrasting results (Plourde et al. 2016). All over Europe, decreasing mortality rates imply that programmes are reaching the recommended participation rate of 70% and 65% for breast cancer and CRC screening, respectively.

There are also inequalities in mortality rates for these cancers. Inequalities in cancer mortality results of social inequalities in incidence resulting from individual health behaviours and exposure, and independently on social inequalities in survival imply inequalities in prevention, stage at diagnosis (the most important prognostic factor for survival) and treatment. For both breast and colorectal cancer, inequalities in screening participation can lead to a delayed diagnosis, a more advanced stage, shorter survival and higher mortality (von Wagner et al. 2011; Damiani et al. 2015).

The prognosis for breast cancer is good, with a 5-year relative survival rate close to 87% in most European countries. However, studies conducted in France (Poiseuil et al. 2019) and the UK (McKenzie et al. 2012; Woods et al. 2016) reported that survival rates were lower in non-attenders than in screening-detected women. The timeliness of diagnosis is one of the possible explanations for these patterns. Among the most deprived women, the survival rate is also significantly different between non-attenders and screening-detected women, suggesting an important effect of mass screening in this group. The absence of difference in survival between screening-detected and non-attending women among the most affluent may be explained by the presence of opportunistic screening in France (Louwman et al. 2007; Poiseuil et al. 2019). There is also a paradox with breast cancer: women in more socioeconomically deprived areas have a lower incidence of breast cancer but higher mortality rates. This may be attributable to lower rates of breast cancer screening participation and to a delayed diagnosis, as well as to suboptimal cancer care and comorbidities that may limit treatment options or increase the likelihood of developing treatment complications (Smith et al. 2019).

In most European countries, the 5-year relative survival rate for colorectal cancer is 63%, although the incidence is less associated with deprivation than in breast cancer (Bryere et al. 2019). As in breast cancer, the negative impact of low socioeconomic status on CRC stage at diagnosis has been demonstrated. In a clinical trial of screening for colorectal cancer in the UK, participation was shown to be associated with earlier diagnosis and longer post-operative survival (Woods et al. 2006). However, the directions were not always clear, and when no associations were found, the tendency could be explained by several factors such as disparities in access to health care, cancer awareness, and/or beliefs and attitudes towards cancer and preventive services such as screening (Feller et al. 2018). Moreover, the incompleteness of screening procedures due to a lack of follow-up after a positive FOBT may result in delayed detection of CRC and possibly a missed opportunity for preventive measures.

Mass screening seems effective regarding cancer survival but remains controversial (Relecom et al. 2018). Differences in stage at diagnosis cannot always fully explain the observed social gradients in survival; therefore, other factors relating to health care may be involved (Merletti et al. 2011). For example, in the UK, which has a universal healthcare system, there is evidence of differential treatment between socioeconomic groups.

More Equity Is Needed in Population-Based Screening Programmes

According to the principle of action to reduce health inequalities (Whitehead 2007) and particularly to the principle of proportionate universalism (Marmot and Bell 2012), the provision of equitable preventive care implies using screening strategies that might differ between socioeconomic groups so that everyone has an equal chance of benefiting from screening. There is also some evidence that rural populations are less likely to adhere to screening programmes and that they receive less chemotherapy and surgery. While the importance of the socioeconomic determinants of poorer health outcomes is now well established, it is likely that rurality and deprivation interact to produce greater disadvantage through lack of access to appropriate health care (Carriere et al. 2018).

Because population-based screening is already available in most European countries, complementary interventions or modalities could be proposed. Interventions could target factors such as information strategies to increase the knowledge and empowerment of individuals by producing informative materials adapted to the needs of specific population groups and catering for their level of literacy. Invitations could also be adapted as follow-up calls to non-attendants and specific accompaniment could be provided on the basis of the patient navigator model (Freeman 2006; Guillaume et al. 2017a). This would also increase the empowerment of entire communities. Other interventions could focus on improving accessibility, for example, by breaking down barriers to transport, waiving fees for transport and facilitating out-of-hours appointments. Mobile units for breast cancer screening already exist in some rural areas in at least 11 European countries and often in a specific region (Altobelli and Lattanzi 2014; Greenwald et al. 2017). Such interventions must be studied and evaluated to enable policymakers to make the right choices regarding healthcare policy (Guillaume et al. 2017a, b; Sandoval et al. 2017).

Conclusion

Screening programmes for the early diagnosis of breast and colorectal cancer have considerably improved in Europe. Several countries have improved their procedures and others are doing so or will do so in the near future (Altobelli et al. 2019). Despite this progress, however, inequalities persist within and between countries with regard to the indicators of participation, survival and mortality, and nearly half of cancer deaths could be avoided if more preventive action were to be taken.

While an early stage at diagnosis is an important prognostic factor concerning survival, particularly for cancers with better prognosis, differences remain between the socioeconomic classes, and this gradient is partly associated with screening participation. These issues are complex because both distal and proximal causes of

inequalities are involved. As recommended by the Commission on Social Determinants of Health (CSDH), structural factors such as the socioeconomic level of the country, health policy, and financial and housing policy are all intertwined and should be addressed (Marmot and Bell 2012).

According to the contextual determinants and resources available in each country, healthcare policies must be based on the tenets laid down by the CSDH if equity in health care is to become a reality. If these recommendations are not taken into consideration, a population-based programme applied at the national level ignoring the principle of proportionate universalism could increase inequalities between countries. Removing these structural inequalities by organising efficient and cost-effective cancer screening services should be seen as an important target in the European Union.

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Chapter 18
The Role of Comorbidities in the Social Gradient in Cancer Survival in Europe

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Social disparities in cancer survival in Europe are evident, as discussed in earlier chapters of this book. Survival is commonly worse among the more socioeconomically deprived cancer patients, an issue that is pertinent for many different cancer types. The prognosis of cancer patients can be affected by the presence of additional diseases or comorbidities, with the more deprived patients tending to experience a higher prevalence of comorbid conditions. This chapter aims to examine the role played by comorbidities in the social gradient in cancer survival that is often observed in Europe.

To illustrate the interconnections of comorbidity—and variables associated with comorbidity—with social inequalities, the directed acyclic graph (Fig. 18.1) depicts

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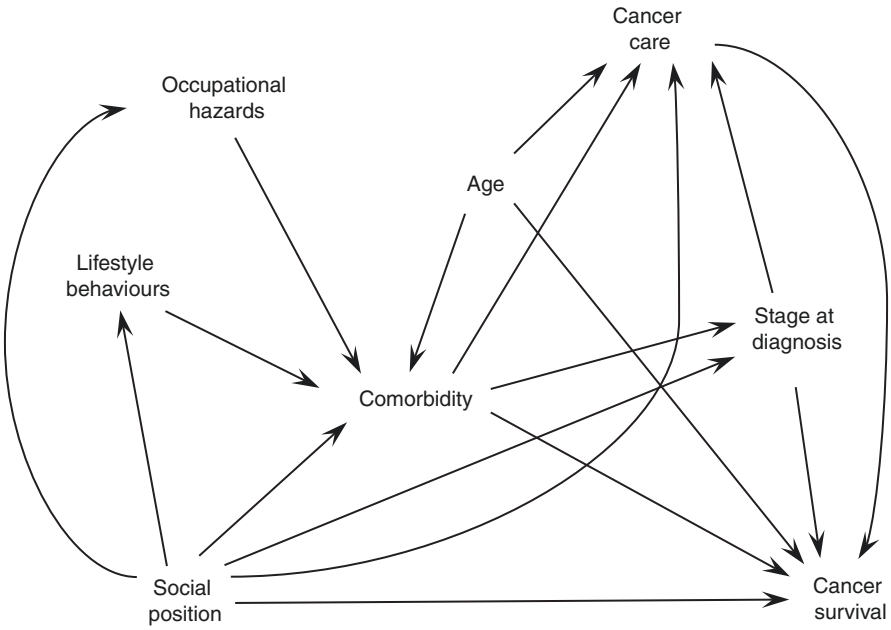

Fig. 18.1 Directed acyclic graph (DAG) illustrating the interconnections of comorbidity in the relationship between social position and survival from cancer

assumed causal relationships between social position and cancer survival. This chapter will discuss these relationships in turn, and will then summarise the findings of scientific studies investigating comorbidity as an explanatory factor in social or socioeconomic inequalities in cancer survival in European countries.

Defining Comorbidity

The terms multimorbidity and comorbidity are frequently used in the literature when discussing disease prevalence. Multimorbidity is a broad term that refers to the presence of two or more chronic diseases, while comorbidity describes one or more other chronic diseases that co-exist with a primary disease of interest (Porta et al. 2014). Comorbidity is commonly considered as a prognostic factor in cancer outcomes (Sarfati et al. 2016). The distinction between multimorbidity, comorbidity and related terms is particularly timely with the ever-increasing number of studies examining the impact of multiple chronic conditions (Nicholson et al. 2019). Indeed, the PubMed Medical Subject Headings (MeSH) were updated in January 2018 to include multimorbidity as a separate term from comorbidity.

Although there are a variety of approaches to quantifying comorbidity within the scientific literature, there is no agreed gold standard for measuring comorbidity in the presence of cancer (Sarfati 2012). The lack of consensus on the best approach to defining and measuring multiple chronic diseases challenges the ability to compare findings across populations and to draw upon the literature for the development of

guidelines and interventions (Johnston et al. 2019). Studies of comorbidity and cancer outcomes may define comorbidity in terms of specific chronic conditions (Bare et al. 2017) or consider the patient's full comorbidity burden based on a summary metric, such as the widely used Charlson Comorbidity Index (CCI) (Charlson et al. 1987). Other metrics of comorbidity often used in the cancer patient setting include the Adult Comorbidity Evaluation – 27 (ACE-27) developed for adult cancer patients (Piccirillo et al. 2008), and the Elixhauser Index (Elixhauser et al. 1998) or age-adjusted CCI (Charlson et al. 1994), which are not specific to cancer patients. Another variable in quantifying comorbidity relates to the time window during which the presence of comorbidities is considered relevant for defining the patient's comorbidity status once the cancer has been diagnosed. Studies have investigated the overall look-back time period for comorbidities or the length of the time that is excluded prior to primary disease diagnosis (Preen et al. 2006; Shack et al. 2010; Maringe et al. 2017), offering different perspectives on the most appropriate time period to use. It may not be possible to establish a universally agreed 'optimal' time window, given that this window may vary between studies, depending on the research question and underlying assumptions about comorbidity. Another anomaly is whether summary metrics used for cancer comorbidity should consider previous malignancies as a comorbidity. Additionally, there are a variety of sources of patient-level information on cancer comorbidity, ranging from information collected during clinical trials to routine, administrative sources such as primary or secondary care data. In comparing data sources, the strengths and limitations of each can vary according to quality, reliability and generalisability (Geraci et al. 2005).

Social Gradient in Comorbidity Prevalence

Comorbidity prevalence has been shown to be associated with socioeconomic position, both in a general context (Macleod et al. 2004; McLean et al. 2014; Moffat and Mercer 2015)—that is, not specific to a nominated primary disease—and within the context of cancer (van Leersum et al. 2013; Aarts et al. 2015; Fowler et al. 2020). For example, one study found mixed physical and mental health multimorbidity was more common among more deprived than less deprived people at all ages under 75 years (McLean et al. 2014). Furthermore, a low socioeconomic position was observed to be associated with a higher risk of comorbidity, independently from the cancer under study (Louwman et al. 2010; Fowler et al. 2020).

Additionally, many cancers and comorbid conditions share common aetiological risk factors, which in turn are associated with increasing levels of socioeconomic deprivation. For example, the development of common cancers, such as lung or colorectal cancer, has been linked to tobacco smoking (Schottenfeld and Fraumeni 2006; Tindle et al. 2018), dietary habits and alcohol use (Danaei et al. 2005; Haggar and Boushey 2009). Tobacco smoking is also linked to conditions such as chronic obstructive pulmonary disease (Devereux 2006; Buist et al. 2007; Laniado-Laborín 2009) and type 2 diabetes (Hu et al. 2001; Wannamethee et al. 2001), and with socioeconomic position (Cavelaars et al. 2000; Giskes et al. 2005; Huisman et al. 2005; Hiscock et al. 2012). Other risk factors such as poor dietary habits, lack of

physical activity and obesity can also typically follow a social gradient (Alcaraz et al. 2020). The risk of excessive alcohol consumption and binge drinking has been shown to be socioeconomically patterned (Fone et al. 2013), while alcohol consumption and raised body mass index are both associated with liver disease, with evidence of a synergistic interaction between the two (Hart et al. 2010). Moreover, health conditions that are typically most prevalent among people of a lower socioeconomic position, such as diabetes (Fano et al. 2013; Grundmann et al. 2014; Kim et al. 2015), can be associated with an increased risk of a wide range of cancers (Dankner et al. 2016).

Comorbidity Prevalence among Cancer Patients in Europe

Within the epidemiological literature, studies investigating the role of comorbidity in cancer outcomes often summarise the overall comorbidity status of a patient. European studies providing a detailed discussion of the prevalence of comorbid conditions among cancer patients are fairly limited in number, and most of the research has been conducted in the north rather than in the south of Europe. Several studies conducted in the Netherlands suggest that the prevalence of chronic disease has increased over time (Uijen and van de Lisdonk 2008; van Leersum et al. 2013; Aarts et al. 2015; van Oostrom et al. 2016). Moreover, the rise in chronic noncommunicable diseases, including cancer, is likely to increase dramatically during the coming years in line with the changing demographic structure of the population due to the ageing phenomenon (Thun et al. 2010; World Health Organization and US National Institute of Aging 2011). The annual number of new cancer cases worldwide was projected to rise to 17 million by 2020 and to reach 27 million by 2030 (Sutcliffe 2012). Although the population of Europe represents only one-eighth of the total world population, currently one-quarter of the global total of cancer cases arise in Europe (World Health Organisation 2020).

Among the studies of cancer comorbidity in Europe, a study of small cell lung cancer (SCLC) patients (Aarts et al. 2015) and another of colorectal cancer patients (van Leersum et al. 2013) found low socioeconomic status was associated with increased odds of having one or more comorbidity or multiple comorbidities. Common conditions among the SCLC patients were pulmonary disease, cardiac disease and hypertension, while hypertension and cardiac diseases were also common among colorectal cancer patients. In a Spanish study of colorectal cancer patients in two provinces, congestive heart failure, diabetes and chronic obstructive pulmonary disease were the most common comorbidities among patients (Luque-Fernandez et al. 2020b), while hypertension, diabetes and chronic obstructive pulmonary disease were the three most common comorbid conditions among patients diagnosed with colorectal cancer or lung cancer in England (Fowler et al. 2020). The prevalence of most of the comorbid conditions studied, and the probability of having the condition as one of multiple comorbidities, was associated with the

highest level of socioeconomic deprivation. The most frequent conditions in breast cancer patients in the south of the Netherlands were cardiovascular disease, diabetes mellitus and previous cancer (Louwman et al. 2005). Some of the studies of multimorbidity prevalence discuss comorbidity among cancer patients. In a Scottish study, chronic obstructive pulmonary disease (COPD) and diabetes were among the most frequent comorbid conditions present in cancer patients, and the prevalence of the comorbid conditions was higher among the most deprived group of cancer patients than among the least deprived group (Barnett et al. 2012). Similar findings were reported in a study of multimorbidity in Denmark (Schiotz et al. 2017).

In examining risk factors for the development of certain comorbidities, studies of tobacco smoking prevalence in Europe suggest that socioeconomic inequalities in smoking were increasing in many countries towards the end of the past century (Giskes et al. 2005). While in northern European countries smoking was more common less well educated than in more educated people at that time, the opposite pattern was reported in southern European countries, where smoking was more common in people with higher educational attainment (Cavelaars et al. 2000), particularly women (Huisman et al. 2005). Tobacco control policies introduced in European countries in the 2000s may have helped to reduce the prevalence of smoking in the total population, particularly in lower socioeconomic groups, but their effect on the extent of socioeconomic inequalities is not clear (Hu et al. 2017). Moreover, socioeconomic inequalities in smoking cessation rates increased during the 2000s (Bosdriesz et al. 2015). In a comparative study of 43 European countries, the countries with the highest summary scores for health policy performance (summarising 10 areas of health policy contributing to major population health gains, including tobacco control) were Nordic countries (Sweden, Norway, Iceland and Finland, in respective order) (Mackenbach and McKee 2013).

Role of Comorbidity as a Prognostic Factor in Cancer Outcomes

Comorbidity May Influence Stage at Diagnosis

Fleming posited four hypotheses to explain the relationship between comorbidity and stage at cancer diagnosis (Fleming et al. 2005), and similar ideas have also been discussed by others (Kiefe et al. 1998; Newschaffer et al. 1998; Vaeth et al. 2000). These are:

- The ‘surveillance’ hypothesis: patients with other chronic diseases are likely to have sought medical assistance more often and had more opportunity for early cancer diagnosis.
- The ‘physiological’ hypothesis: the presence of comorbidity is associated with a more advanced stage of disease. Certain types of comorbidity and cancer may

interact at a cellular or physiological level to increase aggressiveness or metastasis of the tumour.
- The 'competing demands' hypothesis: also relates to a more advanced stage of disease, where management of chronic types of comorbidity may divert patient and clinician attention from early symptoms of a tumour.
- The 'death from other causes' hypothesis: most applicable to patients with a poor prognosis, such as those with a heavy comorbidity burden, where undergoing cancer screening and/or diagnostic testing would not represent a benefit to the patient.

Although the presence of pre-existing comorbidity can be influential in the stage at which a cancer is diagnosed, this may vary according to the type of cancer, the individual comorbid condition and the overall burden of the comorbidity (Sarfati et al. 2016). Research articles endorse the 'surveillance' hypothesis (Fleming et al. 2005; Sarfati et al. 2016; Salika et al. 2018; Renzi et al. 2019a) and the 'competing demands' theory (Sarfati et al. 2016; Park et al. 2017). Others suggest that the presence of comorbidity may increase the likelihood of a patient not receiving a stage of disease at diagnosis (Gurney et al. 2015), supporting the 'death from other causes' hypothesis. In the case of colorectal cancer, a longer time to diagnosis has been observed in patients with pre-existing comorbid conditions, whether the comorbid condition represented a 'competing demand' or an 'alternative explanation' to colorectal cancer (Mounce et al. 2017).

Emergency presentation for medical assistance with symptoms of cancer can be a factor in the relationship between comorbidity and stage of cancer diagnosis. Presentation via an emergency hospital admission is most common in patients with serious or complex pre-existing comorbidities (Renzi et al. 2019b) or a higher overall burden of comorbidity (McPhail et al. 2013). In turn, tumour diagnosis via emergency presentation may be associated with a later stage at diagnosis (McPhail et al. 2013).

Comorbidity May Influence Cancer Management and Therapeutic Options

Comorbid cancer patients may be less likely than those without other chronic diseases to receive treatment of curative intent (Sarfati et al. 2016), although there is some evidence to suggest that patients with comorbidity who receive treatment have a better prognosis than those who do not (Sarfati et al. 2009). Decisions to offer treatment to patients may be based on the type and severity of comorbidity. For example, there is evidence to suggest that the presence of COPD may influence receipt of surgical treatment among early-stage non-small cell lung cancer patients (Belot et al. 2019) and may influence receipt of adjuvant therapy in colon cancer patients (Gross et al. 2007). Treatment decisions made for comorbid patients may also be influenced by the attitude of physicians—for example, in one

study, older physicians were less likely to recommend adjuvant chemotherapy to colon cancer patients than younger physicians (Keating et al. 2008). Older age (Mellemgaard et al. 2015), stage at diagnosis (Noer et al. 2017) and socioeconomic position (Aarts et al. 2013b) may influence treatment received by cancer patients with comorbidity, although socioeconomic inequalities in cancer management have also been related to age at diagnosis rather than comorbidity status (Rollet et al. 2018).

Clinical Management of Comorbidities with Cancer Among European Countries

Despite the high prevalence of multimorbidity among cancer patients, cancer treatment guidelines generally focus on single-disease management (Guthrie et al. 2012; Tinetti et al. 2012). However, the effective management of multimorbidity is important in optimising the cancer patient's health status (McLean et al. 2014), and decisions regarding cancer treatment among elderly cancer patients require careful consideration of comorbidities and multimorbidity (Gurney et al. 2015; Stairmand et al. 2015; Sarfati et al. 2016). Furthermore, postoperative complications occur more frequently in patients with multimorbidity (Sogaard et al. 2013), and certain comorbid conditions have been linked to adverse outcomes following surgery for cancer (Cauley et al. 2015; Sarfati et al. 2016). A challenge for clinicians and oncologists in managing comorbid cancer patients is that healthcare systems may not be designed for the simultaneous management of two or more chronic conditions (Boyd and Fortin 2010; Barnett et al. 2012; Tinetti et al. 2012). In the United Kingdom, clinical guidelines are not adaptive to the cumulative impact of treatment recommendations on those with multiple chronic conditions and do not facilitate a comparison of potential benefits or risks (Hughes et al. 2013). A study that investigated the influence of comorbidity on breast cancer treatment and outcomes in nine European countries concluded that women without comorbidities and of a younger age were most likely to receive prompt, standard treatment for breast cancer (Minicozzi et al. 2019). However, it is unclear from the literature whether the apparent under-treatment reflects appropriate consideration of greater toxicity risk, poorer clinical quality, patient preferences or poor adherence among patients with comorbidity (Sogaard et al. 2013). Ovarian cancer patients in Denmark with moderate or severe comorbidity may often experience longer health system delays than patients with no or mild comorbidity (Noer et al. 2017).

Comorbidity and Cancer Survival in Europe

Much of the research conducted in Europe towards understanding the influence of comorbidity on cancer survival, and on socioeconomic inequalities in cancer survival, is based upon studies of patients in the north of Europe. Commonly studied

cancers in this context are sex-specific cancers such as breast or ovarian cancers in women or prostate cancer in men. Within the literature on this topic, studies have investigated all-cause survival, survival from the cancer, or both. This section discusses the available scientific literature on the role of comorbidity in cancer survival and research that investigates how comorbidity may be an influential factor in social inequalities in cancer survival.

Comorbidity and Survival

The role of comorbidity in survival following cancer diagnosis is complex. The presence and burden of comorbidity can impact or be impacted by other prognostic factors, such as whether the patient receives curative surgery (Sarfati et al. 2016). Thus, it is plausible to have a scenario where cancer survivors with comorbidities have worse survival than those cancer patients without comorbidities, but more evidence is needed regarding the presence of multimorbidity and cancer survival. Similarly, there are scenarios where cancer survivors with a particular comorbidity and cancer have a better relative survival than those with the same comorbidity yet without cancer, but these scenarios are under-reported (Renehan et al. 2019).

In respect to breast cancer prognosis, one study reported little difference in 1-year and 5-year survival between groups of women defined according to their Charlson Comorbidity Index (CCI) (Charlson et al. 1987) score (0, 1 and 2+) (Carlsen et al. 2008), while another reported differences between Charlson score groups and flagged that survival was poorer among patients with comorbid disease (Cronin-Fenton et al. 2007). A study of women with early-stage breast cancer identified that patients with any comorbidities had an increased risk of dying from all causes, but only the presence of peripheral vascular disease, dementia, chronic pulmonary disease, liver disease and renal disease significantly increased the risk of dying due to breast cancer (Ewertz et al. 2018). In studies of women diagnosed with breast cancer in the Netherlands, comorbidity appeared to have an independent prognostic effect on survival (Louwman et al. 2005), except for tumours with poor prognosis (Janssen-Heijnen et al. 2005). The severity or burden of comorbidity was also associated with prognosis (Louwman et al. 2005; Houterman et al. 2004). In a Spanish study of three cancers, including breast cancer, 5-year survival decreased as comorbidity burden increased, but stage at diagnosis was the strongest predictor of survival (Parés-Badell et al. 2017).

Among ovarian cancer patients in Denmark, there was evidence to suggest that women with comorbidity had a 17% higher risk of death than women without comorbidity, after adjusting for other prognostic factors such as age, stage, residual tumour, histology and performance status (Sperling et al. 2013). Similarly, in another study of ovarian cancer patients in Denmark and Sweden, comorbidity was associated with survival (Noer et al. 2018). Prognosis was poorer among the women in Denmark, although comorbidity did not explain survival differences between the two countries. Comorbidity was also an independent predictor of worse 5-year

survival from cancer among surgically treated patients with vulvar carcinoma in Italy (Di Donato et al. 2019).

Among non-small cell lung cancer patients in Denmark, patients with cardiovascular comorbidities (acute myocardial infarction or congestive heart failure) had a 30% excess mortality versus patients without comorbidity, whereas patients with diabetes and patients with cerebrovascular disorders had a 20% excess mortality (Iachina et al. 2015). The severity of comorbidity was predictive of mortality among resected non-small cell lung cancer patients and was associated with lower stage-specific 5-year survival in patients with early-stage (pT1) disease (Luchtenborg et al. 2012). Conversely, Mellemgaard and colleagues found comorbidity to have a limited effect on survival only among lung cancer patients treated with chemotherapy (Mellemgaard et al. 2015). In lung cancer patients in France, comorbidity was only associated with lower survival in patients with small-cell cancers (Seigneurin et al. 2018).

The severity of comorbidity was associated with lower cancer-related 1-year survival in colorectal cancer patients in England, even after adjusting for age and stage (Shack et al. 2010) and was associated with lower 1-year cancer-related survival in invasive bladder cancer patients in Denmark (Lund et al. 2010). Furthermore, it has recently been shown that multimorbidity significantly increased the time to surgery among patients with colorectal cancer in Spain (Luque-Fernandez et al. 2020b). This is possibly because multimorbid patients need to be brought to a healthier status before undergoing a surgical treatment. Also, multimorbidity was a strong independent predictor of short-term mortality at 6 months and 1 year among colorectal cancer patients in Spain (Luque-Fernandez et al. 2020a). Comorbidity was also predictive of mortality in bladder cancer patients in the Netherlands, after adjusting for other prognostic factors such as age, stage and treatment received (Goossens-Laan et al. 2014).

Comorbidity and Social Inequalities in Survival in Europe

Conclusive information on the underlying causes of social inequalities in cancer survival is sparse. As discussed, comorbidity can interact with tumour characteristics and health care (e.g. receipt of treatment and cancer management) in determining patient prognosis. Furthermore, many studies consider comorbidity in combination with other prognostic factors when investigating social inequalities in cancer survival. Different approaches to defining and measuring comorbidity, and variation in measures (or proxy measures) of social or socioeconomic position, can limit the opportunity to draw comparisons across the literature.

We have summarised the published studies reporting on the potential role of comorbidity on the social gradient in cancer survival in European countries (Table 18.1). The results presented in many of these studies were in a format that showed differences in survival or mortality between social groups following progressive adjustment for comorbidity and other factors in the models. Where

Table 18.1 Research articles discussing comorbidity and social inequalities in cancer survival or mortality, according to cancer type

Authors	Cancer	Country	Study population	Study period	Measure of comorbidity	Measure of social position	Other covariates	Outcome measure	Percentage change of social inequalities in outcome due to comorbidity[a, c]	Findings
Cancers in women										
Aarts et al. (2011)	Breast	Netherlands	Women invited for mass breast cancer screening in southern Netherlands	1998–2006	Charlson Comorbidity Index (CCI)	SES indicator by postal code (mean household income, mean economic value of house)	Age, stage, therapy	Mortality (cancer-specific), Hazard ratios (HR)	*SES* inequalities screen-detected: −23% (**1.30** to **1.23**); interval cancer: −7% (**1.72** to **1.67**); not screened: −12% (**1.42** to **1.37**)	Comorbidity explained most of the socioeconomic inequalities in survival among screen-detected patients
Larsen et al. (2015)	Breast	Denmark	Postmenopausal women with breast cancer identified from Danish diet, cancer and health study	December 1993–May 1997	CCI: 1 year before cancer diagnosis, Diabetes: at diagnosis	Educational attainment, income	Age, disease-related prognostic factors (tumour size, lymph node status, number of positive lymph nodes, malignancy grade, oestrogen receptor status)	Mortality (all-cause), HR	**Education**: −6% (**1.35** to 1.33); **Income**: −89% (1.09 to 1.01)	Comorbidity and other prognostic factors affected but did not explain the social gradient in death after breast cancer
Morris et al. (2016)	Breast	England	Women diagnosed with breast cancer aged 50–70 years in the West Midlands region of England	1989–2011	CCI score (continuous)	Deprivation (income domain of indices of multiple deprivation)	Age, year of diagnosis, extent of disease, tumour size, histology, surgery, time to surgery	Mortality (cancer-specific) at five years after diagnosis, HR	Non-screen-detected women: −11% (**1.44** to **1.39**); screen-detected: −18% (**1.66** to **1.54**)	Adjustment for comorbidity resulted in a slight change in excess hazard of death in the most deprived women in both non-screened and screened groups

Morris et al. (2017)	Breast	England	Screening-eligible women diagnosed with breast cancer aged 50–70 years in the West Midlands region of England	1989–2006	CCI score (0, 1+)	Deprivation (income domain of indices of multiple deprivation)	Analysis stratified by each factor of interest in turn	Net survival	Calculation not possible as data not provided	Persistent trend of lower net survival for more deprived women, irrespective of comorbidity status and other factors studied (obesity, alcohol intake and smoking status)
Ibfelt et al. (2013)	Cervical	Denmark	National: women diagnosed with cervical cancer	2005–2010	CCI score (0, 1, 2, ≥3) up to 1 year before cancer diagnosis	Educational attainment, disposable income, cohabitation status	Education adjusted for age, cohabitation status adjusted for age and education, income adjusted for age, education and cohabitation status	Mortality (all-cause), HR	**Education**: −4% (**1.46** to **1.44**); **disposable income**: ALL: +6% (**1.32** to **1.34**), age < 60: −5% (**1.59** to **1.56**); **cohabitation status**: ALL: −88% (1.08 to 1.01), age < 60: −2% (**1.60** to **1.59**)	Socioeconomic differences in survival partly explained by stage and less by comorbidity
Seidelin et al. (2016)	Endometrial	Denmark	National: women diagnosed with endometrial cancer	2005–2009	CCI 1 year before cancer diagnosis	Educational attainment	Age, cohabitation, BMI, smoking status	Mortality (all-cause), HR	Education: −4% (**1.49** to **1.47**)	Social inequalities in survival were not reduced by adjustment for cohabitation status, BMI, smoking and comorbidity, only by further adjustment for stage

(continued)

Table 18.1 (continued)

Authors	Cancer	Country	Study population	Study period	Measure of comorbidity	Measure of social position	Other covariates	Outcome measure	Percentage change of social inequalities in outcome due to comorbidity[a, c]	Findings
Ibfelt et al. (2015)	Ovarian	Denmark	National: women diagnosed with ovarian cancer	2005–2010	CCI score (0, 1, 2, ≥3) up to 1 year before cancer diagnosis, diabetes at diagnosis	Educational attainment, cohabitation status, disposable income	Education adjusted for age, cohabitation status adjusted for age and education, income adjusted for age, education and cohabitation status. Analysis stratified by stage	Mortality (all-cause), HR	**Education**: stage I + II: −4% (**1.75** to **1.72**), stage III + IV: −6% (1.17 to 1.16); **cohabitation status**: stage I + II: +3% (1.38 to 1.39), stage III + IV: 0% (1.24 to 1.24); **disposable income**: stage I + II: −10% (**1.80** to **1.72**), stage III + IV: −2% (0.97 to 0.99)	Socioeconomic differences in survival persisted after adjustment for comorbid conditions, stage, histology operational status and lifestyle factors
Cancers in men										
Aarts et al. (2013b))	Prostate	Netherlands	Men diagnosed with prostate cancer in the South-Eastern Netherlands (Eindhoven Cancer registry region)	1998–2008	CCI (adapted to include additional conditions)	SES indicator by postal code (mean household income, mean economic value of house)	Stage, age, year of diagnosis, therapy/treatment	Overall 10-year survival mortality (all-cause assumed)	Localised stage: ≤59 years: −21% (**2.32** to **2.04**), 60–74 years: −25% (**1.81** to **1.61**); advanced stage: 60–74 years: −6% (**1.36** to **1.34**), ≥ 75 years: −15% (**1.27** to **1.23**)	Socioeconomic differences in 10-year survival were related to treatment and comorbidity

Li et al. (2012)	Prostate	Sweden	Male population of Sweden aged 25 to 74 years,	1990–2008	Previous hospitalisation for chronic obstructive pulmonary disease	Neighbourhood deprivation index, based on low education status, low income, unemployment, social welfare assistance	Year of diagnosis, marital status, immigrant status, urban / rural status, mobility. Analysis stratified by age and stage	Mortality (cancer-specific), odds ratio (OR)	Calculation not possible for comorbidity in isolation: model adjustment made for hospitalisation for COPD plus marital status, family income, educational attainment, immigrant status, urban/rural status and mobility	Men who were older, unmarried, with a low family income or low educational attainment, or who had moved or been hospitalised for COPD had highest odds of all-cause mortality
Other cancers										
Frederiksen et al. (2009a)	Colorectal	Denmark	Patients diagnosed with colon or rectal cancer, recorded in the national clinical database of Danish colorectal cancer (~93% of patients in Denmark with first-time adenocarcinoma of the rectum or colon)	May 2001–December 2004	Dichotomous comorbidity variables: (i) medical treatment for cardiovascular diseases, (ii) hospitalisation for cardiovascular diseases, (iii) medical treatment/ hospitalisation for COPD, (iv) medical treatment/hospitalisation for diabetes, (v) medical treatment or hospitalisation for depression or schizophrenia, vi) medical treatment or hospitalisation for liver, kidney or connective tissue diseases (other)	Annual income, educational attainment, housing status, cohabitation status	Alcohol intake, smoking status, BMI, sex, year of operation. Education is adjusted for age, sex, year of operation. Housing status is adjusted for age, sex, year of operation, cohabiting status, education and income.	Mortality (all-cause), HR	Education: −40% (**0.80** to **0.88**)[b] Housing status: −30% (**0.87** to **0.91**)[b]	The association between SES and all-cause mortality was partly mediated through lifestyle and comorbidity

(continued)

Table 18.1 (continued)

Authors	Cancer	Country	Study population	Study period	Measure of comorbidity	Measure of social position	Other covariates	Outcome measure	Percentage change of social inequalities in outcome due to comorbidity[a, c]	Findings
Frederiksen et al. (2009b)	Colorectal	Denmark	Patients undergoing elective surgery for colorectal cancer, recorded in the national clinical database of Danish colorectal cancer (~93% of patients in Denmark with first-time adenocarcinoma of the rectum or colon)	May 2001–December 2004	Dichotomous comorbidity variables: (i) medical treatment for cardiovascular diseases, (ii) hospitalisation for cardiovascular diseases, (iii) medical treatment/ hospitalisation for COPD, (iv) medical treatment/ hospitalisation for diabetes, (v) medical treatment or hospitalisation for depression or schizophrenia, (vi) medical treatment or hospitalisation for liver, kidney or connective tissue diseases (other)	Educational attainment, housing status	Age, sex, year of operation, alcohol intake, smoking status, BMI	30-day post-operative mortality (cancer-specific), HR	Education: −37% (**0.65** to **0.78**)[b] Housing status: −42% (**0.76** to 0.86)[b]	The social gradient in 30-day postoperative mortality was accounted for by comorbidity and lifestyle, but not by treatment and disease factors
Dalton et al. (2011)	Lung	Denmark	Patients diagnosed with lung cancer	2004–2010	CCI score (0, 1–2, ≥3)	Income, educational attainment, cohabitation status	Age, sex, period of diagnosis, performance status, stage, receipt of first-line treatment	Mortality (all-cause), HR	Calculation not possible for comorbidity in isolation: Model adjustment made for comorbidity plus stage, first-line treatment and performance status	Socioeconomic differences in survival partly explained by differences in stage, treatment and comorbidity

Studies of more than one cancer										
Aarts et al. (2013a)	Breast, prostate, NSCLC	Netherlands	Patients diagnosed with cancer in the South-Eastern Netherlands (Eindhoven cancer registry region)	1991–2008	CCI	Educational attainment	Baseline characteristics: age, year of diagnosis, stage at diagnosis, lifestyle behaviours	Mortality (all-cause assumed), HR	Prostate cancer: adjusting only for baseline characteristics: −10% (**2.9** to **2.7**); adjusting for baseline characteristics and lifestyle behaviours: +5% (**3.00** to **3.01**)	Presence of comorbidities, physical activity levels and smoking status affected survival from prostate cancer, but these factors did not contribute to educational inequalities in survival
Louwman et al. (2010)	Oesophagus, stomach, colon or rectum, pancreas, lung, melanoma, breast, cervix uteri, corpus uteri, ovary, prostate, bladder, kidney, and non-Hodgkin lymphoma (NHL)	Netherlands	Patients diagnosed with cancer in the South-Eastern Netherlands, (Eindhoven Cancer registry region)	1997–2006	Presence of comorbidity	SES indicator by postal code (mean household income, mean economic value of house)	Age Stratified by cancer and by sex	Mortality (all-cause), HR	Colorectal cancer: males: −23% (**1.13** to **1.10**), females: −33% (1.09 to 1.06); lung: males: 0% (**1.11** to **1.11**), females: 0% (**1.09** to **1.09**); prostate (males): 23% (**1.47** to **1.36**); breast (females): 18% (**1.68** to **1.56**); all cancers studied combined: males: −12.5% (**1.40** to **1.35**), females: −15% (**1.40** to **1.34**)	Comorbidity partly explained socioeconomic inequalities in 1-year survival among patients with colorectal, prostate or breast cancers. The gradient of more comorbidity from high to low SES was apparent for all tumour types studied

Abbreviations: *BMI* Body Mass Index, *CCI* Charlson Comorbidity Index, *HR* Hazard ratio, *NHL* Non-Hodgkin lymphoma, *NSCLC* Non-small cell lung cancer, *OR* Odds ratio, *SES* Socioeconomic status

[a]Comparing low versus high measure of social position, unless otherwise indicated

[b]Comparing high versus low measure of social position

[c]Statistically significant results are in bold

possible, we calculated the percentage change of social inequalities in the outcome reported, using the equation $([HR_{\text{Basic model}} - HR_{\text{Basic model + comorbidity}}])/[HR_{\text{Basic model}} - 1] \times 100$, an approach used in a published review of socioeconomic inequalities in prostate cancer survival (Klein and von dem Knesebeck 2015). Of the studies found (n = 14), half were of female cancers: breast (Aarts et al. 2011; Larsen et al. 2015; Morris et al. 2016; Morris et al. 2017), cervical (Ibfelt et al. 2013), endometrial (Seidelin et al. 2016) or ovarian (Ibfelt et al. 2015) cancer. The remaining studies were of prostate (Li et al. 2012; Aarts et al. 2013b), colorectal (Frederiksen et al. 2009a; Frederiksen et al. 2009b) or lung cancer (Dalton et al. 2011), or studies of more than one type of cancer (Aarts et al. 2013a; Louwman et al. 2010). The studies were undertaken in the north of Europe: in Denmark (n = 7), England (n = 2), Netherlands (n = 4) and Sweden (n = 1).

The contribution of comorbidity in reducing social inequalities in breast cancer survival was similar among screen-detected and non-screen-detected patients in the Netherlands (Aarts et al. 2011) and in England (Morris et al. 2016): comorbidity was responsible for approximately 20% and 10% of socioeconomic inequalities in these groups, respectively, in both countries.

Some studies stratified their analyses by stage, reporting results for localised/stage I or II cancer and for advanced/stage III or IV cancer. Adjustment for comorbidity resulted in a larger reduction in socioeconomic inequalities in survival among prostate cancer patients (Aarts et al. 2013b) —and inequalities in survival according to income among ovarian cancer patients (Ibfelt et al. 2015)—with an earlier rather than a later stage at diagnosis. For example, after adjustment for comorbidity, socioeconomic inequalities reduced by 25% among patients aged 60–74 years with localised stage prostate cancer, while the reduction was only 6% among patients of the same age with advanced stage of disease. Comorbidity appeared to account for more of the inequalities in survival according to disposable income and cohabitation status among cervical cancer patients aged under 60 years than among patients of all ages (Ibfelt et al. 2013). However, among prostate cancer patients, the extent of the contribution of comorbidity towards socioeconomic inequalities in survival appeared to increase with increasing age, particularly among patients with advanced stage of disease (15% of inequalities among patients aged 75 years or older compared with 6% of inequalities among patients aged 60–74 years) (Aarts et al. 2013b).

There are limitations in drawing conclusions about the role of comorbidity in social inequalities in cancer survival from the findings of these studies. Of the 14 studies, only five explicitly stated that the results provided were for cancer-specific mortality or survival due to cancer. Of the remaining studies, seven presented results for all-cause mortality and the other two did not specify (all-cause mortality was assumed in these instances). Another limitation is that, based on the methods of analysis used in these studies, the application of causal assumptions to the associations reported is not valid. In Fig. 18.1, the directed acyclic graph illustrates assumed causal relationships between variables in the pathway between social position and cancer survival. To be able to examine and quantify the causal effect of comorbidity and associated variables in this pathway would require analytical approaches such as causal mediation analysis.

Proposing the Need for Life Tables by Deprivation

When interest is in survival from the cancer (e.g. net survival), competing risks of death from other causes need to be accounted for. Because information on the cause of death contained in routine, population-based mortality data is not considered to be robust and accurate enough, the risk of death from other causes among cancer patients is estimated from life tables of the general population. Life tables provide average mortality rates for a geographic area, most commonly according to sex and age. However, when examining the role of comorbidities on social inequalities in cancer survival, it is important that the life tables reflect the social differential in mortality rates observed in the general population. General life tables systematically under-estimate the expected mortality hazards among more deprived populations and over-estimate these in less deprived populations. Using such general life tables can therefore result in under-estimated net survival (i.e. survival from cancer) in deprived populations and over-estimated net survival in less deprived populations (Dickman et al. 1998; Maringe et al. 2008). Furthermore, a simulation-based study showed that the use of life tables lacking stratification by a variable present in the excess hazard model leads to measurement bias in both the effect of this variable and other variables included in the model (Graffeo et al. 2012).

Some strategies have been proposed to compensate for the insufficient stratification of life tables. Sensitivity survival analyses can be performed using modified life tables according to successive plausible scenarios regarding the social gradients in the studied population (Ito et al. 2014; Antunes et al. 2019).

Rubio and colleagues developed models for the estimation of the excess mortality hazard that correct for possible mis-specification of the expected mortality rate occurring due to mismatches in the life table (Rubio et al. 2019). Flexible population-based models were developed to account for cause-of-death misclassification and for the effects of selection when estimating long-term net survival in the clinical trial setting (Goungounga et al. 2019).

Similarly, life tables that do not account for comorbidities may over-estimate the expected survival in populations with an important burden of comorbidities while under-estimating expected survival in populations with a low prevalence of comorbidities. Life tables commonly include the deprivation dimension in the United Kingdom and in several countries of the north of Europe. Whether such life tables (which may also include ethnicity) are sufficient to adjust for social differentials in mortality associated with comorbidity remains debated. A study focussing on the specific lung and laryngeal cancers (for which most patients have comorbidities associated with tobacco smoking) concluded that not using life tables adjusted for tobacco smoking (and deprivation) led to a notable under-estimation of cancer survival for all deprivation groups, but had a fairly small impact on the estimation of the deprivation inequalities in cancer survival (Ellis et al. 2014). Life tables adjusted for comorbidity may nevertheless be helpful to uncover the role of comorbidity in social inequalities in cancer survival. Such life tables are available in the United States (Mariotto et al. 2013).

Conclusions

Among the published studies on this topic in a European setting, the magnitude of the influence of comorbidity in social inequalities in cancer survival varied. The extent of the relationship also varied by the measure of social position. The impact of comorbidity on inequalities in survival was also associated with other prognostic factors, such as tumour stage, patient age and treatment received.

Having one or more comorbid conditions at the time of cancer diagnosis is associated with socioeconomic position, and the prevalence of many comorbid conditions increases with increasing levels of socioeconomic deprivation (Barnett et al. 2012; van Leersum et al. 2013; Aarts et al. 2015; Schiotz et al. 2017; Fowler et al. 2020). The most deprived groups of patients may be disproportionately impacted by clinical guidelines that focus on single disease management and by decision making that leads to non-treatment of cancer patients with comorbidity.

Reviewing the treatment process of cancer patients with comorbidity may help to reduce socioeconomic inequalities in receipt of treatment and ultimate prognosis. Clear guidelines that allow for multiple management scenarios (depending on comorbidity severity and stage of cancer), together with the resources to manage comorbid conditions robustly during cancer treatment, could help reduce adverse outcomes due to the comorbid disease and limit the development of new comorbidities. Moreover, investigation of aspects of comorbidity management, such as the relationship between adherence to comorbidity medication and outcomes among cancer patients, may be informative. In a study of patients with diabetes and ischaemic heart disease, cardioprotective medication adherence was associated with lower all-cause mortality (Ho et al. 2006).

Further studies investigating comorbidity and social inequalities in cancer survival across many European countries, especially with representation of southern European countries, would provide a firmer foundation for comparison of inequalities between countries. Greater efforts in achieving a more consistent approach toward measuring comorbidity would help facilitate a like-for-like comparison.

From the evidence presented, the need for a mechanistic understanding of the causes of socioeconomic inequalities in survival outcomes is apparent. The current lack of understanding illustrates the importance of using causal inference methods with routine medical data and population-based registries to disentangle the contributions of different pathways of cancer diagnosis and treatment to these inequalities in cancer survival (Li et al. 2016).

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Chapter 19
Geographical Remoteness and Cancer Survival in Europe

Olivier Dejardin

Introduction

In this chapter, we discuss the effect of spatial or geographical accessibility on cancer survival. Because geographical inequalities in cancer survival could be the consequence of inequalities at each step of a patient's management, we report the salient elements of the association between geographical disparities and cancer management after diagnosis.

Because it is closely linked to socioeconomic factors, spatial accessibility to health care may greatly influence the delivery of optimal care. As a consequence of the centralisation of care in most countries (Vonlanthen et al. 2018), travel time to receive optimal care is a growing problem for public health decision-makers and patients. Although much of the research evidence comes from the United States, and to a lesser extent from Australia, a number of projects have been undertaken in European countries to understand the nature and magnitude of any loss of opportunity for remote patients.

Ever since the pioneering work of Edward Jarvis in 1850 (Hunter and Shannon 1985), it has been clear that remote patients have less access to healthcare facilities. The distance decay hypothesis, which posits that the use of a healthcare facility will decline with increasing distance, is widely accepted in the fields of medical geography and public health and has been clearly established in numerous research studies (Kelly et al. 2016). Although cancer is a serious illness where treatment is required for a favourable prognosis, there is sound evidence that the problem of distance decay is also apparent for cancer care (Kelly et al. 2016). However, the consequence of distance decay on cancer outcomes is less certain. In the first section of this chapter, we review the evidence for the presence of distance decay and its consequences

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in the cancer care continuum. Worldwide, geographical accessibility to health care is a particular concern in countries where accessibility is especially difficult due to substantial inter-urban distances, including the USA (Baldwin et al. 2008) and Australia (Ireland et al. 2017). In Europe, accessibility to health care has received less attention. Nevertheless, even in countries smaller than those previously cited and mainly covered by universal insurance, remote patients may suffer from inadequate accessibility to health care.

Measuring Accessibility to Health Care

When considering the influence of isolation on health outcomes, one of the main challenges is the measurement of accessibility. In the 1990s, the first publications on the effect of spatial accessibility used either straight-line distance from regional capitals or urban/rural status to estimate the influence of remoteness on cancer outcomes. Urban/rural status is used worldwide, and numerous studies have been published with this indicator (Afshar et al. 2019). Although rural patients face difficulty in accessing health care, urban/rural status may not directly reflect the level of accessibility that a patient may have.

In Europe, most studies have used a quantitative measure of accessibility. Among the wide range of techniques for measuring distance, straight-line distance has typically been the most common. A systematic review by Kelly et al. on the effect of distance to health care on health outcomes in northern hemisphere countries showed that nearly 25% of all publications on the association between distance and health outcomes used straight-line distance (Kelly et al. 2016). Straight-line distance from residence to hospital clearly gives only a very rough measure of accessibility, especially in urban settings.

During the past decade, owing to the increasing uptake of geographical information systems (GIS), a growing number of publications have used estimated road driving time to reach one's general practitioner (GP) or healthcare facilities. This unidimensional measure is now the most common measure of healthcare accessibility. Based on the road network and legal speed limit according to the type of road, researchers have been able to calculate a wide variety of travel time measures (which are intrinsically still closely linked to distance), including travel time to cancer centres, travel time to the nearest GP, and travel time to the nearest radiotherapy centre. The underlying assumption is that all patients travel by car.

Beyond potential access, a growing number of publications have investigated the effect of actual travelled distance instead of the shortest distance to healthcare facilities (Speicher et al. 2017; Vetterlein et al. 2017). Owing to the typically better health status of patients who travel far and the positive effect of high-volume hospitals on health outcomes, these publications usually report better cancer outcomes for patients who have travelled the furthest.

The reason why one measure of travel time is preferred to another is often unclear in publications. The main limitation of these studies is the use of car travel time,

especially in populations living in highly populated areas where public transportation is well developed.

Similar to the measurement of deprivation, some authors have suggested using a composite index instead of a unique measure based on road distance. Recently, several methods have been developed to create an index of spatial accessibility. They are based on density as in two-step floating catchment area methods (2SFCA) (Xu et al. 2017) and in other methods (Launay et al. 2019). In addition to overcoming the problems of dealing with administrative boundaries, this kind of index can provide useful information on the availability of medical resources. The use of such indices is rare and should be encouraged.

Influence of Healthcare Accessibility on Cancer Management

Because access to health care involves a complex combination of spatial and aspatial problems, it is difficult to clearly differentiate the real effect of accessibility to health care from the effect of social position. On the one hand, a systematic adjustment on deprivation may reduce the effect of accessibility; on the other hand, no adjustment on deprivation may lead to overestimating the association. The advent of causal models in the coming years could probably help to clarify this distinction. Nonetheless, the cost of overcoming distance is clearly affected by social position and distance may affect a patient's experience (Payne et al. 2000). Nevertheless, while the concept of distance decay is widely accepted in medical geography, the consequence of this under-utilisation of health care by remote patients is less clear. The systematic review by Kelly et al. on the effect of distance to health care on health outcomes in northern hemisphere countries showed that 77% of all publications reported a distance decay association, and more than 50% of these publications concerned cancer, especially colorectal and breast cancer. While the authors identified a wide range of techniques for measuring distances, they found that no study took residential mobility into account (Kelly et al. 2016).

Cancer Screening, Stage at Diagnosis

For eligible cancer localisations, early detection and mass screening are the best way to reduce the aggressiveness of a cancer. Unfortunately, only a few cancer localisations benefit from mass screening or efficient early detection. For most of the common cancer localisations, geographical inequalities were found to be widespread in the USA for breast cancer screening (Khan-Gates et al. 2015) and colorectal screening (Wang et al. 2019).

In Europe, occult blood tests are widely used for colorectal cancer screening, while a colonoscopy is recommended every 10 years in the USA. Importantly,

there is still no harmonisation of screening procedures in Europe, with each country organising its own campaign. Consequently, the effect of accessibility to health care varies from one European country to another. Unlike colorectal cancer, however, breast cancer screening procedures are easier to compare across Europe.

Keeping in mind these potential differences in organisation, the distance decay hypothesis has been highlighted in most studies. In addition to a tendency to less breast cancer screening uptake as deprivation increases, a UK study of nearly 35,000 women showed a slight decrease in the likelihood of breast cancer screening uptake with increasing travel time to screening facilities (Maheswaran et al. 2006). In Denmark, a study investigating the influence of distance to breast cancer screening facilities showed that a long distance was associated with less participation and that women who had access to a vehicle had a greater likelihood of receiving screening (Jensen et al. 2014). In this study and in another (Jewett et al. 2018), the relationship between distance and utilisation of screening facilities was not linear.

Using information on 13,565 women invited for breast cancer screening in 13 French departments, a French study showed that living more than 15 minutes away from screening facilities was a barrier to breast cancer screening (Ouédraogo et al. 2014). With more than 100,000 participants included in their study, Pornet et al. showed that rural patients were more likely to participate regularly in colorectal cancer screening than urban ones (Pornet et al. 2014). Of note, deprivation had a greater influence than remoteness in both studies.

The hypothesis that remote patients receive a later-stage diagnosis than urban ones has received much attention. Distance may have a different effect according to the cancer diagnostic pathway. In a cohort study conducted in Denmark between 2005 and 2006, Virgilsen et al. found that increasing travel-time to the hospital of diagnosis increased the odds of advanced stage for 'easy-to-diagnose' cancer types (rectal cancer, testicular cancer, malignant melanoma). For hard-to-diagnose cancer types (stomach cancer, pancreatic cancer, lung cancer), increasing travel-times to the hospital of diagnosis was associated with a decreased probability of advanced cancer (Virgilsen et al. 2019). For both types of cancer, distance to GP's office was not associated with stage at diagnosis. The association with distance to hospital and worst stage at diagnosis was also reported for breast cancer (Dalton et al. 2006) and in Switzerland (Ess et al. 2010).

Geographical inequalities in mass screening could be reduced by promoting the benefits of screening patients as close as possible to their home. To this end, some interesting projects have already been set up. For breast cancer, the creation of a mobile mammography unit in addition to mammography facilities already present in urban areas is an attractive idea (Guillaume et al. 2017) to increase participation in underserved areas. While such mobile mammography units are already deployed, their crude effect is currently unknown and will be assessed in the light of their cost-effectiveness.

Access to Facilities Providing Cancer Care

For many surgical procedures, access to hospitals with high throughput is associated with better health outcomes (Birkmeyer et al. 2002). Obviously, such hospitals are located in metropolitan areas and may therefore be far from where many patients live. In France, studies investigating access to reference care centres have shown that patients who live far from high-volume hospitals have a lower probability of being operated in them (Dejardin et al. 2005; Blais et al. 2006). Because reference care centres must provide equal access for all patients in the regional area, this constitutes a geographical inequality. This is hardly surprising because one of the major tenets of the French healthcare system is that the patient is free to choose the hospital they wish to be treated in, even if this choice is clearly influenced by their GP. An interesting finding was made by Bouche et al. in breast cancer patients. By dividing hospitals into four categories according to the volume of breast cancer surgical procedures (low, middle and high), they found that proximity to their residence was crucial when patients were involved in the decision process (Bouche et al. 2008).

The influence of accessibility has been reported at every step in cancer care management. A study was conducted on six major cancer localisations (breast, colon, rectum, lung, prostate and ovary) in more than 13,000 patients in the North West of England. It showed that, after adjustment for age, sex and stage, the probability of being operated on decreased with the increase in travel time to hospital for lung cancer but not for the other localisations. For all cancer localisations, travel time was not associated with the probability of receiving chemotherapy. Travel time was associated with the likelihood of receiving radiotherapy for breast, colon, prostate and lung cancer (Jones et al. 2008a). In France, the waiting time between surgery and radiotherapy for breast cancer patients was associated with distance to the nearest radiotherapy centre (Bouche et al. 2010).

As previously mentioned, the cost of overcoming the hurdle of remoteness is affected by social position. Using a population-based study on nearly 35,000 patients, Crawford et al. showed that lung cancer patients living in a deprived area received suboptimal treatment, an effect that was accentuated by travel time (Crawford et al. 2009). Performing the same analysis on colorectal cancer, they found that although deprivation was associated with outcomes, travel time was not associated with treatment options (Crawford et al. 2012).

More surprisingly, the choice of a surgical procedure may also be affected by accessibility to health care. For example, two options are possible after surgical resection in rectal cancer: sphincter preservation or not. While the choice has little impact on survival, it mainly affects quality of life. If clinical characteristics are obviously the main determinants for the choice of surgical techniques, a recent study reported that the odds of sphincter preservation for rectal cancer are also affected by accessibility to healthcare structure (Dolet et al. 2019).

Comparable evidence also has been reported for breast-conserving surgery for breast cancer (Gu et al. 2018) or for treatment choices in head and neck cancer (Ringstrom et al. 2018).

Influence of Accessibility to Health Facilities on Cancer Survival

Cancer survival reflects the quality of management, including timely presentation, throughout the course of the disease. Geographical inequalities have been highlighted in cancer survival in numerous European countries as a consequence of distance decay in cancer management. However, depending on the healthcare organisation, the strength of this association varies greatly from one country to another.

A population-based study conducted in Scotland using a GIS method reported that a longer straight-line distance from the cancer centre was associated with poorer survival in patients diagnosed with prostate and lung cancer (Campbell et al. 2000). Interestingly, travel time was also associated with a greater probability of being diagnosed at death (death certificate only) in patients diagnosed with stomach, breast or colorectal cancer, which clearly reflects either a late stage at diagnosis or a less-than-complete diagnostic work-up.

In France, a country with a universal healthcare system and theoretically a free choice of hospital, numerous studies have demonstrated the influence of accessibility to health care on cancer survival for numerous cancer localisations (Dejardin et al. 2006, 2008; Le Guyader-Peyrou et al. 2017). To compare the influence of travel time to the reference care centre on colorectal cancer patients overall survival (OS) in North West England and in France, a population-based study was conducted using the same methodology in both countries. After adjustment on cancer characteristics and deprivation, there was no effect of travel time on OS for the English patients. Although the gap in survival was not major, the influence of travel time was significant in France (Dejardin et al. 2014). The absence of effect of travel time to hospital on colorectal cancer OS in England was previously reported in a population-based study (Jones et al. 2008b). The authors found that travel time to GP was the only significant geographical variable associated with survival. As underlined by the authors, this absence of secondary access variables reflected the fact that as soon as a diagnosis was made, patients made every effort to overcome the hurdle of distance.

Kim et al. found that in patients who had undergone colorectal cancer surgery, those living remotely had a greater risk of death shortly after the colorectal surgery, whilst OS was not affected by travel time (Kim et al. 2000).

Two recent meta-analyses that included studies from all high-income countries reported that rural patients had a worse survival than urban patients (Carriere et al. 2018; Afshar et al. 2019). Although the inclusion of different cancer localisations in the same meta-analysis may have weakened the strength of the association, the

study found that rural patients had a significantly lower probability of surviving their cancer (HR = 1.05 (1.02–1.07)) (Carriere et al. 2018).

Another study found that patients travelling far from their residence to receive care had a better prognosis (Lamont et al. 2003). As explained in the section on the measurement of accessibility, this apparent contradiction may be explained by the better health status of patients who travel further, combined with the effect of better health outcomes in high-volume hospitals.

Conclusion

As for other pathologies, geographical inequalities affect cancer management from the initial diagnosis to recovery (or death). Even if international comparisons are difficult due to differences in healthcare systems and in country size, the magnitude of geographical inequality in survival across the European Union seems to be relatively modest compared to the deprivation gap in survival. Nonetheless, ways to tackle geographical inequalities have been proposed. One of the most attractive ones is to relocate some crucial infrastructure of cancer management, for example, deploying mobile mammography units to increase screening uptake in remote areas and deploying experienced surgeons in local hospitals. This experimentation is ongoing; therefore, it is too early to draw conclusions about their effectiveness. Nevertheless, they represent an opportunity to take geographical disparities into account in the organisation of cancer care.

Unfortunately, very few studies have been conducted on the impact of travel time on patients quality of life and medical expenditure. To our knowledge, the only studies to date were conducted in the USA (Payne et al. 2000; Rocque et al. 2019). This is an emerging issue that will need to be addressed more thoroughly in the coming years.

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Part IV
Towards an Evidence-Based Policy for Tackling Social Inequalities in Cancer

Chapter 20
Links Between Research in Public Health and Public Health Policy: The Conceptual Framework of Interventional Research

Elodie Guillaume

Social Inequalities in Health

As laid down by the European Commission, health systems must be accessible, effective and resilient to change and be able to meet future challenges. A major concern is inequalities in health. Indeed, the existence and persistence of social and geographical inequalities in health are being reported in an increasing number of studies, as in reports from health agencies. In terms of health status, access and quality of care, the trend is towards increasing inequalities between and within countries (Whitehead and Dahlgren 1991; Potvin et al. 2010; Marmot, Allen et al. 2012). These differences concern the entire social hierarchy, creating what is known as a 'social gradient' in health inequalities for indicators, including mortality (Mackenbach et al. 2017), life expectancy (Seaman et al. 2019) and the adoption of healthy behaviours regarding the use of the health system. The concept of inequality in health refers to these avoidable differences which are considered as unfair because people have little choice in their conditions of life (Ritsatakis 2013).

The main causes of inequalities in health are the social determinants (Evans 2001). These are the circumstances in which people are born, grow, live, work and age, and the systems set up to deal with diseases. These determinants are multiple and interact in a complex manner. To meet the challenge of the persistence and worsening of inequalities, the World Health Organization set up the Commission of Social Determinants of Health (CSDH) in 2005 as a global network of policymakers, researchers and civil society organisations. The CSDH was tasked with

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collecting, collating and synthesising global evidence on the social determinants of health and their impact on health inequality from countries at all levels of income and development.

The most recent causal model comprises three main components: (a) the socioeconomic and political context, (b) structural determinants of health inequalities, that is, all social and political mechanisms that define an individual's socioeconomic position, (c) intermediary determinants of health, including material circumstances, psychosocial circumstances, behavioural and/or biological factors and the health system itself. The structural determinants function through intermediary determinants of health to shape health outcomes (Commission on Social Determinants of Health 2008).

In 2008, the CSDH drew up a conceptual framework for tackling social inequalities in health and established a set of recommendations and action plans. Interventions addressing intermediary determinants can improve average health indicators while leaving health inequalities unchanged; therefore, policy action on structural determinants is necessary to reduce health inequalities. Interventions and policies must not be limited to the intermediary determinants but must include policies crafted to overcome the structural determinants (Solar and Irwin 2010). Some general and consensually recognised principles have to be considered when implementing health interventions aimed at reducing inequalities. As the target determinants are multifactorial, actions must also be multifactorial. Moreover, as structural determinants of health inequalities can be addressed by policies that reach beyond the health sector, intersectoral action is required. More policies on social determinants of health must be designed with a focus on contextual specificities. If the social gradient is to be taken into account across the whole of society, then interventions must have a universal outreach that is proportional to inequalities experienced by the underserved, i.e. application of the principle of proportionate universalism (Marmot and Bell 2012). Another point concerns the participation of civil society and the empowerment of affected communities to become active protagonists in shaping their own health (Whitehead 2007). Other principles are also important such as ensuring the individual's informed choice, the incorporation of literacy, care and ethics in interventions.

Investing the reduction of health inequalities also contributes to social cohesion and breaks the vicious circle of poor health that both contributes to and results from poverty and exclusion. All countries recognise that health inequalities are caused by unfavourable socioeconomic and environmental conditions. In 2012, the European Regional Office of the World Health Organization published a new health policy strategy, Health 2020, and an accompanying European Action Plan, with both documents being endorsed by the 53 member states. 'It aims to support action across government and society to: "significantly improve the health and well-being of populations, reduce health inequalities, strengthen public health and ensure people-centred health systems that are universal, equitable, sustainable and of high quality"' (Donkin et al. 2018).

Population Health Intervention Research

Definition

In 2009, the Population Health Intervention Research Initiative for Canada (PHIRIC) defined population health intervention research (PHIR) as '*the use of scientific methods to produce knowledge about policy and program interventions that operate within or outside of the health sector and have the potential to impact health at the population level.*' (Hawe and Potvin 2009). This definition reflects an interest in the social determinants of health: economic policy, education policy and environmental policy. Indeed, these interventions intended to modify the distribution of health risk, also called 'causes of causes'. Therefore, all systematic inquiry and learning from the observation of an intervention's process or implementation, impact or outcome is encompassed in the term 'intervention research'. Therefore, while PHIR involves the evaluation of the results and impacts of an intervention, other objectives such as the conceptualisation and development of the intervention and the analysis and evaluation of the processes are essential to produce new knowledge and to ensure its transferability and its integration in health policy. In other words, PHIR intends to address several issues: What could work? Could it work? Does it work? How does it work? Is it replicable? (Hawe and Potvin 2009).

Characteristics

To date, there is no consensual definition of what a population health intervention is. However, there is no doubt that interventions involve complex systems of action. This complexity is twofold: it is both one of the properties of any intervention, and it is the property of any system in which an intervention is implemented (Shiell et al. 2008). Population health interventions are multifaceted, involving program evaluation, community health and psychology, political science and social epidemiology. This multidisciplinary aspect of population health interventions requires all the partners to coordinate their actions according to the conditions and the environment in which they are implemented. Finally, PHIR is increasingly associated with the promotion of health equity. The complexity of this research is expressed in each of its characteristics.

Interdisciplinarity

Terms such as multidisciplinary, interdisciplinary and transdisciplinary are currently used to denote this multiple disciplinary approach and are often used interchangeably. The precise definitions of these terms will not be detailed in this chapter

but are to be found in the article by Choi et al. (Choi and Pak 2006). Interventions are considered as interdisciplinary if they involve two or more scientific disciplines and an interactive research process. As mentioned above, PHIR arose from the collaboration of various disciplines, and an interdisciplinary approach throws more light on its complexity. It is also a prerequisite for acting upon the determinants of health and reducing inequalities. Although well accepted in principle, interdisciplinary practice continues to prove a real challenge. According to Alla (2016), it is a question of 'valuing each discipline as well as possible in a common work, by preserving the expression and the specificity of disciplinary knowledge'. Working with and between disciplines requires constant explanation, adaptation and scientific readjustment from all researchers involved (Kivits et al. 2019).

Researcher–Practitioner Partnership

As the aim of PHIR is to study interventions according to their conditions and environment, the partners (in and outside the health sector) should be involved in a researcher–practitioner partnership, collaboration or even in the co-construction of the intervention. This partnership offers mutual advantages: it allows researchers to have a better knowledge of the territory, the population and actions already undertaken, and it allows partners to value their knowledge, their actions and their experiences. Furthermore, as the partners are also the future users of the results of the research, their conclusions will be more accessible, acceptable and applicable by practitioners, and therefore more useful if they correspond to their needs and constraints. By providing mutual support, practitioners and researchers can reinforce their respective capacities to significantly influence decisions and public health policies (Alla 2016).

Empowerment

Empowerment consists in getting people to identify and define their own health problems. Thus, it can help communities and individuals develop opportunities, capacities and tools that benefit them and ensure that communities have the tools to use in advocating for their members' access to prevention, screening and treatment. This approach is most likely to develop sustainable solutions that work for both individuals and communities. Involving collaboration between and participation by community members, researchers and policymakers is an essential step in achieving health equity through social action (Thompson et al. 2016).

Context

The question of context is important since the effects of the intervention are modified by the characteristics and dynamics of the context in which it is deployed and because there is a constant interplay between the intervention and its context. In

fact, interactions may be seen as a permanent feedback loop where the context modifies the intervention, which in turn can modify the context. While the subject has received much attention, there is little consensus on it. For example, the Medical Research Council guidelines propose to distinguish between human (participation staff, decision-makers, human beings) and non-human (financial resources, scientific knowledge and material) entities (Moore et al. 2015). Some authors refer to an interventional system without distinguishing intervention and context (Hawe et al. 2009). Others focus on the connections between the intervention and context entities (Bilodeau and Potvin 2018). The effect of the context is nevertheless important for providing knowledge about the mechanisms of an intervention and for its evaluation and transferability.

Evaluation

Therefore, both outcome evaluations, generally focused on reach and efficacy, and process evaluations are necessary for fully understanding if an intervention works, how it works, and for whom and where. After the publication of its framework dedicated to recognising and adopting appropriate methods (Campbell et al. 2000), the Medical Research Council published widely recognised guidelines for the evaluation of complex interventions (Craig et al. 2008). They provide the theoretical and practical foundations for evaluating complex health interventions with a view to improving policies and practices. In 2015, the MRC published a new framework for conducting and reporting process evaluation studies. It covers the fidelity and quality of implementation, clarifies causal mechanisms and identifies contextual factors associated with variation in outcomes (Moore et al. 2015). It lists key considerations for reporting relations between quantitative and qualitative components, and discusses the relationship between process evaluation and other components of evaluation, such as outcomes and economic evaluation. This approach is designed to be a complement to, not a replacement for, a high-quality outcome evaluation.

As the problems posed are complex, PHIR mobilises a full range of methods from the randomised trial in clusters often preferred in epidemiology to the research action, which is more associated with the social sciences. Some combined approaches have also emerged, such as realistic randomised controlled trials. Bonell et al. propose a synergistic relationship between realist and randomised evaluation (Bonell et al. 2012). As set forth by (Blackwood et al. 2010), '*The RCT can be used to ascertain whether, all other things being equal, a particular causal mechanism (intervention) is efficacious, while realistic evaluation can establish what effect the interaction of other mechanisms operating in the open contexts studied has upon its effectiveness, and identify which mechanisms promote, and which inhibit that effectiveness'*. It aims to take a realistic approach, but within an RCT, using theory which goes beyond logical models to describe mechanisms and contextual contingencies, refining theory using embedded qualitative research *and* testing hypotheses concerning what works for whom and how to use moderator and mediator statistical analyses.

The theory-driven approach to evaluation was first developed by Pawson and Tilley. This realistic evaluation consists in identifying context–mechanism–outcome configurations (CMOs), and their recurrences are observed in successive case studies or in mixed protocols, such as realistic trials (Pawson et al. 2005). Another approach developed by De Silva (De Silva et al. 2014) to enhance the Medical Research Council's framework for complex interventions is the theory of change (ToC). It is an answer to whether, how and why an intervention works. ToCs describe how interventions can bring about long-term outcomes through a logical sequence of intermediate outcomes. Furthermore, ToCs help to clarify any underlying assumptions, acknowledge the role of context and provide evidence to justify the chain of causal pathways. It is thus imperative to adopt a theory-based approach to guide the development and implementation of actions aimed at tackling social inequalities in health.

Example

Cancer screening programmes provide an interesting example of the impact of interventions on inequalities. Organised breast cancer screening (OBCS) exists in many European countries and is faced with the problem of low participation and/or inequalities in participation. Women facing adverse economic conditions (e.g. low income, lacking food sometimes or often, financial difficulties) and those living far from an accredited radiologist centre are less likely to participate in breast cancer screening, even when a nationwide organised screening programme exists (Menvielle et al. 2014; Ouédraogo et al. 2015).

Various strategies such as mobile mammography units (MMUs) seem effective in the fight against inequalities (Guillaume et al. 2017). However, in the European context, there is little evidence about how to intervene to reduce health socio-territorial inequalities in screening; therefore, public health decision-makers are unable to base proposals on evidence. This example is the typical scope of a PHIR. It demonstrates the need to act upon the social determinants of health, to evaluate new breast cancer screening modalities by taking into account contextual elements, to establish the optimal conditions for making an MMU efficient and to generate knowledge on the mechanisms involved in order to assure the transferability of the scheme.

Schematically, the intervention research integrates the principle of actions to reduce inequalities set out in the introduction. It must be collaborative by bringing together several partners such as researchers, stakeholders and local organisations from both inside and outside the health sector with an intersectoral multidisciplinary approach. The intervention should be conducted as a realistic RCT. MMUs are a new screening modality for reducing the barriers of access to screening. MMU interventions are to be offered solely to women living far from an accredited radiologist centre, according to the principle of proportionate universalism. In addition, local stakeholders will conduct campaigns to mobilise women and inform them

about breast cancer screening. By doing so, community empowerment is strengthened. Specific information tools that explain screening in an MMU will be developed to cater to the beneficiaries' level of literacy, as is the case with the MMU currently being tested in Normandy, France. At the individual level, this type of intervention will enhance women's knowledge and empowerment. At the community level, a more widespread awareness about the issues of screening may be obtained. RCTs provide the strongest evidence about the effects that MMUs can have, particularly regarding the main outcomes such as participation rate and the reduction in inequalities. In the case of the Normandy MMU, an intervention theory will be developed to explain underlying causal mechanisms, taking into account contextual factors such as stakeholders' actions and focusing on mechanisms that can help to improve knowledge about breast screening and to change behaviour with regard to screening. Qualitative data obtained from interviews and a survey on knowledge about breast cancer screening will serve to construct and validate the theory. Finally, the key points of the intervention will be identified to determine how the concept of the Normandy MMU could be rolled out elsewhere.

Conclusions

This chapter has described the current state of knowledge of PHIR with a focus on the reduction of inequalities. It is a growing area of complex research and remains subject to numerous methodological, logistic and administrative challenges in a discipline where research is still guided by the biomedical approach. The complexity inherent in PHIR creates many challenges for conceptualisation, implementation and evaluation. Any intervention must be the subject of theorisation early in the research process (Moore et al. 2019). The interdisciplinary and intersectoral nature of such interventions constitutes a supplementary challenge. Hurdles remain to be crossed concerning the definition of concepts, objectives and methods, which may differ from one study to another. With the intersectoral approach, there may also be a time lag between the period when the research is undertaken and the moment when policymakers take decisions based on it. Getting the stakeholders together and coordinating them is also complicated and very time-consuming; however, this is mandatory if knowledge is to be transferred. The current challenge is evaluation: what is the most appropriate methodology to evaluate an intervention in specific contexts? Evaluation requires a rethink by combining the qualitative and quantitative approaches from several disciplines. Another issue is ethics. Because there are no tailored ethical standards and oversight mechanisms for PHIR, scientists and governments may be faced with unacceptable alternatives such as forgoing important research opportunities, violating ethical standards and trying to circumvent ethical review. If these temptations are succumbed to, there is a great risk that potentially important novel initiatives are never published. A new global framework for ethical design and oversight of PHIR is thus needed (Bärnighausen 2017).

PHIR should therefore produce knowledge on policy and intervention programmes so that the mechanisms that make an intervention effective are fully understood. Often when policies are being designed, there is a lack of understanding of the social, cultural and economic conditions of the target population. This is key for reproducing the mechanisms that are transferred, allowing the intervention to adapt to the context in which it is deployed. If these basic tenets are adhered to, policymakers may be better informed, especially in the long-term, and will be in a position to deploy effective policies targeting the underlying social and economic causes of health inequalities.

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Chapter 21
Social Inequalities in Cancer: The Policies of the European Commission

Tit Albreht and Ana Molina-Barceló

Introduction

Social inequalities have a significant impact on many facets of life and on many health determinants, which in turn have an impact on health care. This can affect susceptibility to prevention, self-care and readiness to participate in preventative and early detection programmes, compliance and adherence to treatment and the potential for social networks to enable respite care, support in the rehabilitation and survivorship phases as well as in end-of-life care.

Modern social systems, where health and social care are interlinked, are expected to deliver care and services in ways that reduce the impact of social inequalities, which are not directly amenable to either of the two systems. Social systems should try their best to mitigate social inequalities, as they have already contributed to the adverse impact of negative health determinants (Whitehead and Dahlgren 2007). They may also increase the risk of cancer development in certain social strata of the population.

The European Union (EU) is concerned with the problems related to health inequalities, a burning issue adversely affecting health (European Commission 2009). This is visible at the EU level, within groups of countries and within countries themselves. The most important study to date dealing with health inequalities in the EU is the Consortium Report published in 2013 and the work led by Prof. Michael Marmot (European Commission 2013). Apart from the review of the

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evidence on health inequalities in mortality and morbidity in general, the report reviews studies that point to some of the important social inequalities in cancer-related mortality and morbidity. It focuses on gender differences, the educational gradient and differences across various regions of the EU. The report offers an important insight into the body of evidence on health inequalities in cancer. However, its main limitation is that it focuses on mortality and morbidity relative to risk factors and educational levels but does not analyse differences in treatment outcomes or the quality of cancer care, which may show differences both across the EU as well as within countries. In particular, the EUROCARE (Baili et al. 2015) study on survival and the CONCORD study (Allemani et al. 2018) clearly showed the relationship between cancer outcomes and socioeconomic position. Many of these differences are likely to have roots in socioeconomic differences in the distribution of the burden of health determinants in the population, as well as in differences in access to different socioeconomic groups within and between countries.

Several initiatives have sought to explore differences in diagnosis, care and access to treatment across the EU for different cancer locations. One of the more recent ones is the LuCE Report on lung cancer (Lung Cancer Europe 2017), which was prepared in 2017 by the advocacy group Lung Cancer Europe (LuCE). Another EU-wide analysis is the European Social Survey, which showed regional inequalities in self-reported conditions and noncommunicable diseases within and between countries and focused on the social determinants of health (Thomson et al. 2017).

Social Inequalities and their Dimensions and Impact Across the Cancer Trajectory

Social inequalities in cancer are important at different points in the course of the disease (Krieger 2005). Health determinants have a significant impact on the origins of cancer, in particular smoking, excessive use of alcohol, physical inactivity and inappropriate diet, resulting in overweight and obesity. In most Member States, these problems and challenges tend to concentrate in the lower socioeconomic strata. While some people see this issue as a given in the development of present-day society, it still needs to be adequately addressed. Secondly, there are clear differences and important social inequalities in attitudes towards prevention, early detection of cancer (and other chronic diseases), as well as in screening programmes. Lower participation in cancer screening programmes and delayed diagnosis have been reported in those with lower socioeconomic status (Merletti et al. 2011; Neal and Allgar 2005; Woods et al. 2006). In some cases, this can be related to the challenges of health literacy and its unequal distribution in society. In other cases, there may be a closer relationship with other factors, such as traditions, habits, scepticism towards science and expert opinion, as well as cultural and gender values (Molina-Barceló et al. 2018).

Cancer is a disease that still bears considerable stigma due to its potential severity and, in some organ locations, also to its poor prognosis. Cancer encompasses the entire trajectory in the course of a chronic disease, ranging from lifestyle, early detection, signs and symptoms, through diagnosis and treatment, to challenges of living with cancer or after it, reintegration into pre-morbid life and comprehensive rehabilitation, and eventually palliative and end-of-life care. The complexity of this trajectory poses challenges that reflect either the socioeconomic position of the individual in the society or the impact that the disease will have on the cancer patient's life. These may range from anxiety and stress from the diagnosis or side effects of treatment to challenges related to remaining in employment and potential modifications in post-treatment life that are necessary due to the partial or complete loss of organ function.

European health systems generally prevent cancer patients from incurring exorbitant costs such as those related to cancer screening. Diagnosis and treatment are usually included in the public coverage of healthcare costs. This reduces the worst financial impact cancer may have on an individual. However, challenges remain that are not related to the reimbursement models of cancer care and early detection.

These challenges mostly concern the following:

1. Overall attitude to health and dealing with lifestyle, including health determinants and decision to undertake any kind of preventative action.
2. Decision and threshold regarding when to decide to seek medical assistance for an existing medical problem, whether a symptom or sign.
3. Access to early diagnosis, diagnostic process and appropriate treatment given the distribution and quality of care facilities available to the population in a given country.

European Actions in the Field of Inequalities in Cancer

To reduce inequalities in cancer, it is advisable to embed equity within the cancer prevention and control policies in all EU Member States (Peiró Pérez et al. 2017). The EU's competences in the field of health care are rather limited, although some recent policy developments show that there is increasing willingness on the part of Member States to seek solutions at the EU level that would benefit both levels, that is, both the EU and the Member States. With the clear contrast between public health issues, where the EU does have a role to play, and the regulation of healthcare delivery, there remains a desire to overcome the rather large and clearly unacceptable differences in access to high-quality cancer care, well-developed screening programmes and survivorship solutions across the Member States.

Joint Actions (JAs), i.e., projects co-financed by the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) and the Member States, are projects which aim to contribute to the development of sound policy advice and

inform different stakeholders about the approaches, solutions and models that represent examples of good practice. The latter are designed to serve as references for other countries, which may learn directly from their experience.

In the two JAs already completed, important activities led to two key outputs. In JA European Partnership for Action Against Cancer (EPAAC), an entire chapter in the final book was dedicated to questions relating to social inequalities in cancer (Martin-Moreno et al. 2013). In addition, there have been three specific reports on social inequalities in cancer screening in EU Member States prepared by The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) (Molina-Barceló et al. 2012, 2013; Moreno et al. 2012).

A specific focus on health inequalities and cancer was adopted by CanCon, the second JA project on cancer policies in the EU. The project was co-financed by the European Commission and led to a policy paper specifically dedicated to this topic (Peiró Pérez et al. 2017). A group of authors prepared an overview of terminology in the field and then provided a consistent set of 13 recommendations with a total of 27 specific recommendations covering all aspects of cancer control and cancer care addressing social inequalities in cancer. Their aim was to address all aspects of cancer prevention and cancer care where action is needed. Box 21.1 lists their main recommendations. They are the result of the combined work of a research team at FISABIO and the experts who were involved in the work on the respective topic. The groundwork was prepared by FISABIO in the form of a literature review, which was later examined and supplemented by consensus through discussions within the expert panel.

Box 21.1 Recommendations on health inequalities and cancer

1: Embed equity within the cancer prevention and control policies in all European Union Member States.
2: Align cancer prevention and control policies with a Health in all Policies approach.
3: Adopt a Health Equity Impact Assessment framework.
4: Engage and empower communities and patients in cancer prevention and control activities.
5: Promote the exchange of experiences of good practice and support the development of professional expertise in social inequalities in cancer in all European Union Member States.
6: Support the development of European research programmes that help deliver equity in cancer prevention and control in all European Union Member States.
7: Implement proportionate universalism policies to develop and maintain living environments that facilitate compliance with the European Code Against Cancer.
8: Improve equitable access and compliance with cancer screening programmes.
9: Ensure equitable access to timely, high-quality and multi-disciplinary cancer care.
10: Ensure equitable access to high-quality surgical care in all European Union Member States.
11: Ensure availability of sufficient radiotherapy capacity with appropriate technology innovation in all European Union Member States.

12: Ensure that all patients have timely access to appropriate systemic therapy.
13: Develop national cancer rehabilitation and survivorship policies, underpinned by an equity perspective. Prepared by authors based on: Peiró Pérez et al. (2017). https://cancercontrol.eu/archived/uploads/PolicyPapers27032017/Policy_Paper_4_Tackling.pdf

In terms of supporting patients facing the challenges of survivorship, some Member States have taken important steps to help them overcome some of life's important financial burdens. Such is the case with the legislation following the principle of *droit à l'oubli* (Gouvernement: Le portail de l'Économie, des Finances, de l'Action et des Comptes publics 2019) (in English: 'the right to forget'), where France and Belgium adopted legislation that gives cancer patients the right not to declare having been treated for cancer after five years (in the case of childhood cancers) or 10 years (in all other cancers) after the successful completion of treatment and having remained in remission ever since. Such a decision is vital for persons applying for life insurance, either on its own for financial security or related to mortgages as well as for more substantial loans. We can only hope that other countries will follow this example and that the European Commission helps such decisions to be taken in all other Member States, obviously based on a social pact.

Current and Potential EU Activities in the Field of Health Inequalities in Cancer

The JA on cancer, innovative Partnership for Action Against Cancer (iPAAC, www.ipaac.eu), which started in 2018, is another activity that addresses health inequalities in cancer. It focuses particularly on issues related to cancer prevention, both in the implementation of the European Code Against Cancer (ECAC), as well as in screening programmes. Another important activity in this respect is the redefinition of the data set for population-based cancer registries. These should also include socioeconomic data in order to obtain a better insight into the socioeconomic differences in cancer at all levels. This has become increasingly relevant, as survival from cancer is constantly rising, which means that we need a better insight into what happens to (former) patients' social position, their employment and rehabilitation, as well as financial security. Specifically, iPAAC will:

1. Deliver recommendations and good practice for enhancing activities concerning the ECAC from an equity perspective.
2. Define clear steps on how to secure equitable access to screening programmes in all Member States.
3. Prepare recommendations for an additional set of variables to be analysed within national cancer registries, which would in turn facilitate multi-national and EU-level based analyses concerning health inequalities in cancer.

Some examples already identified as good practices tackling social inequalities in cancer prevention, both primary and secondary prevention, are accessible through the iPAAC website (https://www.ipaac.eu/en/contest-best-practices/).

Additionally, some outstanding areas currently not adequately covered by the EU-level activities are in a more extensive focus on outcomes in cancer care and challenges through the various facets of the survivorship period.

The most exciting and important initiatives at the EU level in terms of cancer policy and cancer research are: (a) the development and implementation of a European Action Plan Against Cancer and (b) the establishment of the Cancer Mission, in terms of advancing research in the field of cancer and prioritising its sub-topics. Health promotion and its related health determinants are one of the key areas of the EU's competencies related to health, and they represent the core of the public health actions in DG SANTE.

Apart from policy-oriented projects, there is also legislative activity to improve lifestyles across the EU. Marmot's report quoted above clearly indicated some of the trends in health determinants, which will also need action in the future. There are three key areas in view of the current negative trends and/or situations: smoking prevalence, consumption of alcohol and nutrition. All three areas show clear socio-economic gradients and selective activities needed to address them diversely across the societal pyramid from a proportionate universalism perspective, based on universal actions but with a scale and intensity that are proportionate to the level of social disadvantage (Marmot 2010).

Moreover, while some screening programmes have been in existence a very long time, they still show a lack of quality control and assurance as well as principles that are too uniform, and do not take socioeconomic differences into account (Deandrea et al. 2016). The latter play an important role in the decision a person may or may not take with respect to their participation in a screening programme. Attention needs to be sustained in reaching out to all segments of the target population in all population-based cancer-screening programmes.

Areas with the Most Immediate Need of Action at the European Level

EU action is required in several areas. The following are just some of the topics that need to be addressed in close collaboration between the EU and its Member States:

1. Compliance with the European Code Against Cancer from an equity perspective.
2. Equity in access to cancer screening programmes.
3. Bridging health literacy challenges in reducing the time from symptoms to the establishment of the diagnosis of cancer.
4. Equitable access to timely treatment, inclusive decisions on cancer treatment, explanation of options and the potential consequences of treatment.

5. An after-care framework that is consistent, well-planned and well-grounded in guidelines, and which needs to include all segments of care that a cancer survivor would ideally need.
6. Role of primary, secondary and tertiary prevention in cancer patients.
7. Challenges related to survivorship and its different facets; for example, keeping employment, shorter sickness leave, insufficient or non-existent rehabilitation programmes.
8. Social rights, support and economic aspects of the survivorship process: the need for comprehensive legislative support.

Because the causes of social inequalities in cancer are interrelated, a Health in All Policies Approach involving different sectors is needed (World Health Organization 2014).

Conclusions

Cancer remains the top public health problem in Europe, as both incidence and mortality continue to rise in many countries. While this is being addressed by preventative actions ranging from primary prevention to screening and early detection, awareness about the impact of socioeconomic differences is also rising. This is mostly happening at the level of Member States, which have implemented various activities addressing these differences. The wealth of Member State experience in tackling socioeconomic inequalities in cancer at different stages in diagnosis and treatment heralds the advent of more general solutions applicable to a wider range of countries. During Slovenia's Presidency of the Council of the European Union, conclusions on reducing the burden of cancer were adopted (Council of the European Union 2008). This initiative will now be revived and taken to the highest level of policy-making at the European Commission with Europe's Beating Cancer Plan (European Commission 2020). This plan will certainly be another important stepping stone in bringing together the experience of the Member States and in the regulatory role played by the European Commission. This should lead to a broader range of rights of cancer patients and their access to diagnosis, treatment, after-care, rehabilitation and supportive care, all according to each patient's specific needs. These actions should contribute to a further reduction in socioeconomic differences in cancer within and between Member States. At the same time, an entire strand called Mission in the new European research programme will be dedicated to cancer.

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