Tampere University

ANTON BARCHUK

Measuring the Burden of Cancer in Russia

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ACADEMIC DISSERTATION
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Dedicated to the memory of my parents, Ludmila Putinova and Alexey Barchuk.

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ABSTRACT

Cancer is a major global health threat. Despite progress in cancer management, the number of deaths is increasing. The growing cancer burden is driven by population ageing and suboptimal approaches to cancer control, but there are marked differences in cancer incidence and mortality globally. Russia is the largest country in Europe, representing about 14% of the European population with cancer mortality above the average European rates. Unfortunately, cancer epidemiologic studies are carried out sporadically in Russia. They rarely include comprehensive cancer burden analysis. The cancer trends analysis could explain historical changes, predict future burdens, and set cancer control goals.

Well-validated population-based cancer registries (PBCRs) are reliable and unique sources of structured information for cancer surveillance and multiple research purposes. Russia, then part of the USSR, introduced compulsory cancer registration in 1953. However, regional PBCRs, which collect and store individual-level data, were fully established nationally only in 1999. The four key aspects of quality: comparability, validity, completeness, and timeliness, were never applied to evaluate the quality of cancer registration in Russia.

This study aimed to assess the quality of cancer statistics in regions of Northwest Russia. Data from ten Russian PBCRs from regions with a population of approximately 13 million were processed and analysed. Overall, data collection in Northwest Russia was according to international standards; even though national instructions for cancer registration were outdated, it was generally comparable. The proportion of multiple primaries ranged from 6.7% in Vologda Oblast to 12.4% in St. Petersburg (between 2008 and 2017), similar to most European PBCRs. Substantial regional heterogeneity for most indicators of quality was observed. Certain cancer types (e.g., pancreas, liver, haematological malignancies, and CNS tumours) and cancers in older age groups showed lower validity and completeness. The overall quality of PBCRs data of at least four Northwest regions meets international

standards.

The study covered the incidence and mortality trends of two cancer types in women in Russia, breast and cervical cancer, and predicted the future burden. Breast and cervical cancer incidence age-standardised rates (Segi-Doll world standard population) increased from 33.0 to 47.0 per 100,000 and 10.6 to 14.2 per 100,000, respectively. Breast cancer mortality ASRs declined from 17.6 to 15.7 per 100,000 in 2013. At the same time, cervical cancer mortality ASRs increased steadily from 5.6 to 6.7 per 100,000. Changes in the risk in cohorts born between 1937-1953 indicated a recent generational decrease in breast cancer mortality and an increase in cervical cancer incidence and mortality. The annual years of life lost to cervical cancer mortality could reach 1.2 million, and years of life lost to breast cancer could decline to 1.8 million by 2030. These changes highlight the need to prioritise national screening and vaccination programs.

This study also focused on national mortality trends collected through the centralised state civil registration system. Cancer burden related to mortality data was approached through years of life lost and productivity losses. Mortality for most cancer types decreased between 2001 and 2015. There was an upward trend for melanoma, pancreas, brain and CNS cancer mortality. In addition, larynx, lip, oral and pharynx, and cervical cancer mortality increased only in women and prostate cancer mortality in men. Overall, years of life lost increased for most cancer types. Productivity losses due to premature cancer mortality amounted to $8 billion. The losses were expected to drop from 0.28% of GDP in 2001 to 0.14% in 2030, primarily because of a decline in cancer mortality. The increase in productivity losses was highest for HPV-related cancer mortality. The losses in absolute terms were highest for breast cancer in women and lung cancer in men.

This study sets a standard for measuring the burden of cancer in Russia. It includes a comprehensive assessment of PBCRs data quality, which is supposed to guide changes in cancer registration procedures and practices. National cancer statistics can be enhanced through contemporary trend analysis, predictions, and additional measures like years of life lost and costs. Future research projects should focus on specific cancer types to guide a pragmatic approach to evidence-based cancer control activities supported by cancer epidemiologic research.

TIIVISTELMÄ

Syöpä on globaalisti yksi kansanterveydellisesti merkittävimmistä tekijöitä. Vaikka syövän hoidossa on saavutettu merkittävää edistystä, syöpäkuolemien määrä kasvaa edelleen. Syöpätaakan suureneminen johtuu ikääntymisestä sekä syövän torjunnan ja resurssien puutteista. Eri maiden välillä on merkittäviä eroja syöpään sairastumisen ja kuoleman riskissä. Venäjä on Euroopan suurin maa, joka kattaa noin 14 % Euroopan väestöstä, ja syöpäkuolemien määrä Venäjällä on eurooppalaisen keskitason yläpuolella. Valitettavasti syöpäepidemiologisia tutkimuksia tehdään Venäjällä vain satunnaisesti. Syöpätaakkaa niissä arvioidaan kattavasti vain harvoin. Syöpätrendien analysointi voisi selittää muutoksia, ennustaa tulevaa kehitystä ja ohjata prioriteetteja ja tavoitteen asettelua.

Väestöpohjaiset syöpärekisterit ovat ainutlaatuisia ja luotettavia tietolähteitä syövän seurantaan ja erilaisiin tutkimuksiin. Syöpärekisteröinti alkoi Venäjällä vuonna 1953, osana silloista Neuvostoliittoa. Kuitenkin yksilötason tietoja keräävät ja tallentavat alueelliset syöpärekisterit kattoivat koko Venäjän vasta vuonna 1999. Valitettavasti kaikkien neljän keskeisen laatutekijän: vertailukelpoisuuden, validiteetin, kattavuuden ja ajantasaisuuden, arviointia ei ole Venäjällä koskaan toteutettu kattavasti.

Tämän tutkimuksen tavoitteena oli arvioida Luoteis-Venäjän alueiden syöpätilastojen laatua. Aineistona on 10 alueellisen syöpärekisterin tiedot, jotka kattavat noin 13 miljoonan asukkaan väestön. Analyysissa ovat mukana kaikki syöpärekisterien kattamat tapaukset. Kokonaisuutena tiedonkeruu Luoteis-Venäjällä noudattaa kansainvälisiä standardeja, ja vaikka kansalliset syöpärekisteröintiohjeet olivat vanhentuneet, ne olivat yleisesti vertailukelpoisia. Monien primaarien osuus vuosina 2008–2017 vaihteli Vologda Oblastin 6,7 prosentista 12,4 prosenttiin Pietarissa, mikä vastaa useimpia eurooppalaisia syöpärekistereitä. Useimmissa laatuindikaattoreissa oli huomattavia alueellisia eroja. Validiteetti ja kattavuus oli alhaisempaa haima- ja maksasyövässä, hematologisissa syövissä sekä keskushermostokasvaimissa ja vanhoissa ikäryhmissä. Vaikka Luoteis-Venäjän neljän syöpärekisterin tietojen laatu

täyttää kansainvälisten standardien vaatimukset.

Tutkimuksessa analysoitiin rintasyövän ja kohdunkaulasyövän ilmaantuvuus- ja kuolleisuustrendejä tavoitteenamme ennustaa tulevaa syöpätaakkaa. Rintasyövän ilmaantuvuus oli noussut kahden vuosikymmenen aikana 33,0:sta 47,0:een 100 000:ta kohti ja kohdunkaulan syövän 10,6:sta 14,2:een 100 000:ta kohti (Segi-Doll maailman standardiväestöön vakioituna). Kuitenkin rintasyöpäkuolleisuus oli laskenut 17,6:sta 15,7:een vuonna 2013, kun taas kohdunkaulan syövän kuolleisuus oli noussut 5,6:sta 6,7:een. Käänne tapahtui vuosina 1937-1953 syntyneiden kohortissa, mikä osoittaa, että syntymäkohortteina tarkasteltuna rintasyövän kuolleisuus on laskenut, kun taas kohdunkaulan syövän riski on suurentunut. Ennusteet osoittavat, että kohdunkaulan syövän takia menetettyjen elinvuosien määrä voi saavuttaa 1,2 miljoonaa ja rintasyövän 1,8 miljoonaa vuoteen 2030 mennessä. Nämä trendit korostavat kansallisen kohdunkaulan rokotus- ja seulontaohjelmien tarvetta.

Työssä analysoitiin myös kansallisia kuolleisuustrendejä, joita koskevat tiedot kerättiin väestörekisterijärjestelmästä. Syöpätaakan kuvaamisen käytettiin myös menetetty elinvuosia ja tuottavuusmenetyksiä. Kuolleisuus laski useimmissa syöpätyypeissä tutkimusjakson aikana. Melanooman, haiman, aivojen ja aivokalvojen syövän, huulen, suun ja nielun, kurkun ja kohdun syövän kuolleisuus nousi vuosina 2001–2015 naisilla ja eturauhassyövän kuolleisuus miehillä. Yleisesti ottaen menetettyjen elinvuosien määrä lisääntyi useimmissa syöpätyypeissä. Syöpäkuolemien aiheuttamat tuottavuusmenetykset ovat Venäjällä huomattavat, vuositasolla noin 8 miljardia dollaria. Kustannusten odotetaan laskevan vuoden 2001 0,28 prosentista bruttokansantuotteesta vuonna 2030 0,14 prosenttiin, pääasiassa kuolleisuuden vähenemisen ansiosta. Suurimmat kustannukset johtuvat naisilla rintasyövästä ja miehillä keuhkosyövästä, mutta eniten lisääntyivät HPV-infektioon liittyvien syöpien aiheuttamista kuolemista johtuvat tuottavuusmenetykset.

Tutkimuksen tulokset asettaa standardin syöpätaakan arvioimiseen Venäjällä. Se kattaa syöpärekisterien tiedon laadun systemaattisen seurannan, jonka pohjalta tulee ohjata rekisteröintimenetelmiä ja käytäntöjä. Kansallisia syöpätilastoja voidaan kehittää nykyaikaisen trendianalyysin, ennusteiden ja muiden tekijöiden kuten menetettyjen elinvuosien ja kustannusten analyysin avulla. Tulevien tutkimusprojektien tulisi keskittyä tiettyihin syöpätyyppeihin jotta syöpäepidemiologisen tutkimuksen avulla voidaan kehittää näyttöön perustuvia syöväntorjuntatoimia.

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ABBREVIATIONS

APC	Annual percentage change
DCI	Death certificate initiated (case)
DCN	Death certificate notification
DCO	Death certificate only (case)
ENCR	European Network of Cancer Registries
FSSS	Federal state statistics service
GDP	Gross domestic product
HCA	Human capital approach
HPV	Human papillomavirus
IACR	The International Association of Cancer Registries
IARC	The International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
LMIC	Low and middle-income countries
M:I	Mortality-to-incidence (ratio)
MV	Morphological verification
PBCR	Population-based cancer registry
SEER	The Surveillance, Epidemiology, and End Results Program
UICC	Union for International Cancer Control

ORIGINAL PUBLICATIONS

Publication I **Barchuk**, **Anton**, Rustam Tursun-zade, Alexey Belyaev, Malcolm Moore, Yuri Komarov, Nataliia Moshina, Ahti Anttila, Jaakko Nevalainen, Anssi Auvinen, Anton Ryzhov, and Ariana Znaor (2021). "Comparability and validity of cancer registry data in the northwest of Russia". In: *Acta Oncologica* 60.10, pp. 1264–1271. DOI: 10.1080/0284186X.2021.1967443.

Publication II **Barchuk**, **Anton**, Rustam Tursun-zade, Ekaterina Nazarova, Yuri Komarov, Ekaterina Tyurina, Yulia Tumanova, Alexey Belyaev, and Znaor Ariana (2023). "Completeness of cancer registry data in northwest Russia 2008-2017". In: *Submitted*.

Publication III **Barchuk**, **Anton**, Aleksandr Bespalov, Heini Huhtala, Tuvshinjargal Chimed, Irina Laricheva, Alexey Belyaev, Freddie Bray, Ahti Anttila, and Anssi Auvinen (2018). "Breast and cervical cancer incidence and mortality trends in Russia 1980–2013". In: *Cancer Epidemiology* 55, pp. 73–80. DOI: 10.1016/j.canep.2018.05.008.

Publication IV **Barchuk**, **Anton**, Aleksandr Bespalov, Heini Huhtala, Tuvshinjargal Chimed, Alexey Belyaev, Malcolm Moore, Ahti Anttila, Anssi Auvinen, Alison Pearce, and Isabelle Soerjomataram (2019). "Productivity losses associated with premature mortality due to cancer in Russia: a population-wide study covering 2001–2030". In: *Scandinavian Journal of Public Health* 47.5, pp. 482–491. DOI: 10.1177/1403494819845565.

Author's contribution

All four papers report on original research I conducted with the support of my supervisors and collaborators during the period when I studied and worked at the School of Health Sciences and the Faculty of Social Sciences/Health Sciences at Tampere University, Finland, and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary and sole first author of all four papers in this thesis. I also acted as the corresponding author for all four papers.

Publication I	I conceived and designed the study, led the data acquisition and analysis, and drafted the first version of the manuscript. Other authors contributed to the research and publication drafting process and critically reviewed, edited, and approved the manuscript.
Publication II	I conceived and designed the study, led the data acquisition and analysis, and drafted the first version of the manuscript. Other authors contributed to the research and publication drafting process and critically reviewed, edited, and approved the manuscript.
Publication III	I was responsible for the study design, literature search and review, data identification and extraction, data analysis, writing, reviewing and revising the manuscript, and final approval of the version to be submitted. Other authors contributed to the research and publication drafting process and critically reviewed, edited, and approved the manuscript.
Publication IV	I was responsible for the study design, literature search and review, data identification and extraction, data analysis, data interpretation, writing, reviewing and revising the manuscript, and final approval of the version to be submitted. Other authors contributed to the research and publication drafting process and critically reviewed, edited, and approved the manuscript.

1 INTRODUCTION

Cancer is a group of diseases characterised by uncontrolled cell growth that can result in large masses of abnormal cells. There are hundreds of cancer subtypes, including those originating from blood cells such as leukaemias. Cancer is linked to different factors that include environmental exposures, genetics, lifestyle choices, and infections. Cancer is a major public health issue and one of the leading causes of death worldwide, accounting for approximately 10 million deaths in 2020 (Ferlay, Colombet, et al. 2021). It is also projected that in the next 50 years, the greatest increment of the worldwide cancer load will be borne by low- and middle-income countries (LMIC). Low-income countries will experience a 400% increase in cancer incidence compared to a 53% increase in very high-income countries (Soerjomataram and Bray 2021).

Cancer control activities, such as primary prevention, screening, early detection, treatment, and palliative care, are essential components of a successful public health strategy to reduce the burden of cancer (World Health Organization 2020). Unfortunately, much of the research on cancer focuses on developing new treatments, such as drug therapy, with fewer incentives for prevention research (Bode and Dong 2009; Budish, Roin, and Williams 2015). Nevertheless, primary prevention efforts, such as reducing risk factors for cancer, are vital for lessening the disease burden, especially in countries where preventable cancer types represent a large proportion of cases.

For effective cancer control policies, it is essential to define and measure the burden of cancer accurately. Efforts to measure the burden of cancer vary according to region and context and may involve estimating prevalence, incidence, mortality, survival, costs, and quality of life (Kalager et al. 2021). GLOBOCAN, created by the International Agency for Research on Cancer (IARC), aggregates global cancer data on disease prevalence, incidence and mortality (Ferlay, Colombet, et al. 2021). In addition, healthcare ministries, research consortia and cancer registries generate

regional and national estimates. Epidemiologic research is another crucial tool for understanding the burden of cancer. Epidemiological studies can provide information on cancer risk factors in different populations and assess the impact of preventive measures and treatments. For example, epidemiological studies have identified several risk factors for cancer, including smoking (Doll and Hill 1950), alcohol consumption (Zaridze, Brennan, et al. 2009), obesity (Kyrgiou et al. 2017), exposure to radiation (Virtanen, Pukkala, and Auvinen 2006), and certain infections (Bosch et al. 1993). Epidemiological studies have also provided information on the effectiveness of prevention and screening programmes (Anttila, Sarkeala, et al. 2008; Vaccarella et al. 2016). Modern epidemiology methods set the standards for cancer burden estimation, making projections for cancer incidence and mortality (Møller, Fekjær, Hakulinen, Sigvaldason, et al. 2003), evaluating the impact of cancer on quality of life and economic burden (Pearce et al. 2018), and helping to identify disparities in cancer outcomes among different populations (Fidler, Soerjomataram, and Bray 2016).

In addition, measuring cancer burden contributes to a better understanding of the impact of cancer on countries' healthcare infrastructures, resources and regulations. For example, a detailed assessment of the burden of cancer can help identify the geographical areas with the highest cancer rates or predict the number of future cases in order to direct the targeted allocation of services and resources (Soerjomataram and Bray 2021). Measurements of cancer burden also provide a basis for creating and improving epidemiologically sound cancer control plans that meet medical and social needs (Mosquera et al. 2022). Ultimately, a comprehensive understanding of the global and regional cancer burden is integral to developing effective policies and interventions to reduce the impact of cancer worldwide.

Studies have shown that developed countries allocate more resources for epidemiological research, enabling them to generate better quality data and evidence. However, the current epidemiological evidence from countries with a lower income is rarely available and considered less reliable (Pramesh et al. 2022). This fact contributes to a gap in knowledge on certain diseases in specific populations, particularly in LMIC. Therefore, unequal access to epidemiological research hinders a comprehensive understanding of global health threats. Crucially, this is complicated by the additional challenges related to a lack of evidence-based decision-making tools and resources in lower-income settings, further limiting cancer control and care quality.

Russia is one of the 15 countries that emerged after the collapse of the Soviet Union in 1991, and it has been predominantly considered a middle-income country since then. Cancer is among the leading causes of death in Russia, with nearly 270,000 cancer deaths reported as of 2021 (Kaprin, Starinskiy, and Shakhzadova 2022). The Soviet Union introduced the first compulsory cancer registration system in 1953 and updated the data collection and procedures to meet international standards in 1963 (Barchuk, Belyaev, et al. 2021). In 1998, IARC published Technical Report N35, which summarised the state of cancer registration in the New Independent States of the former USSR (Winkelmann et al. 1998). The report highlighted the need for computerisation, the introduction of international coding classifications and systematic quality monitoring. However, despite the introduction of national legislative acts at the end of the 1990s, information on regional cancer registration practices has not been systematically analysed. Cancer epidemiologic research in Russia was primarily limited to local descriptive publications, several international collaborative projects and a few analytical international publications. This lack of resources and methodological rigour impeded advancing epidemiological research. Most epidemiological studies conducted in Russia were not adequately supported by dedicated funding, and utilised low-quality data and poor methodology (Vlassov 2000), which has led to a lack of confidence in the results of epidemiological research in the region, hindering its ability to inform policy decisions and public health interventions (M. Rahu, Vlassov, et al. 2013). It remains unclear if Russia has reliable data sources at regional or national levels. Despite the long tradition of cancer registration, the lack of internationally verified data sources leads to challenges when assessing the cancer burden accurately. Furthermore, it hinders Russia's ability to measure its cancer control initiatives' impact and ensure that those efforts improve health outcomes.

This study aimed to assess the quality of cancer data sources in Russia and implement a framework for methodologically rigorous cancer burden estimation. Firstly, this study included a review of cancer surveillance in Russia to obtain and describe the data sources. Secondly, the data sources were systematically evaluated, focusing on the data quality from several regional population-based cancer registries in Northwest Russia. Thirdly, a systematic approach was applied to estimate the burden of specific cancer types (cervical and breast). Estimates related to the economic burden of cancer (years of life lost and productivity costs) were also evaluated. This

approach considered the data quality, international organisations' methodological guidelines, and potential regional peculiarities. Finally, this study provided a preliminary assessment of the conditions necessary for implementing approaches to future reliable cancer burden assessment. Moreover, this study's results will be relevant to other countries, as it will set an example of a systematic approach to assessing and improving the quality of cancer data and making it usable for cancer control policy at national and international levels.

2 REVIEW OF THE LITERATURE

2.1 Definitions and classifications

Despite numerous historical mentions, the first systematic studies of the group of diseases known nowadays as "cancer" (also called "malignant neoplasms") started at the end of the eighteenth century (dos Santos Silva 1999). Cancer was a relatively rare disease before the twentieth century, turning into a global public health issue through population ageing in countries experiencing the epidemiological transition (Omran 1971). Understanding the spread and causes of cancer was strongly linked with the development of modern epidemiology as a new scientific field. Several studies of cancer causes were the starting point for developing modern epidemiological study designs. The most prominent example was case-control studies conducted in the middle of the twentieth century, establishing the link between smoking and lung cancer (Wynder and Graham 1950; Doll and Hill 1950). The development of modern epidemiology in the twentieth century and the assessment of cancer burden have been instrumental in understanding its causes and strategies for cancer control.

The definition of the cancer case is a critical issue in measuring cancer burden. Cancer symptoms are non-specific; pathological tissues and cells usually characterise malignant diseases. Therefore, the definition of a cancer case usually requires pathological verification. So, even though most diseases represent a clinical concept, pathologists typically define cancer in terms of tissue and cell malignant features and the extent of invasion (Bray and Parkin 2009). Historically, death records were the first available and the most affordable source for disease statistics (Wagner 1991), so the cause of death information and autopsy were likely used to define cancer cases. The development of microscopic methods in pathology in the nineteenth century allowed for more precise diagnostics (Hajdu 2012). Tumour biopsy has become a gold standard for accurate cancer diagnosis. However, several critical issues in cancer case definition limit our ability to apply universal criteria for cancer diagnosis.

First, the cancer case definition and incident date definition are related to the natural history of the disease. The formation of malignant cells and tissues requires months or even years (Brenner, Altenhofen, et al. 2011). The invasion and metastatic disease represent the late stage of cancer development, which can be preceded by a period with minor or no manifestations. Therefore, the diagnosis often depends on the probability and frequency of diagnostic interventions.

Second, microscopic morphology is not universally available and the performance of pathological assessment varies worldwide, limiting accurate cancer verification (Wilson et al. 2018). Finally, in several cases, even untreated cancers do not progress to the stage of the patients' death or other serious outcomes. For example, skin non-melanoma cancers are an example of malignant neoplasms that often do not exhibit the typical pattern of malignant disease and rarely progress to lethal stages or metastases. They are often excluded from overall cancer statistics.

A systematic approach to cancer case definition can be illustrated by the recommendation for the basis of diagnosis codes, going from less to more accurate diagnostic methods (Table 2.1). The case and incident date definition, however, still remains the core issue in cancer data comparability assessment (Bray and Parkin 2009).

Before the twentieth century, estimating the burden of cancer was not only limited by the lack of instrumental diagnostics and definitions but also by the absence of classifications. Classifications are needed to group and discern disease entities that are probably heterogenic regarding their causes and prognosis. William Farr and Marc d'Espine developed two conflicting nomenclature systems for grouping diseases, presented in 1853 at the first Session of the International Statistical Congress (Lewes 1988). While Farr's nomenclature was based on human anatomy and became the basis for the International Classification of Disease, d'Espine's focused on disease pathology. This difference in the approach to group diseases remains relevant for modern cancer epidemiology. The International Agency for Research on Cancer (IARC), established by the WHO, made a major step in developing and implementing malignant neoplasm classification (Fritz et al. 2013). In contrast to the International Classification of Diseases (ICD), classifying malignant neoplasms using anatomical sites and morphological type was the fundamental principle of the International Classification of Diseases for Oncology (ICD-O) developed by IARC in 1976. At the same time, ICD-O was connected to ICD and the pathological nomenclatures developed by different organisations (Figure 2.1). The step towards

two-dimensional classification was a breakthrough in setting a standard for a comparable and meaningful way to classify and record cancer cases.

ICD-11, approved by WHO Health Assembly in 2019, took advantage of this approach, adding a complex structure that includes a semantic knowledge base (the Foundation), a biomedical ontology linked to the Foundation and classifications derived from it (Harrison et al. 2021). A recent study suggested ICD-11 is superior to ICD-O as it facilitates statistics, multiaxial coding, and coding granularity, compatibility and intelligence (Xu, Zhou, and Wang 2022). However, such a conclusion should be met with caution. Healthcare professionals are always tempted to include as much information in a classification system as possible. At the same time, the complexity of classification makes it difficult to implement this in low-resource settings.

Furthermore, international classifications should be applied worldwide to facilitate comparable data collection. In LMIC, where diagnostic resources lag behind those in developed countries, it is still challenging to implement ICD-O (Bray, Znaor, et al. 2014). In addition, the difference in approaches to disease grouping in ICD and ICD-O remains a source of constant confusion in many countries. Therefore IARC made additional attempts to ensure comparability between ICD and ICD-O, offering conversion tools (Ferlay, Burkhard, et al. 2005).

Classifications are also important in clinical decision-making and allow for the assessment and implementation of treatment options. The emergence of international nomenclatures and classifications allowed for comparable and systematic approaches to cancer burden measurement.

2.2 Measuring the burden of cancer

There is no standardised definition of "burden" in contrast to the different cancer statistics used to capture it. Cancer statistics are often represented by well-defined epidemiological measures or their derivatives. Comparison of those measures in populations grouped by specific characteristics (including those related to several time dimensions) lies behind the epidemiological cancer research targeted at cancer burden assessment.

Table 2.1 IARC-IACR basis of diagnosis codes. Adapted from Fritz et al. 2013.

Code	Description	Criteria
0	Death certificate only	Information provided is from a death certificate.
Non-microscopic		
1	Clinical	Diagnosis made before death, but without any of the following (codes 2-7).
2	Clinical investigation	All diagnostic techniques, including X-ray, endoscopy, imaging, ultrasound, exploratory surgery (such as laparotomy), and autopsy, without a tissue diagnosis.
4	Specific tumour markers	Including biochemical and/or immunologic markers that are specific for a tumour site.
Microscopic		
5	Cytology	Examination of cells from a primary or secondary site, including fluids aspirated by endoscopy or needle; also includes the microscopic examination of peripheral blood and bone marrow aspirates.
6	Histology of a metastasis	Histologic examination of tissue from a metastasis, including autopsy specimens.
7	Histology of a primary tumour	Histologic examination of tissue from primary tumour, however obtained, including all cutting techniques and bone marrow biopsies; also includes autopsy specimens of primary tumour.
9	Unknown	

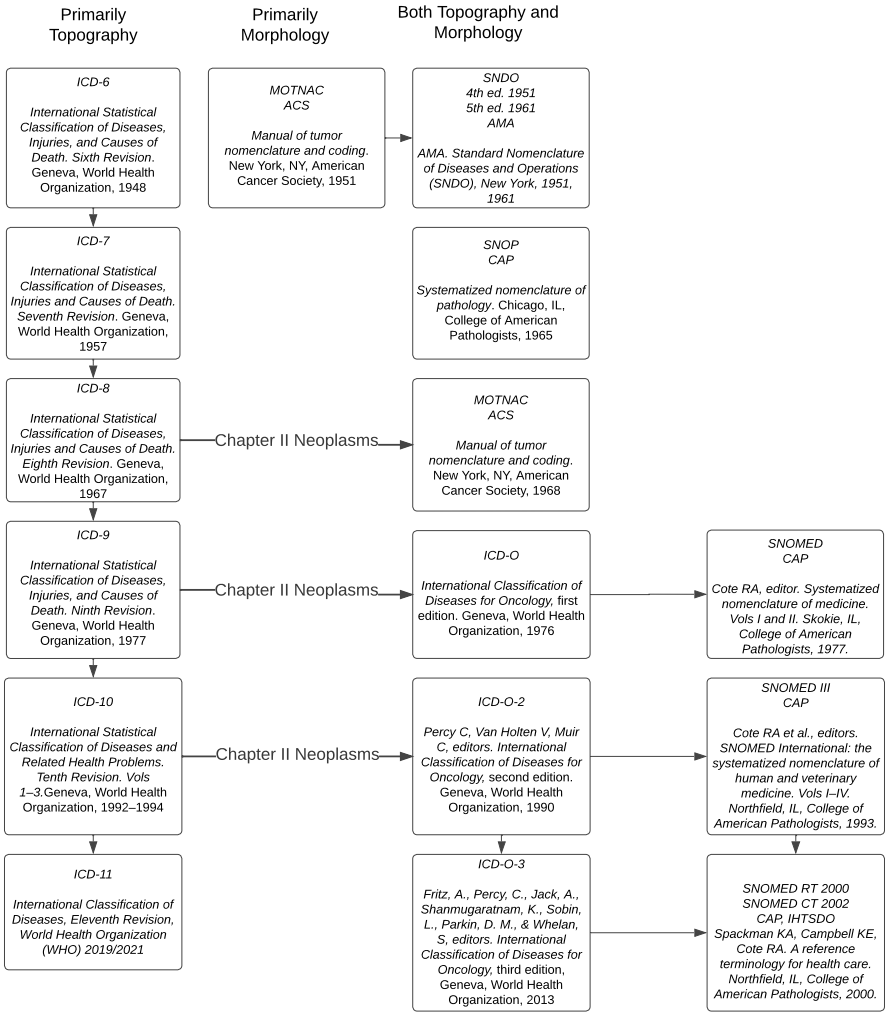

Figure 2.1 The history of the international classifications of malignant neoplasms. Adapted from Fritz et al. 2013.

2.2.1 Epidemiological measures

Core measures used to assess the "burden" of cancer in the general population include the absolute number of cases and deaths and incidence risks or rates for cancer diagnosis and death (cancer incidence and mortality). The risk of death can be assessed in the general population or among cancer patients. In epidemiological terms, these statistics can be defined as measures of occurrence.

Cancer incidence (or, more formally, cancer morbidity incidence) is the core statistic in cancer burden assessment, and it remains the most important outcome for cancer prevention and some "preventive" screening (Parkin 2008; Wender et al. 2019; Adami et al. 2019). Unfortunately, cancer incidence statistics were rarely available until PBCR became widespread. However, many regions and countries still lack reliable cancer incidence statistics in the absence of high-quality cancer registry data (Wagner 1991; Whelan 2010; Parkin 2006).

Mortality (or the incidence of death) data were probably the first reliable cancer statistics available worldwide and are still used to approximate cancer incidence in countries where high-quality PBCR data are not available (Wagner 1991). Furthermore, mortality is relevant by itself, as it is the most severe outcome of the disease (Parkin 2008) and the ultimate target for several cancer screening programmes and particular curative treatment regimens (e.g. adjuvant therapy) (Wender et al. 2019).

Prevalence as a measure of cancer burden is less straightforward, as it requires additional assumptions about the period between diagnosis and the moment a patient can be considered to be cured (Parkin 2008). However, prevalence is essential for cancer control planning, e.g. in terms of palliative care and rehabilitation.

Assessment of risks of death is also evaluated in the cohort of individuals with a cancer diagnosis, usually as a part of survival analysis (Parkin and Hakulinen 1991). Several frameworks for survival analysis and recent advancements in the field allowed for its comprehensive implementation using data from PBCR (Perme and Pavlic 2018).

Several other measures used to assess cancer burden offer a comparative approach, e.g. when the individuals diagnosed with cancer are compared to the general population, or based on some exposure status, theoretically reflecting the concept of epidemiological measure of association, i.e. offering some quantitative comparison between groups. However, these estimates require additional assumptions and knowl-

edge about the comparator group (e.g. overall mortality in the general population) and may not be comparable between different countries or regions.

Attributable risks and population-attributable fractions are formally epidemiological measures of association used to understand the burden of cancer. They require information on risk factor prevalence in the population, which is usually acquired through extensive surveys. These epidemiological measures offer additional insight into cancer burden by providing estimates for individual risk factors and understanding the proportion of disease among a population that can be attributed to each risk factor. Knowing attributable risks and fractions enables researchers to inform cancer prevention strategies.

Premature mortality and years of life lost (YLL) complement cancer mortality and estimate the years of potential life lost due to premature cancer death compared to life expectancy in the country or region. Several methods and assumptions exist in the YLL calculations (Parkin 2008). In addition, quality-adjusted (QALY) and disability-adjusted years of life lost (DALY) capture information on the quality of life and the disease duration.

The use of quality-of-life measures has become a widely accepted tool for monitoring cancer patients' well-being nowadays. Quality of life measures are used to assess the overall emotional, social, and physical health and can be a valuable indicator for understanding the complete picture of individual health. According to the World Health Organization, quality of life is determined by an individual's perception of their position in life, which is influenced by their values, expectations, goals and standards, as well as the culture and environment they live in (Kalager et al. 2021). In addition, factors like physical and mental health, economic security, and access to educational opportunities can considerably impact a person's quality of life. Questionnaires (e.g. EQ-5D, SF-36/12) are typically designed to focus on the self-assessment of the quality of life. However, as with many self-reported outcomes, there are multiple difficulties in their interpretation and comparison.

YLL and QALY are also used in economic analyses. YLL can also be linked to monetary values, e.g. productivity losses. The economic burden of cancer can be assessed from the healthcare sector and societal perspective and includes direct and indirect medical and non-medical costs (Russell et al. 1996; Sanders et al. 2016; Krol, Brouwer, and Rutten 2013). The societal perspective can often be dismissed in cost-effectiveness analyses of public health interventions, despite representing a

major proportion of the economic cancer burden.

WHO (World Health Organization 2020) distinguished between core surveillance measures, extended surveillance measures and surveillance strategies to obtain those measures. Core surveillance in relation to cancer control includes data on risk factors, prevention and screening programmes, incidence, survival and mortality. Extended surveillance measures include attributable risks, prevalence, DALYs, and economic costs. Surveillance strategies, according to WHO, include population surveys, screening and prevention programme registries, PBCRs and vital statistics registries.

Tables 2.3 and 2.2 summarise core data sources and measures used in cancer burden assessment. In addition, some of the data sources, measures and methods are discussed in the following sections.

Table 2.2 Core data sources used for cancer burden assessment

Data	Main source
Mortality	Vital statistics registry
Population	Vital statistics registry
Morbidity	Population-based cancer registry
Population exposures	Surveys, cohorts
Population-based interventions	Specific registries (screening, vaccination, etc.)
Quality of life	Surveys, cohorts
Treatment	Hospital-based registries
Costs	Surveys, administrative registries

2.2.2 Population-based cancer registration

Mortality data were probably the first source of reliable cancer statistics available. Vital statistics registries collected mortality data in many countries for various purposes, and pathological assessment of solid malignant tumours was possible even without microscopic verification methods (Wagner 1991). However, rising mortality rates and overall interest in cancer epidemiology in the middle of the twentieth century led to the understanding that reliable incidence data was also needed. Surveys were ineffective in collecting information on cancer, a relatively rare disease.

Table 2.3 Core epidemiological measures used in cancer burden assessment

Measures	Study examples
Incidence (cancer incidence and mortality rates, cancer survival)	Eileen Morgan et al. (2023). "Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN". in: *Gut* 72.2, pp. 338–344; Claudia Allemani et al. (2018). "Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries". In: *The Lancet* 391.10125, pp. 1023–1075
Prevalence (risk factor prevalence or screening coverage)	Laia Bruni et al. (2022). "Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis". In: *The Lancet Global Health* 10.8, e1115–e1127; Gary M Clifford et al. (2005). "Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis". In: *The Lancet* 366.9490, pp. 991–998
Relative measures (relative risk, percentage change)	Kristina Lindemann et al. (2010). "Endometrial cancer incidence trends in Norway during 1953–2007 and predictions for 2008–2027". In: *International journal of cancer* 127.11, pp. 2661–2668; Maiju Pankakoski et al. (2019). "Effectiveness of cervical cancer screening at age 65—A register-based cohort study". In: *PloS one* 14.3, e0214486
Absolute measures (attributable risk)	Olli Kurkela et al. (2022). "Lung cancer incidence attributable to residential radon exposure in Finland". In: *Radiation and Environmental Biophysics*, pp. 1–15
Years of life lost	Diana Withrow et al. (2022). "Current and projected number of years of life lost due to prostate cancer: A global study". In: *The Prostate*

In the late 1950s, cancer registries were already established in several regions (Hamburg (Germany), Connecticut and New York (USA), Denmark, Belgium, Finland, Saskatchewan (Canada), England and Wales and others), and an international group gathered upon the initiative of the Danish Cancer Registry recommended the worldwide establishment of cancer registries (Whelan 2010; Wagner 1991).

The process involved several international organisations: WHO, the Union for International Cancer Control (UICC), and later IARC, established in 1965, and the International Association of Cancer Registries (IACR), established in 1966. Since then, several countries have established compulsory cancer registration nationally. In 1990, the European Network of Cancer Registries (ENCR) was established within the framework of the Europe Against Cancer Programme of the European Commission. As of 2014, there were more than 700 PBCRs worldwide, but the number of registries is probably more now as it continues to grow (Bray, Znaor, et al. 2014).

Since registries worldwide started reporting cancer incidence data, several publications have been devoted to the components of the quality of information collected in PBCRs (Benn, Leck, and Nwene 1982; Hans H Storm 1988; Teppo, Pukkala, and Lehtonen 1994; Brenner, Stegmaier, and Ziegler 1995). In addition, IARC publications summarised fundamental principles of PBCR quality assessment (Skeet 1991; Parkin, Chen, et al. 1994).

PBCR quality assessment included four components analysed using different methods. Comparability addresses whether coding and classification procedures and rules follow international recommendations developed by ENCR, IACR and IARC. Validity addresses whether the information in the registry is accurately recorded in line with those recommendations. Timeliness covers the time aspect of the information collection, and completeness reflects the degree to which cancer cases in the population are included in the registry.

A publication that covered the data collected by the Cancer Registry of Norway demonstrated a systematic and comprehensive approach to quality assessment (Larsen et al. 2009) and closely followed what would become a new standard for quality assessment (Bray and Parkin 2009; Parkin and Bray 2009).

Cancer registry assessments that included all four quality criteria were later published for several countries, including Iceland (Sigurdardottir et al. 2012), Bulgaria (Dimitrova and Parkin 2015), Singapore (Fung et al. 2016), Finland (Leinonen et al. 2017), Switzerland (Wanner et al. 2018), Ukraine (Ryzhov, Bray, et al. 2018) and

Hungary (Wéber et al. 2023).

Table 2.4 summarises the methods used in quality assessment.

Table 2.4 Core methods used in cancer registry quality assessment. Adapted from Bray and Parkin 2009; Parkin and Bray 2009; Larsen et al. 2009.

Quality dimension	Methods
Comparability	Assessment of the system used for classification and coding of neoplasms
	The definition of incident case and the definition of the incidence date
	The distinction between a primary cancer and extension, recurrence or metastasis of an existing one
	Assessment of the the recoding of cancers detected in asymptomatic individuals (screening, autopsy)
Validity	Reabstracting and recoding
	Diagnostic criteria assessment (histological verification proportion (MV%), and death certificate-only proportion (DCO%)
	Missing information analyses
	Internal consistency checks
Timeliness	Comparison of registry database frozen at different timepoints
Completeness	
Semi-quantitative	Historic data methods (stability of incidence rates over time, comparison of incidence rates, shape of age-specific curves, incidence rates of childhood cancers)
	Mortality-to-incidence ratios
	Sources of information (notifications per case)
Quantitative	Independent case ascertainment
	Capture-recapture methods
	Death certificates methods (DCN/M:I method, the "flow" method)

2.2.3 Comparative analysis of cancer burden

Data from different sources are collected to estimate and compare cancer burden in specific populations. This assessment can be semi-quantitative, including standard tables and data visualisation techniques, or quantitative (Jensen and Hans H Storm 1991). For example, rates from different periods (i.e. people at risk at different periods) can be used to calculate the relative rates. Other core characteristics used in cancer burden assessment include but are not limited to gender, age, socioeconomic status, ethnicity, and place of residence (Parkin 2008). The choice of characteristics depends on the data available at cancer registries, research hypotheses and capabilities for data linkage. These characteristics can be associated with chosen incidence measures, and comparisons should consider the possible confusion of these. When researchers are interested in such comparison, analysis within or between subgroups can be made, e.g. cancer rates are analysed separately in men and women or in specific age groups.

The effect of age on cancer rates is often considerable. Some cancer types are exclusive to specific age groups. The population's age structure influences the crude rates; thus, comparisons that do not consider age may be misleading. In that case, age adjustment is usually performed. Direct standardisation applies weights based on standard population, and the indirect method can be used to compare expected and observed rates based on a population with a known age distribution (Boyle and Parkin 1991; dos Santos Silva 1999).

Age and period represent time dimensions. The birth cohort is another time dimension used to assess changes in cancer burden. Age-period cohort models play a crucial role in cancer trend analyses (or temporal variations of cancer rates) and predictions (Carstensen 2007; Clayton and Schifflers 1987a; Clayton and Schifflers 1987b).

2.2.3.1 Cancer trends

Cancer trend analyses are often mentioned as a descriptive tool in cancer epidemiology (Clayton and Schifflers 1987a). However, any trend analysis is comparative by nature. For example, simple relative measures (relative rates) can be calculated for two periods. Cancer researchers usually have rates for more than two periods and are interested in measures that capture information on the trends or changes over

time. Trend analyses may involve linear modelling when rates are usually put as a function of time.

Traditionally, when rates are put as a function of time, percentage change captures information on the relative change of the rates in the pre-specified period and is analogous to attributable risk proportion. Statistical methods can assess the random error and form confidence bounds with a hypothesis that this change does not differ from the null. Average percentage change calculations often assume there is a linear homogenous trend. In general, many statistical models assume a linear combination of the explanatory variables. However, when determining how one or more variables impacts a response variable, it is sometimes discovered that the relationship between them is non-linear, which means that their effect on the response suddenly changes or shifts at specific values. This can be seen as a curve instead of one straight line on a graph, which is often the case for cancer rates.

In that case, the trend analyses can be done in the framework of segmented regression (also called piecewise, joinpoint or broken-stick regression), where thresholds (also called break-points, change-points, transition-points, switch-points, or joinpoints) can be estimated (Muggeo 2003). Percentage changes can be identified between the thresholds and point to the different magnitudes or the directions of changes.

Comparison of cancer rates in different periods (or cohorts) is meaningful by itself as it provides a broader picture of cancer burden assessment. However, changes in time that influence the rates are often of primary interest to cancer researchers. Moreover, the nature of those changes can differ, from cancer causes and control intervention to diagnostic practices and classification changes.

Two studies published in one of the first issues of the British Journal of Cancer presented an example of how trend analyses have been used to build hypotheses on the aetiology of cancer. First, the time-related changes in lung cancer rates in men in Denmark were attributed to changes in diagnostic practices (Clemmesen and Busk 1947). At the same time, authors from England discussed, among other possible causes, changes in tobacco consumption (E. Kennaway and N. M. Kennaway 1947). While both explanations were probably correct, the consequent analytical studies confirmed the dramatic effect of tobacco consumption on cancer rates (Doll and Hill 1950).

In addition to hypothesis generation, trend analyses can be used to assess the

possible effect of exposures already evaluated in cohort or case-control studies. For example, a recent study examined glioma incidence rates in Denmark, Finland, Norway and Sweden from 1979 to 2016 among middle-aged men. The results showed no major increase in glioma incidence over the study period and that the observed incidence rate was incompatible with risk ratios in previously reported case-control studies (Deltour et al. 2022). In this study, the effect of time on cancer rates was a proxy for exposure (mobile phone use); formally speaking, populations with different levels of exposure were compared.

Trend analyses can be instrumental in evaluating the effectiveness of interventions aimed at reducing the burden of cancer, such as cancer screening programmes and early detection strategies, and monitoring the progress of interventions over time (Parkin 2008). Post-hoc evaluation of already implemented programmes has been greatly facilitated by the availability of cancer registry data, providing valuable insight into whether a programme has successfully reduced cancer incidence and/or mortality. For example, a Finnish study examined the impact of the breast cancer screening programme on the population-based incidence and mortality rates. The incidence of localised breast cancer increased, and the incidence of non-localised breast cancer decreased, especially in age groups where screening had been going on for several years. In addition, the mortality rate from breast cancer diagnosed in ages 50-69 decreased by 11.1%, suggesting the effectiveness of screening. However, the programme's impact on the population level was smaller than expected due to the young age group targeted (Anttila, Sarkeala, et al. 2008).

Unfortunately, it is not always possible to distinguish the effects of several cancer control interventions and changes in exposure happening simultaneously. In addition, lack of information on exposure and intervention status at the individual level may lead to ecological bias (Greenland and Morgenstern 1989).

2.3 Cancer statistics in Russia

Cancer statistics from Russia come from several sometimes conflicting sources and publications. There is still a large amount of confusion about the source of cancer incidence and mortality data, amplified by a lack of trust in any statistics from Russia and the lack of reliable scientific publications. For example, an international report that focused on challenges to effective cancer control in China, India, and Russia

presented conflicting statements about cancer statistics in Russia (Goss et al. 2014).

According to this report, the National Cancer Registry is managed by the Department of Health Statistics and the Ministry of Health, which collects data annually from hospitals and treatment centres, and and two cancer centres, NN Blokhin Russian Cancer Research Centre and P. Hertsen Moscow Oncology Research Institute, both in Moscow, independently review the data and publish the findings. The report mentioned several concerns, such as the methods used to collect cancer burden data and the quality of this information. The report concluded that the national statistics might not be comprehensive and could show trends for only specific subregions of the country. Despite several Russian experts and oncologists being co-authors of this report, it relied mainly on GLOBOCAN 2012 data. It would be safe to conclude that it probably represented a standard view among oncologists and confusion about cancer statistics in Russia.

2.3.1 Cancer incidence data

The statistics regularly published by the P. Hertsen Moscow Oncology Research Institute, now the branch of the National Medical Radiology Research Centre of the Ministry of Health of the Russian Federation, remain the sole source of national cancer incidence statistics (Kaprin, Starinskiy, and Shakhzadova 2022). This source represents detailed aggregated data that include age-, site- and sex-specific national, and site and sex-specific regional incidence estimates, including the absolute number of cases and rates. Unfortunately, not all the cancer sites are presented, but several have been added through the years. Annual cancer reports include mortality data acquired from the Federal State Statistics Service (FSSS) and available from other sources. Reports have been available online since 2007, but printed versions are also available for earlier periods, making data available from 1995 to 2021. An additional report was published by the P. Hertsen Moscow Oncology Research Institute group in 2015, including site-, age- and sex-specific incidence data from 1993 till 2013 (Kaprin, Starinskiy, and Shakhzadova 2022). Data come from aggregated reports collected from regional population-based registries in the first two months of the following year. Attempts to collect individual-level data for the report are still ongoing. This was never implemented due to a lack of resources, bureaucratic reasons (the failure to update Ministry of Healthcare laws relating to cancer registration led to disparity in interpretation of regulations by different regions), and varying states

of cancer registration in different regions. The aggregated data are then summarised in the national incidence report.

NN Blokhin Russian Cancer Research Centre independently published several cancer statistics reports, but they included the same amount of data with an attempt to include statistics from other former Soviet Union countries. Unfortunately, this project was short-lived, with the most recent reports containing data from 2012-2013.

Local reports, monographs and publications in Russian were also published regularly based on St. Petersburg PBCR data. Along with incidence and mortality, they included survival estimates. Later, several monographs were published based on regional data from Northwest Russia. Unfortunately, those publications were primarily available in print and only in Russian (V. Merabishvili and E. Merabishvili 2020).

2.3.2 Cancer mortality data

The source of mortality data is civil registration collected by FSSS. Overall mortality data in Russia is regarded as reliable (Barbieri et al. 2015). Both regional and national data were used to estimate excess mortality after the COVID-19 pandemic (Timonin et al. 2022). Unfortunately, the information on causes of death in Russia was criticised, especially in older age groups.

A demographic study examined the decrease in cancer mortality in Russia and Ukraine in the late 1980s and 1990s. It investigated four possible explanations for the decrease, including changes in data collection, cohort effects, increased mortality from other causes, and improvements in health care. It found that each explanation affects different age groups and that there is evidence of cancer deaths going under-recorded among the elderly, particularly in rural areas. The paper suggested that understanding recent changes in mortality in Russia requires a multidisciplinary approach (V. Shkolnikov, McKee, et al. 1999).

Another study examined the quality of cause-specific mortality statistics in Russia, focusing on regional differences in approaches to choosing the underlying cause of death and comparing Russian coding practices to those of other European countries (Danilova 2016). The study results suggested problems with the quality of cause-of-death coding among older age groups in Russia. No unified approach to coding deaths caused by senility was used at the subnational level, leading to distorted re-

gional mortality structures. Additionally, Russian death rates from some causes were much lower than those in other European countries due to the specificity of Russian cause-of-death coding practices. This resulted in underestimating mortality from specific causes in old age.

Another report focused on the uniformity of cause-of-death coding practices across 52 Russian regions by analysing 2002-2012 mortality data. The results showed a high consistency across regions and over time for some causes of death (including transport accidents, most neoplasms, congenital malformations, and perinatal conditions), while others had a high degree of inconsistency. When grouped into broader diagnostic categories, the level of consistency improved. This study suggested that coding practices for specific causes of death are not uniform across regions and that mortality statistics may not reflect the actual epidemiological situation. However, causes of death related to most neoplasms were coded consistently (Danilova, V. Shkolnikov, et al. 2016).

Finally, the latest report compared subnational consistency of causes of death coding in Russia, Germany, USA and France (Danilova, Rau, et al. 2021). Research has found that neoplasms, the group of causes classified in ICD-10 Chapter II, have the highest consistency in Russia, the USA, and Germany. This consistency is evidenced by an average regional deviation of less than 20% from the mean. Only seven causes from other ICD-10 chapters also meet this threshold in Russia. Of the top 20 least varying causes in Russia, only three were not neoplasms, and only one of these was among the top 10 (Danilova, Rau, et al. 2021).

It is worth mentioning that cause-of-death data has been available to demographic researchers in categories up to the third digit of ICD classification since 2000. However, national and regional cancer reports operate with low-resolution mortality data aggregated in broader categories, making the comparison with incidence impossible for some cancer types.

2.3.3 Russian statistics in international reports

International statistics published for Russia are based on the national report, FSSS data and limited population-based cancer registry data.

For example, GLOBOCAN calculates incidence rates for Russia based on the national report, except for anus and non-melanoma skin cancers, mesothelioma and Kaposi sarcoma (cases computed by year using sex- and age-specific proportions

from the local registries (2008-2012), and oesophageal, gastric, liver, pancreatic and lung cancers (cases (2009-2018) supplemented with cancer deaths (2009-2018, source WHO). Mortality rates are acquired from the WHO mortality database to 2018 and supplemented with data from two cancer registries (St. Petersburg and Arkhangelsk, 2008-2012) used to separate out lip, oral cavity and pharynx incidence; categories of colon, rectum and anus, gallbladder, non-melanoma skin, testis, kidney and thyroid cancers, mesothelioma, Kaposi sarcoma, Hodgkin lymphoma, and "other and unspecified sites". (Ferlay, Soerjomataram, et al. 2015).

The Global Burden of Disease (GBD) programme also provides health statistics for Russia (Starodubov et al. 2018). GBD cancer statistics for Russia were based on a common source, cancer mortality data from WHO and St. Petersburg population-based cancer registry data 1983-2007 used in "the cause of death Ensemble model and Bayesian meta-regression".

Figure 2.2 summarises information about major sources of cancer statistics in Russia used nationally and internationally. Population-based registries are the sole source of cancer incidence data, and civil registration provides mortality data with the cause of death information.

2.3.4 Cancer registration in Russia

As part of the USSR, Russia introduced compulsory cancer registration in 1953 and later updated its procedures in 1963 to be comparable to Western cancer registries. In 1976, the Health Ministry prepared a plan to create a computerised cancer registration system throughout all the regions of the USSR. However, the project was unsuccessful due to a lack of organisation, supplies, and technical expertise and was eventually abandoned. In 1983, the Health Ministry ordered the introduction of an "experimental centralised processing of information" into cancer dispensaries, covering a population of around 30 million (12% of the USSR population). This programme was likely based on the SEER Program in the USA (M. Rahu 1992). IARC described the Soviet cancer registration system in 1983 in the report "Cancer Incidence in the USSR" (IARC 1982). It is worth mentioning that according to instructions at that time, the official annual regional cancer statistics report in the USSR was completed about six weeks after the year's end. This practice was later adopted in Russia. Besides the official annual reporting, epidemiological research projects were not generally conducted, and individual-level data were rarely

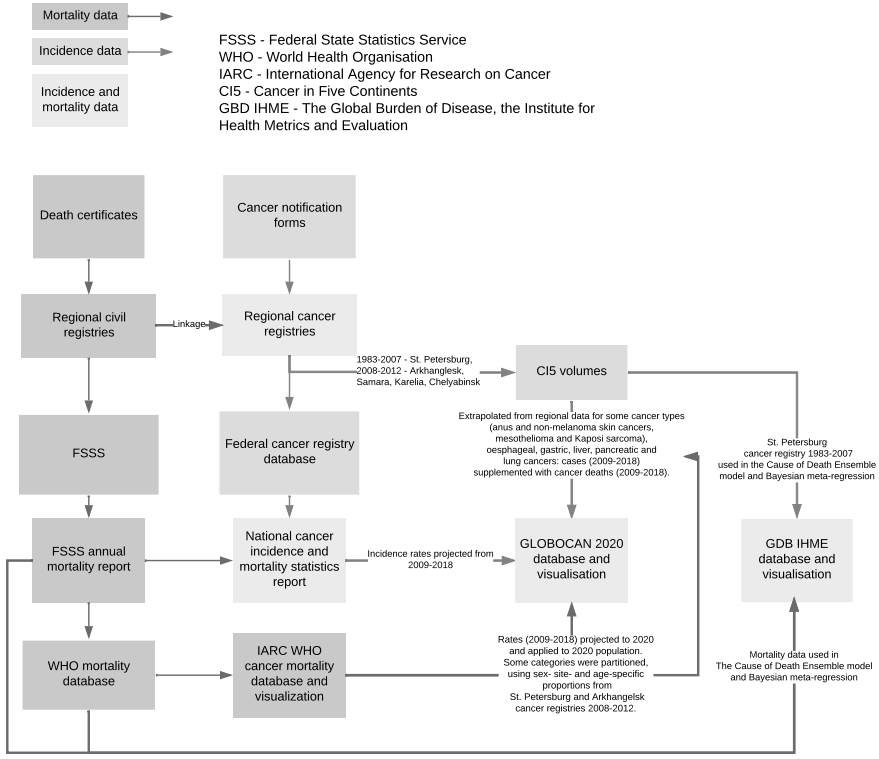

Figure 2.2 Sources of cancer statistics in Russia. Adapted from Barchuk, Belyaev, et al. 2021.

available (M. Rahu 1992).

After the collapse of the USSR, an assessment of cancer registration in several newly independent states of the former Soviet Union was conducted by the IARC in Technical Report N35 (Winkelmann et al. 1998). The report described data collection processes which were quite similar to Soviet practice and highlighted the need for better infrastructure, classifications, and systematic monitoring to gain data suitable for research. It should be mentioned that some regions started independent data collection using approaches and infrastructure based on the Finnish cancer registry. One of the first regions to start individual data collection was St. Petersburg (V. M. Merabishvili and Moiseenko 1993). This allowed for the publication of St. Petersburg cancer registry data in "Cancer in five continents" Volume VIII (1994-1997) (Parkin, Whelan, et al. 2002). Individual-level data collection was not limited to St. Petersburg in the early 1990s. It was the only region that submitted the data to "Cancer in five continents".

Definitions for Regional and National Cancer Registries were introduced by the Ministry of Health in Russia in 1996 in Order N420 (*[Prikaz Minzdrava RF ot 23 dekabrya 1996 g. N420 "O sozdanii Gosudarstvennogo rakovogo registra"], The order of the Ministry of Healthcare of the Russian Federation N420 from 23.12.1996 "On the foundation of the State Cancer registry"* 1996). Although this order introduced regional and national PBCRs in 1996, in practice the national cancer registration system was established in 1999 with Order N135, which described procedures and classification (*[Prikaz Minzdrava RF ot 19 aprelja 1999 g. N 135 "O sovershenstvovanii sistemy Gosudarstvennogo rakovogo registra"], The order of the Ministry of Health of the Russian Federation N135 from 19.04.1999 "On the Enhancement of the System of the State Cancer Registry"* 1999). This order introduced the ICD-O-2 morphological classification and ICD-10 instead of ICD-O-2 for topography codes, which most Russian PBCRs still use.

Figure 2.3 describes the procedures and data collection forms recommended in Russia's cancer registries. Briefly, standardised paper notifications, collected before or after diagnosis, should be forwarded to regional population-based cancer registries.

All healthcare organisations (not only cancer hospitals) were obliged to forward notifications to cancer registries. Most of the registries in Russia are based in the regional cancer hospitals (Oncology Dispensaries), except for some regions (e.g. St. Petersburg). All malignant and in situ neoplasms with ICD codes C00-96 and D00-

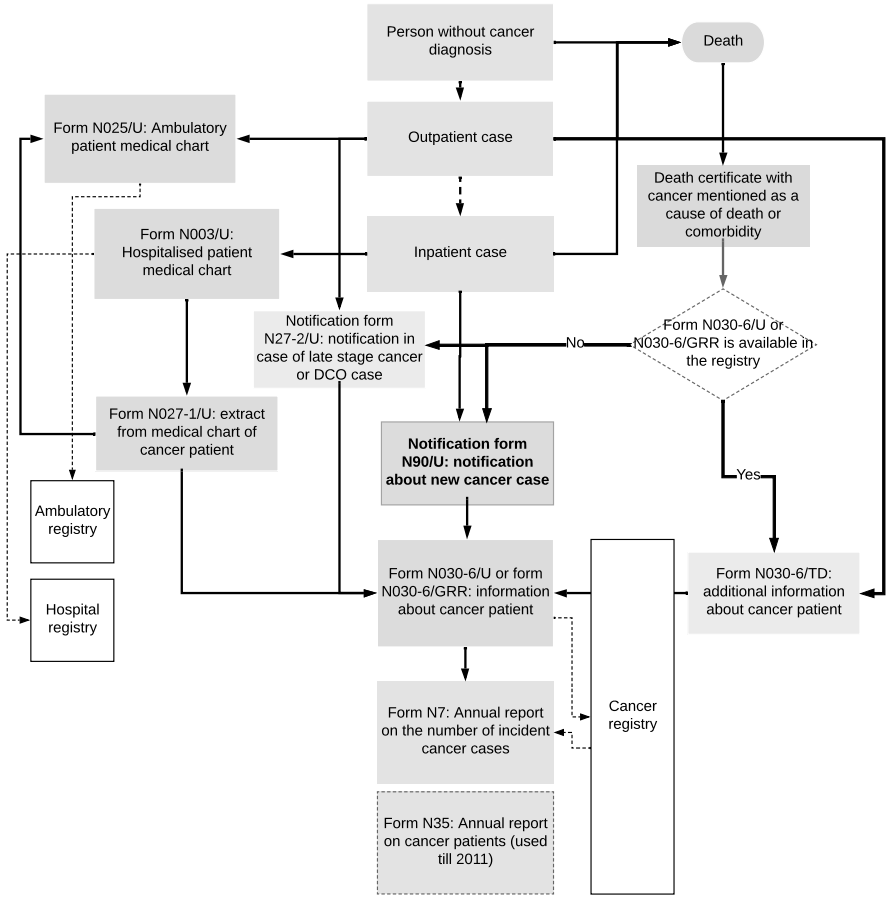

Figure 2.3 Data collection process described in the instruction for cancer registries. Adapted from Barchuk, Belyaev, et al. 2021.

09 are supposed to be recorded. Pathology laboratories do not send information to cancer registries directly, but information from pathologists should be included in the clinical notification. Personal information is supposed to be used by PBCRs to link with mortality data from civil registries. Regional practices vary regarding linkage with mortality records. In Northwest Russia, PBCRs established linkage procedures with mortality in all regions. However, it may be manual. The most common software used by PBCRs has been created in Moscow ("Cancer-register FB6") and St. Petersburg ("NovelSPB Population-based Cancer Registry"), and some regions used in-house software (Barchuk, Belyaev, et al. 2021).

Comparison of national recommendations for cancer registration in Russia with recommendations proposed by ENCR (Tyczynski, Démaret, and Parkin 2003) revealed that the Russian system was consistent with some of the recommendations (Table 2.5). However, some definitions and recommendations were outdated or missing (Barchuk, Belyaev, et al. 2021). More recently, Russia tried implementing the ICD-O-3, but the process is still ongoing.

In conclusion, the changes adopted at the end of the 1990s in the cancer registration system in Russia allowed for systematic cancer incidence data collection across regions. Unfortunately, quality assessment procedures were not explicitly described in the cancer registry national instruction and were never conducted.

2.3.5 Cancer epidemiological research in Russia

The development of cancer epidemiology witnessed unprecedented growth worldwide from the mid-1950s. Cancer epidemiologists have helped shape the basis and strategies of modern epidemiology. Studies of cancer risk factors broadened the methods of analytical epidemiological designs, and trials in oncology helped advance clinical epidemiology. Consequently, cancer epidemiology continues to influence the whole field of modern epidemiology today and is likely to remain a salient factor in epidemiological research. How modern epidemiology, specifically cancer epidemiology, has been practised in the former Soviet Union reflects science's unbalanced and disorganised research progress in the country. Only a tiny proportion of the "hard" scientific disciplines were developed to the same level as other nations by the end of the USSR's existence. This limited scientific advancement prevented the successful implementation of modern epidemiology, resulting in fewer opportunities to identify, fight and mitigate public health issues. Furthermore, economic challenges

Table 2.5 Comparison of the ENCR recommendation and cancer registration instructions in Russia. Adapted from Barchuk, Belyaev, et al. 2021.

The ENCR recommendation	Order 135	Comments
Minimum dataset of variables	Available	
Incidence date	Available	
Basis of diagnosis	Available	In-house codes for the basis of diagnosis.
Topography, morphology, behaviour	Available	The topography is collected with ICD-10 codes.
Recording multiple primary tumours	Available	Rules for registration, but not reporting.
Recording bladder tumours	Not available	
Recording central nervous system tumours	Not available	
Recording non-melanoma skin cancers	Available	All skin cancers are recorded. It is recommended to stop follow-up for non-recurrent basal cell carcinoma (M8090-M8093) after radical treatment.
Method of detection in relation to screening	Available	In-house codes without detailed instruction to the registries.
Recording and coding extent of disease	Available	No clear instructions on how to record TNM are given.

resulted in limited resources for conducting epidemiological research and promoting health reforms, compounding health professionals' challenges. Ultimately, the Soviet Union could not adequately apply modern epidemiological knowledge and practice to address health disparities and improve the quality of life of its citizens. That resulted in poor quality of medical care, outdated medical technologies, and irresponsible, sometimes unethical, medical practices (Vlassov 2000).

A comprehensive review of cancer epidemiology in the former Soviet Union was published in 1992 (M. Rahu 1992) soon after it split into 15 independent countries. It described how most Soviet research on cancer was focused on descriptive epidemiology and derived mainly from cancer registry data following the introduction of countrywide compulsory cancer registration in 1953. The USSR was not a founding member of IARC but joined soon after its establishment (Saracci and Wild 2015). IARC assessed the cancer burden in the USSR in 1983 in the report "Cancer Incidence in the USSR" (IARC 1982). Several IARC publications covered cancer epidemiology in the USSR (Bogovski, Purde, and M. Rahu 1977; Zaridze and Gurevicius 1986). Attempts were made to expose cancer researchers and oncologists in the USSR to modern cancer epidemiologic research through publications by Finnish researchers in Russian oncology journals (Hakama 1983; Hakama 1985; Teppo and Pukkala 1983; Isomäki, Hakulinen, and Joutsenlahti 1979). However, this approach was non-systematic, and Soviet oncologists rarely recognised the complexity of the epidemiological methods and data analysis (Vlassov 2000). Still, thanks to support from IARC and Finnish researchers in the early 1990s, St. Petersburg cancer registry data were regularly used to evaluate cancer survival. However, results were published only in local and not international journals. St. Petersburg was also the only Russian registry represented in "Cancer in five continents" volumes VI, VIII, IX and X until only recently, complemented by the data from Arkhangelsk oblast, Chelyabinsk oblast, Samara oblast and the republic of Karelia registries in volume XI.

One epidemiologic research group in Moscow at NN Blokhin Russian Cancer Research Centre affiliated with IARC contributed several sound epidemiological studies related to prevalent risk factors (e.g. smoking and alcohol) for specific cancer types in Russia (Zaridze, Dvoirin, et al. 1986; Zaridze, Brennan, et al. 2009; Zaridze and Basieva 1990; Zaridze, Evstifeeva, et al. 1993). This was, however, an exception in the absence of other studies and research groups.

Since the collapse of the USSR, attempts to re-establish modern cancer epidemiology in Russia have been limited, and the number of international publications has been small. Several attempts to establish western-like education programmes in epidemiology and public health were unsuccessful. Only two international programmes are worth mentioning. St. Petersburg's Medical Academy for Postgraduate Studies programme was founded in 1999 in cooperation with Finnish and Swedish partners and supported by the Soros Foundation. The Northern State Medical University's Arkhangelsk International School of Public Health was founded in 2006 and organised a joint master's programme with the School of Public Health, University of Gothenburg in Sweden (M. Rahu, Vlassov, et al. 2013).

Only a few international publications focused on the cancer burden in regions of Russia. Several papers were published using Arkhangelsk oblast PBCR data. A study published in 2005 by Norwegian and Russian researchers assessed the content and quality of a population-based cancer registry in Arkhangelsk oblast (Vaktskjold, Lebedintseva, Korotov, Tkatsjov, et al. 2005). The study analysed the age-standardised cancer incidence rate in Arkhangelsk oblast. The highest rate was found for lung cancer in males and breast cancer in females. Results also showed that the incidences of many cancer types are quite different in Russia than in many other European countries, and the quality of the data from the Arkhangelsk oblast was sufficient to reflect the cancer situation in the region. Another study compared the cancer incidence rates in Arkhangelsk oblast and Norway (Vaktskjold, Lebedintseva, Korotov, Podjakova, et al. 2007). Compared to Norway, the cancer incidence in women was 31% lower, while it was the same in men.

Another study by the same group assessed the overall and site-specific cancer incidence in Nenetskij okrug (NAO) in Northwest Russia, a circumpolar region with a population of about 40,000 submitting cancer cases to the population-based registry in Arkhangelsk oblast (Vaktskjold, Ungurjanu, and Klestsjinov 2008). Results showed that the average crude cancer incidence per year was higher in men than in women, with the most frequent primary site being lung, followed by stomach cancer. The authors generalised the results to the whole country and concluded that women in Russia had a lower cancer risk than in Western countries. At the same time, men face a high risk of developing lung cancer and other cancer types, such as the pancreas, kidney, and oesophagus.

Most recent papers were devoted to stage-specific rates in Russia using cancer

registry data (Ryzhov, Corbex, et al. 2021). A WHO- and IARC-supported study compared the stage-specific distribution and changes over time in breast cancer and cervical cancer incidence in the newly independent states of the former Soviet Union. The study included data from the population-based cancer registries of Arkhangelsk oblast, Samara oblast, Tomsk oblast, and the regions of Northwest Russia. Results showed that over 50% of breast cancers were registered at early stages (I-II) and that the stage-specific incidence rates of the disease had increased over the studied period, most prominently for stage I cancers. For cervical cancer, the proportions of late-stage (III and IV) cancers were high in several countries, and the stage-specific incidence rates of the disease had generally increased over time. Overall, the results suggested that early detection of breast cancer had modestly improved, but cervical cancer programs should be improved with organised, population-based, quality-assured vaccination and screening programmes.

The most recent study examined the differences in rates by the stage at diagnosis of breast cancer in two Russian regions (Tomsk oblast and Arkhangelsk oblast) compared to 12 regions in Germany (Mahanani et al. 2022). Analysis of breast cancer incidence rates among women aged 30+ revealed that while the proportion of the T1 stage at diagnosis in Russia was half that of Germany, there was a trend of increasing early-stage diagnoses and a decrease in advanced-stage diagnoses in Russia. The findings suggest that, while still far behind Germany, advances in breast cancer detection efforts in Russia may help to reduce the breast cancer burden.

A few demographic studies focused on cancer mortality in Russia and Ukraine. One study found that breast cancer mortality has increased steadily in both countries over the last 40 years but faster in Russia than in Ukraine. Birth cohort effects showed that those born in the first half of the twentieth century had the highest mortality, with a decrease in mortality among those born after the 1950s. Additionally, there has been a decline in mortality among younger women since the mid-1990s, likely from improvements in treatment. The results suggest that the increase in breast cancer mortality can be explained by historical fertility trends, while recent trends may be due to better treatments (Hirte et al. 2007).

Another study examined mortality from cancer in Russia and Ukraine from the late 1980s to the 1990s. It found that mortality from cancer decreased slightly, while mortality from cardiovascular disease, accidents, and violence increased. Authors attributed this decrease to changes in data collection, cohort effects, competing mor-

tality from other causes of death, and improvements in health care (V. Shkolnikov, McKee, et al. 1999).

Several international studies included and analysed data from Russia. A series of publications assessed cancer mortality in Australasian countries, Russia, and Ukraine (Carioli et al. 2019; Pizzato, Carioli, et al. 2021; Pizzato, La Vecchia, et al. 2022). In the latest publication of the series, Russia had the highest total cancer predicted rates for 2022: 156.4/100,000 (world standard) in men and 81.4 in women.

The CONCORD programme established global surveillance of cancer survival and acquired data from Arkhangelsk oblast, the Republic of Karelia, Omsk oblast, Samara oblast, and Tomsk oblast (Allemani et al. 2018). According to this report, survival estimates were the lowest in the world for most cancer types in Russia.

One study quantified the economic costs of premature mortality from cancer in five developing countries (Brazil, Russia, India, China and South Africa) (Pearce et al. 2018). Researchers applied an incidence-based human capital approach and estimated total productivity losses due to cancer death in these countries to be 46.3 billion dollars in 2012 or 0.33% of their combined GDP. An IARC study estimated preventable fractions of cervical cancer in six countries in Estonia, Latvia, Lithuania, Belarus, Bulgaria, and Russia via effective screening using age-period-cohort analysis. National incidence data from Russia was used in this study. Due to the population size, number of women who could avoid cervical cancer was almost 150,000 in Russia, with almost 180,000 in all six countries (Vaccarella et al. 2016).

Another international study examined gastric cancer incidence and mortality rates in circumpolar nations between 1999 and 2016 (Simkin et al. 2021). The study included PBCR data from regions in Northwest Russia. The results reported most populations showing declining trends. Notably, incidence and mortality rates among Greenland males and females, Alaska Native males and females, and Northern Canadian males and females were elevated compared to regional counterparts and remained stable.

Local and international studies on the effect of the Chernobyl fallout on cancer incidence were mainly focused on clean-up workers in Russia and rarely involved the general population (Victor K Ivanov 2007; Rivkind et al. 2020). Studies involving Russian data were mainly published by a research group from the Medical Radiological Research Centre of the Russian Academy of Medical Sciences in Obninsk. For example, one study has shown that the thyroid cancer risk among children below

5 years old at the time of exposure was higher than among adults (V. Ivanov et al. 1999). International epidemiological studies of the effects of Chernobyl fallout on cancer incidence in adult populations in post-Soviet countries focused mainly on the data from Ukraine and Belarus (Pukkala et al. 2006).

Finally, IARC-supported epidemiological cohorts in the Southern Urals (Krestinina et al. 2017) and in the town of Asbest, Sverdlovsk oblast (Schüz et al. 2020), explored the effect of radiation and chrysotile, respectively.

This was almost an exhaustive list of research activities in the field of cancer epidemiology in Russia, both at national and regional levels. Most studies were international collaborations, with occasional contributions from university-based research groups. The limited scope and number of cancer epidemiological studies in Russia, a country with a population of almost 140 million, can be contrasted with Estonia, its opposite among former Soviet Union countries, where researchers took advantage of the cancer registration system established almost half a century ago (M. Rahu and K. Rahu 2018).

Table 2.6 summarises all the main research activities and publications using data from Russia. Despite the wide range of seemingly available data sources and a population-based cancer registration system, Russia's cancer epidemiological research remained archaic. As a result, information on the quality of data sources, especially cancer incidence, is missing from the international research community, and cancer incidence and mortality trends are rarely described or discussed.

Table 2.6 International publication and research activities based on data from Russia

Research and publication activities	Data sources	Reference
IARC/NN Blokhin Cancer Research Medical Centre cancer epidemiology group	Cohort and case-control studies, national cancer incidence and mortality	(Zaridze, Brennan, et al. 2009; Zaridze and Basieva 1990; Zaridze, Evstifeeva, et al. 1993)
IARC "Cancer in five continents" volumes	St. Petersburg, the Republic of Karelia, Arkhangelsk oblast, Samara oblast and Chelyabinsk oblast population-based cancer registries data	(Parkin, Whelan, et al. 2002)
IARC-supported projects and cohorts	Cohort data, national cancer incidence and mortality data	(Krestinina et al. 2017; Schüz et al. 2020; Vaccarella et al. 2016; Pearce et al. 2018)
Cancer epidemiological studies in Arkhangelsk oblast	Arkhangelsk oblast population-based cancer registry	(Vaktskjold, Lebedintseva, Korotov, Tkatsjov, et al. 2005)
CONCORD programme (survival surveillance)	Arkhangelsk oblast, the Republic of Karelia, Omsk oblast, Samara oblast, Tomsk oblast population-based cancer registries	(Allemani et al. 2018)
Chernobyl fallout	Case-control studies data	(V. Ivanov et al. 1999; Rivkind et al. 2020)
Demographic research	National and regional cancer mortality	(Hirte et al. 2007; V. Shkolnikov, McKee, et al. 1999)
Other international projects	National and regional incidence and mortality data	(Carioli et al. 2019; Pizzato, Carioli, et al. 2021; Pizzato, La Vecchia, et al. 2022; Simkin et al. 2021)

3 OBJECTIVES OF THE STUDY

The overall aim of this dissertation was to assess the quality of the population-based cancer registries as the primary source of cancer incidence data and to apply methods to measure the cancer burden nationally and subnationally in Northwest Russia.
The specific objectives of this research were as follows:
1. To assess the quality (comparability, validity, completeness, timeliness) of regional population-based cancer registry data in the regions of Northwest Russia (Study I and II).
2. To describe breast and cervical cancer incidence and mortality trends in Russia, quantifying changes using several indicators of the cancer burden between 1980 and 2013 (Study III).
3. To quantify mortality, years of life lost and productivity costs due to premature cancer mortality in Russia between 2001 and 2015 and project this to 2030 (Study IV).

4 MATERIALS AND METHODS

4.1 Data sources and dataset descriptions

Several independent data sources were used in the study. In brief, for quality assessment, individual-level regional data was provided by PBCRs of the regions in Northwest Russia. Cervical and breast cancer trends assessment used aggregated regional and nationwide incidence data available in the national cancer incidence and mortality report and mortality data produced by the Federal State Statistics Services. For economic assessment, data from the above sources were complemented by labour-force participation and earning data produced by the Federal State Statistics Services (FSSS). Additionally, data from the WHO mortality database, "Cancer Incidence in Five Continents (CI5)", GLOBOCAN and NORDCAN were used for corrections and comparisons.

4.1.1 Regional cancer registry data in Northwest Russia

The quality assessment part of the study used data from regional PBCRs collected and stored at NN Petrov National Medical Research Centre of Oncology. In line with Russian national regulation (The Order of the Ministry of Health N420 12/23/96), NN Petrov National Medical Research Centre of Oncology has established a cancer registry database from the individual-level databases of Northwest regional PBCRs. Anonymised data are gathered and secured at the NN Petrov National Medical Research Centre of Oncology for various goals. This includes epidemiological research, as well as international collaboration. In Russia, additional ethical review is not required for such registry-based research.

For our study, data from the ten PBCR databases from the eleven regions of the NWFD were analysed. This included the Arkhangelsk oblast (including the Nenets Autonomous Okrug), the Murmansk oblast, the Republic of Komi, the

Republic of Karelia, the Pskov oblast, the Kaliningrad oblast, the Leningrad oblast, the Novgorod oblast, the Vologda oblast, and St. Petersburg which was extracted in December 2019 (Figure 4.1).

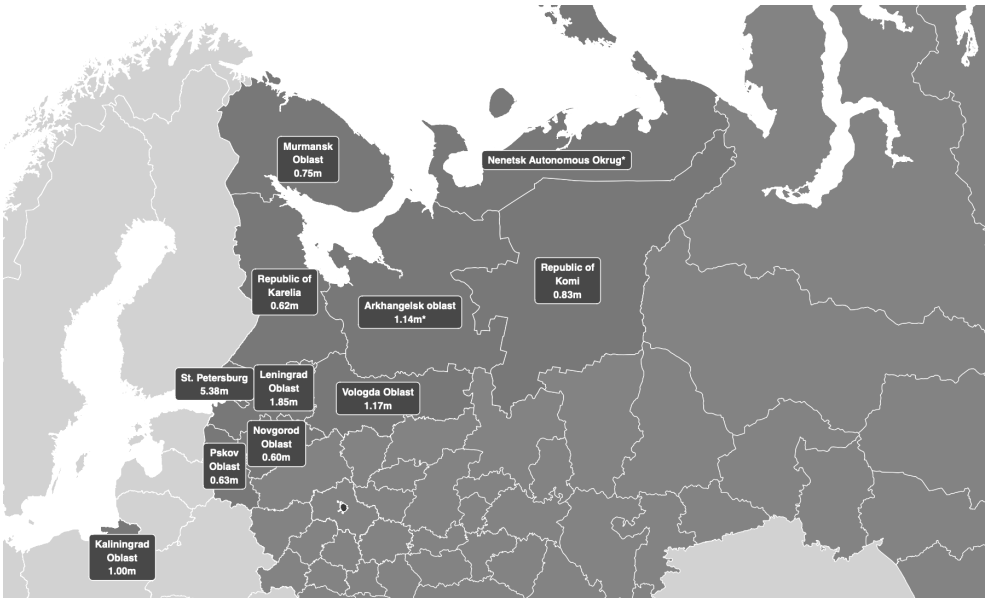

Figure 4.1 Map of the regions in Northwest Russia with corresponding population size (* – Arkhangelsk oblast population including the Nenets Autonomous Okrug.

For quality assessment, datasets were extracted according to the essential variables list recommendations for PBCRs (Bray, Znaor, et al. 2014). Datasets were recreated based on individual-level anonymised records of all cancer cases collected in PBCR databases from the start of electronic data collection specific for each region. The variables stored in the database were collected according to national recommendations, and regional PBCRs updated their records if new notifications or information entered the registry.

The following variables were available for analysis in the dataset: date of birth, sex, group, incidence date, primary tumour site, laterality, primary tumour histology, behaviour, basis of diagnosis, number of morphological slides, stage, TNM stage categories, tumour number (in case of multiple primaries), initial therapy with dates, type of registration, follow-up date, follow-up, vital status, date of death, autopsy in-

formation, and the primary source for registration.

Data cleaning procedures were performed using the "IARC/IACR Tools for Cancer Registries" software (IARC tools) (Ferlay, Burkhard, et al. 2005). Additionally, a multistep conversion was performed to assign ICD-O-3 codes to all cases. After this, IARC/IACR/ENCR multiple primary rules were used to delete duplicates (Ferlay, Burkhard, et al. 2005). Figure 4.2 summarises this entire data processing. For primary analysis purposes, we narrowed down the data to cases diagnosed between 2008 and 2017; this resulted in a total of 569,445 cases.

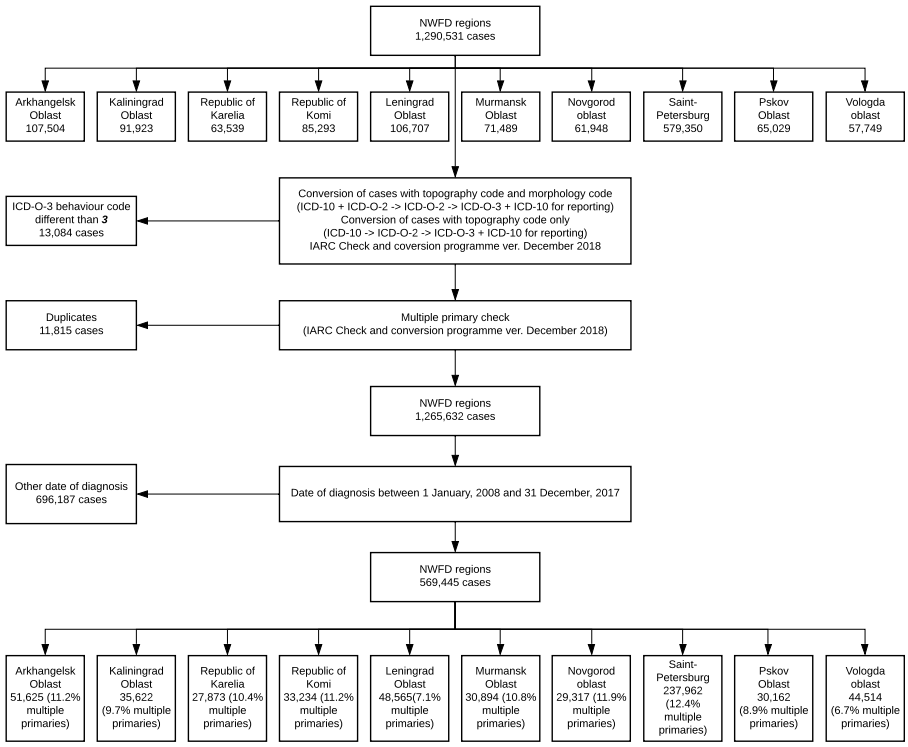

Figure 4.2 Population-based cancer registry data used in the quality assessment.

4.1.2 National incidence data

Aggregated national cancer incidence datasets were used to analyse cervical and breast cancer trends. The datasets included the number of cases registered nationally by

cancer type, age group and sex. The data were published in 2015 and covered the period from 1993 to 2013 (Petrova et al. 2015). The extracted dataset consisted of all incident cases of women's breast (C50), cervix uteri (C53), corpus uteri and uterus NOS cancer (C54-55). Additionally, data were categorised by age and the calendar period in which the diagnosis was made (age groups from 0-4 years old to 85+ years old and all 21 one-year intervals between 1993 and 2013).

4.1.3 Mortality data

Both regional and national cancer mortality datasets are available in Russia from the FSSS, having been collected by the centralised state civil registration system (V. M. Shkolnikov and Jdanov 2010). The highly centralised system consisted of the Central Statistical Office, now the FSSS (formerly State Statistical Committee of the Russian Federation or Goskomstat), regional statistical offices, and district statistical bureaux (ZAGS). District bureaus register events (deaths, births) and provide information to the regional statistical offices (individual records). Datasets with mortality data were obtained from the Russian Fertility and Mortality Database (RFMD) of the Centre of Demographic Research of the New Economic School, which contains detailed fertility and mortality indicators of Russia's regions and contains extracts from the official FSSS data (*Russian Fertility and Mortality Database* 2022). The same data were used in all the national cancer incidence and mortality reports from 1998 up to today in the mortality section of this report (Kaprin, Starinskiy, and Shakhzadova 2022). Detailed national mortality data from this database can also be found in the Human Mortality Database (Barbieri et al. 2015). Demographers have discussed the problems and concerns with the quality of mortality data (V. M. Shkolnikov and Jdanov 2010).

Mortality rates by age and sex and cause of death were extracted from 1980 to 1993 to study cervical and breast cancer trends. Additionally, regional (for all regions) breast and cervical mortality rates were extracted for 2008 and 2013 and used in the supplementary material for the study.

Mortality rates for all major cancer types and overall mortality between 2001 and 2015 were extracted from this database to assess years of life lost and premature mortality.

Regional mortality rates by sex, age, cause of death and year from 2008 to 2017 were extracted for the study of the quality of cancer registry data in the regions

of Northwest Russia (the Arkhangelsk oblast (including the Nenets Autonomous Okrug), the Murmansk oblast, the Republic of Komi, the Republic of Karelia, the Pskov oblast, the Kaliningrad oblast, the Leningrad oblast, the Novgorod oblast, the Vologda oblast, and St. Petersburg). Absolute numbers of deaths were back-calculated from the rates using population data.

4.1.3.1 Cervical cancer mortality correction

Deaths from uterine cancers in mortality statistics are not always reported separately for cervical cancer (ICD-10 code C53) and corpus uteri (C54). Also, one category includes non-specified uterine cancers (uterus NOS, C55). Several correction or reallocation algorithms were developed to adjust for uterine cancer mortality statistics (Loos et al. 2004; Arbyn et al. 2009).

Algorithms depend on data availability and the proportion of uterus NOS cases. For cancer mortality data in Russia (reported using the so-called "shortlist" mortality nomenclature (Table 4.1)), two possible reallocation algorithms with reference population can be applied.

Table 4.1 The nomenclature used in the WHO mortality database to report uterine cancers

Period	Nomenclature	Codes for cervical cancer (C53)	Code for other uterus cancers (C54, 55)
1980-1998	09N – ICD-9th revision	B120 – Malignant neoplasm of cervix uteri	B122 – Malignant neoplasm of uterus, other and unspecified
1999-2013	101 – ICD-10	1037 – Malignant neoplasm of cervix uteri	1038 – Malignant neoplasm of other and unspecified parts of the uterus

In brief, the reference population should be chosen. The previous report (Arbyn et al. 2009) used Hungary as a reference population. Lithuania was also used as a reference in the sensitivity analysis of this study. For correction, first cases (grouped by age and period) from the NOS category (C55) in the reference country should be reallocated to cervical cancer (C53) and uterus cancer (C54) by applying C53/C54 in proportion to divide C55 cases. This procedure was applied first to reference

cervical cancer mortality in Hungary and Lithuania.

Then similar reallocation procedures were applied to Russian mortality. First, cases in categories C54 and 55 were divided, and then C55 was divided based on the corresponding proportion in Hungary or Lithuania. This option assumes that the NOS cases proportion in Russia is low.

For the second option, the proportion of C53 deaths out of all uterine cancer deaths (C53+C54+C55) was assumed to be the same as the reference population. Corrected C53 estimates were derived by dividing the sum of all uterine cancer deaths.

4.1.4 Population data

Both regional and national population datasets were extracted from the same source as mortality data (V. M. Shkolnikov and Jdanov 2010). FSSS provides data in sex-specific age distributions (in one-year age groups) (*Russian Fertility and Mortality Database* 2022). Population data extracted for the study were based on population demographic surveys (censuses) taken in 1989, 2002, and 2010. These data were adjusted for annual mortality and birth statistics; the mid-year population was aggregated into five-year age groups for the study. Population estimates were used to approximate person-years at risk (Boyle and Parkin 1991).

4.1.5 Labour-force participation and economic data

For the part of the study that involved the assessment of productivity losses, additional age- and sex-specific economic data were obtained from the FSSS (*Demography: Federal State Statistics Service* n.d.). Datasets included labour-force participation rates (2001–2014, including information on retirement and labour-force participation after retirement age (60 for men and 55 for women)); averaged annual earnings (biennial, between 2002 and 2014); and inflation rates (2001–2016).

4.1.6 International data

The WHO Mortality Database was an additional source of Hungarian mortality data for the uterus NOS category (C55), cervical cancer (C53) and uterus cancer (C54) (*World Health Organization, health statistics and information systems, mortality*

database, *WHO* n.d.). Hungarian mortality data were used to correct cervical cancer mortality rates in Russian national mortality data.

Incidence data from "Cancer Incidence in Five Continents (CI5)" volume XI (Bray, Colombet, et al. 2017) and mortality data from GLOBOCAN were also extracted for Bulgaria, Czech Republic, Poland, Latvia, Lithuania, and Estonia between 2008 and 2012, and from NORDCAN (Engholm et al. 2010) for Norway to calculate mortality-to-incidence ratios for comparison (Ervik et al. 2021) in the PBCR data quality assessment. Incidence data from "Cancer Incidence in Five Continents (CI5)" volume XI were also used to compare age-specific curves.

In conclusion, Figure 4.3 summarises all data sources used in this study.

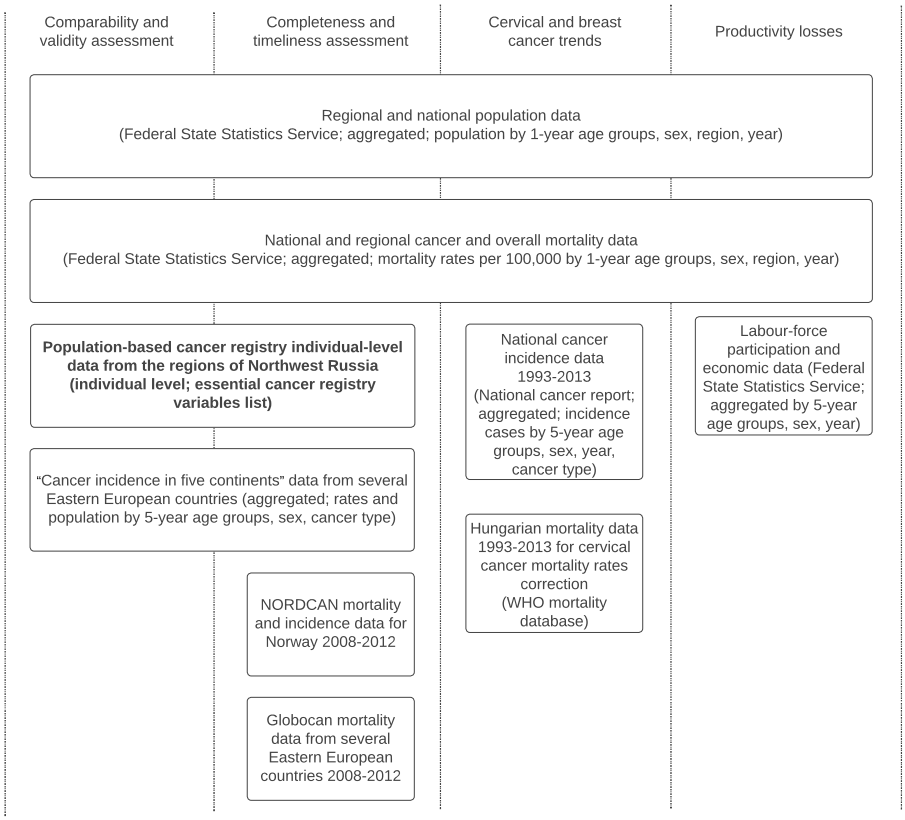

Figure 4.3 Population-based cancer registry data used in the quality assessment.

4.2 Data analysis

4.2.1 Methods for data quality assessment

Cancer registry quality assessment followed the international recommendation published in an IARC Technical Report (Parkin, Chen, et al. 1994) and updated in more recent publications (Bray and Parkin 2009; Parkin and Bray 2009; Bray, Znaor, et al. 2014). A similar approach was previously applied for quality assessment of cancer registries data in several countries (Larsen et al. 2009; Sigurdardottir et al. 2012; Dimitrova and Parkin 2015; Fung et al. 2016; Leinonen et al. 2017; Ryzhov, Bray, et al. 2018). These methods address four cancer registry data quality dimensions: comparability, validity, completeness and timeliness.

4.2.1.1 Methods for comparability assessment

Comparability was assessed by analysing the definitions for incidence dates, multiple primary tumours, and incidental cancer cases.

The distribution of incidence dates was analysed to detect and reflect possible deviations from the recommendations. The proportions of multiple primaries initially reported in the databases were compared to the data that underwent conversion using the IARC tools software (Ferlay, Burkhard, et al. 2005). Temporal changes in stage-specific age-standardised rates (ASRs) were analysed to explore possible changes in diagnostic patterns or screening programme implementation. Additionally, autopsy proportions along with DCO% were assessed. All estimates were adjusted for age, region, cancer type, and period as covariates.

4.2.1.2 Methods for validity assessment

Diagnostic criteria methods, missing information assessment and internal consistency checks were used in the validity assessment.

The following proportions were calculated: the proportion of morphologically verified cases (MV%), cases reported with the information from the death certificate only (DCO%), the proportions of missing information for different variables, cases with primary site uncertain (PSU%), cases with stage unknown (SU%), cases with missing TNM coding, and cases with non-specific morphology codes. All estimates

were adjusted for age, region, cancer type, and period as covariates.

Additionally, the distribution of warnings produced by IARC tools (Ferlay, Burkhard, et al. 2005) was assessed. ASRs per 100,000 using the Segi-Doll world standard population were calculated and compared using the initial database and database after all checks and conversions were performed.

Tables similar to IARC "Cancer Incidence in Five Continents" (CI5) volumes were constructed to summarise the statistics measures and validity indicators. Estimates were compared to 12 East European cancer registries from CI5 volume X (2003-2007): (Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia) using statistical tests that were recommended for such comparisons (Parkin and Plummer 2002). Registries were selected for comparison based on the assumption of similar cancer incidence patterns.

4.2.1.3 Methods for completeness assessment

Completeness, the degree to which the PBCR covers all the incident cases, was assessed using historic data methods, mortality-to-incidence ratios (M:I), and capture-recapture (death certificate) methods.

Historical data methods included the assessment of the stability of incidence rates (ASRs for cases registered between 1993 and 2017) over time, comparison of incidence rates, the shape of age-specific curves (in comparison to European cancer registries from "Cancer Incidence in Five Continents" volume XI (2008-2012) (Bulgaria, Czech Republic, Latvia, Lithuania, Estonia and Poland (Cracow, Lower Silesia, Kielce, Podkarpackie)), and incidence rates of childhood cancers with the corresponding reference intervals based on deciles for childhood cancer published in that volume (Bray, Colombet, et al. 2017).

M:I ratios were compared to similar estimates from several registries in Eastern Europe and Norway. M:I ratios were also compared to one minus five-year survival estimates using a value of 10% to define a relevant absolute difference (Vostakolaei et al. 2011). Survival was calculated using the Ederer II method (Ederer and Heise 1959; Perme and Pavlic 2018).

Two sources were used for the capture-recapture analysis – "official cancer case notification" and "death certificate notification". Death certificate methods were also used to calculate completeness. The following formula was applied to estimate the

degree of completeness:

$$\frac{RA + RD + DCI}{RA + RD + DCI + UC}.$$

where DCI = "the proportion of cases for which the first information comes via a death certificate, and, without it, the case would not have been identified", UC = a numerical estimate of undetected cases, RD = registered cases that die, and RA = registered cases that are alive. "The proportion of cases for which the information was received first via a death certificate notification" (DCN) was used to approximate "the proportion of cases for which the first information comes via a death certificate, and, without it, the case would not have been identified" (DCI). This formula was equivalent to capture-recapture logit models, considering the region and cancer type, (Tilling and Sterne 1999) that quantify the Lincoln-Petersen estimator.

The Ajiki formula (Ajiki, Tsukuma, and Oshima 1998) was also applied to estimate completeness:

$$\frac{1 - DCI \times \frac{1}{M:I}}{1 - DCI.}$$

4.2.1.4 Methods for timeliness assessment

To assess timeliness, the absolute number of cases in the registry database in 2008-2017, extracted in December 2019, was compared to estimates published in ten annual national reports (Kaprin, Starinskiy, and Shakhzadova 2022).

4.2.2 Methods for cancer burden assessment

The study focused on cervical and breast cancer burden and productivity losses associated with cancer. The following national statistics were estimated: cervical and breast cancer incidence, cancer-specific mortality rates, YLL and productivity losses. In addition, regional cancer incidence and mortality were also estimated.

4.2.2.1 Estimation of incidence and mortality rates

Cancer incidence and mortality ASRs were calculated per 100,000 person-years using the world standard population (Segi et al. 1960; Doll, Payne, and Waterhouse 1966). Additionally, age-specific rates per 100,000 person-years and an absolute number of cases and deaths were calculated. Predictions were made using the Nordpred

software package, which also utilised the age-period-cohort model (Møller, Fekjær, Hakulinen, Tryggvadóttir, et al. 2002; Møller, Fekjær, Hakulinen, Sigvaldason, et al. 2003).

4.2.2.2 Estimation of years of life lost

YLL were calculated by sex and age for the following cancer sites (ICD-10): lip, oral cavity and pharynx (C00–14), oesophagus (C15), stomach (C16), colorectum (C18–21), liver (C22), pancreas (C25), larynx (C32), trachea and lung (C33–34), bone (C40), skin (melanoma) (C43), soft tissues (C46.1, 3, 7-9, 47, 49), female breast (C50), cervix uteri (C53), corpus uteri (C54), ovaries (C56), prostate (C61), kidney (C64), bladder (C67), brain and central nervous system (C70–72, CNS), haematopoietic and lymphoid malignancies (C81-96) and all cancers combined including non-melanoma skin cancers (C00-96), and also for the other category (the difference between the number of all cancer deaths and the number of deaths from cancer-specific sites).

Age-specific YLL were calculated from cancer mortality data and life expectancy based on data from the Human Mortality Database. The number of observed and projected deaths at certain age groups was multiplied by the estimated expected remaining life years at the same age. Life expectancy was based on the cause-deleted period life tables, obtained via subtraction of the mortality rates from cancer of interest from the overall mortality rate. Cause-deleted life tables by period were generated using mortality forecasts with a functional demographic model (Hyndman and Ullah 2007; Barbieri et al. 2015).

4.2.2.3 Estimation of productivity losses

Productivity losses due to cancer-related premature mortality were calculated using an incidence-based method using the human capital approach (HCA). According to the HCA, individual economic output is equal to the wage rate, so premature death results in economic losses to society, equal to the lost earnings. Age- and period-specific death and economic data were used to calculate productivity losses.

For example, cancer death at age 30-34 in 2001-2005 would result in 40 YLL. Loss of future earnings was approximated as the product of wages (adjusted for growth and labour participation) for ages 35-39 in 2006-2010, 40-44 in 2011-2015 until

65-69 in 2036-2040 and also 2.5 years of earnings were added to the first (30-34 in 2001-2005) and the last (70-75 in 2041-2045) period.

All earnings were converted from Rubles to 2016 US dollars after adjustment for inflation based on annual average currency exchange rates. Natural splines were applied to interpolate employment rate and mean wages for the study period and also to project employment rates.

Average age-specific wages were calculated and adjusted by age-specific labour force participation. An annual discount rate of 2.5% was applied for base case calculations. The World Bank GDP based on international purchasing power parity in 2011 US dollars was used along with a deflator to adjust it to 2016 US dollars. In the base case, earnings were discontinued at 70 years old.

4.2.3 Methods for cancer trends assessment

4.2.3.1 Segmented regression

Segmented regression was used to assess the temporal changes in cancer rates. In brief, the linear regression model was fitted with rates as a function of time, and an iterative procedure to estimate models with piecewise linear relationships having a fixed number of breakpoints was applied (Muggeo 2003). Starting breakpoints for this procedure were selected by visual inspection of plots. Then the bootstrap restarting was applied to make the algorithm less sensitive to starting values (Wood 2001). Additionally, an "automatic" breakpoint selection that deals with an unknown number of breakpoints was applied (Muggeo and Adelfio 2011). Breakpoints and slopes representing percent changes between them were then estimated with 95% confidence intervals. Slopes (percent changes) were then compared, and in the event of an overlap, the procedure was repeated with fewer breakpoints. This ensured only meaningful breakpoints were reported. The final segmented regression was then put against the original rates plot, and percent changes and breakpoints were reported with 95% confidence intervals.

4.2.3.2 Age, period, and cohort effects

Age (A), calendar period (P), and birth cohort (C=P-A) effects were estimated using age-period-cohort Poisson regression models (Carstensen 2007). A log-linear model

with Poisson errors and a logarithmic link was used to describe rates as a function of time:

$$log[\lambda(A, P)] = a(A) + p(P) + c(C),$$

where a, p, and c are the functions parameterised with a limited number of parameters.

Sub-models were derived using classical maximum likelihood and sequential procedures (age-drift, age-period, age-cohort, age-period-cohort and similar models from sequential procedures). To solve the identifiability problem, constraints were put on cohort and period effects (C0=1945 or P0=2000). The drift parameter was extracted by a weighted approach in maximum likelihood models. Natural splines with seven knots constrained to be linear beyond them were used to model the functions (a, p and c). Overall goodness-of-fit of models were not reported because of a lack of information on model fit (Carstensen 2007). Comparisons based on residual deviances and degrees of freedom, their differences and Akaike's information criterion (AIC) were also made. Pairwise comparisons for the difference in residual deviance were made using χ^2 tests. Sub-model comparisons were used to evaluate the effects: the linear effect of period/cohort (drift), the non-linear effect of the period, the non-linear effect of the cohort, the non-linear effect of the cohort (in the presence of the period effect), and the non-linear effect of the period (in the presence of the cohort effect).

The study focused on the non-linear component of cohort effects after the likelihood ratio statistics comparison. For reporting, the model was applied where age effects were rates for the reference cohort in the age-cohort model and cohort effects were rate ratios (with C0 cohort as a reference), and period effects were from the period model, which used log (fitted values) from the age-cohort model as an offset (Bray, Carstensen, et al. 2005).

The drift parameter (analogous to percent change) was extracted from the age-drift model ((exp(drift) - 1) × 100) and reported with a 95% confidence interval.

4.2.3.3 Predictions

Predictions were made using the Nordpred software package, which also utilised the age-period-cohort model (Møller, Fekjær, Hakulinen, Tryggvadóttir, et al. 2002; Møller, Fekjær, Hakulinen, Sigvaldason, et al. 2003). For the prediction, data were

tabulated using five-year age groups and five-year period intervals. The recent slope method (the slope for the last 10 years) and the power link were used in the model. Three prediction scenarios were constructed: without drift reduction, with 100% reduction for all periods, and with 0-25%-50%-75% reduction scheme for each following projection period. The predictions were made for four five-year periods from 2014 to 2033 (2014-2018, 2019-2023, 2024-2028, 2029-2033) based on the most recent five-year periods from 1994 to 2013, and the goodness of fit was also reported. The absolute number of cases for the projected periods was calculated using the official projections of the population obtained from the FSSS.

4.3 Ethical considerations

PBCRs quality assessment was part of a collaborative effort between the NN Petrov National Research Medical Centre of Oncology, the European University at St. Petersburg, St. Petersburg, Russia, Tampere University, Tampere, Finland and the International Agency for Research on Cancer, Lyon, France.

All data analysis was performed at NN Petrov National Research Medical Centre of Oncology and later at the European University at St. Petersburg upon written agreement between both organisations. According to the Russian national regulation (The Order of the Ministry of Health N420 12/23/96), anonymised cancer registry data from Northwest regions are collected and maintained in NN Petrov National Research Medical Centre of Oncology for various purposes, including epidemiological analysis and international cooperation. In Russia, additional ethical review is not required for registry-based research if performed in or under the supervision of the national research medical centres. Individual-level data were not published or conveyed in any form.

In line with the Ministry of Health Regulations, all data from PBCRs were anonymised and kept confidential. Confidentiality was maintained at the individual level by using only de-identified patient data, eliminating any potential to link individuals to their specific data points. Identifying information, such as names, addresses, and contact information, was unavailable to researchers at the NN Petrov National Research Medical Centre of Oncology or the European University at St. Petersburg. This information was removed from the dataset before being sent to NN Petrov National Research Medical Centre of Oncology from regional PBCRs to maintain

the individuals' privacy.

Data integrity was also essential to the study, and the researcher ensured that the data collected was free from bias or possible manipulation. Security and privacy measures were also adopted when storing and managing data to prevent unauthorised changes or modifications. Access was limited only to staff responsible for data storage and analysis. All the datasets were kept securely using encryption methods on NN Petrov National Research Medical Centre of Oncology servers and were updated by designated staff. Datasets were updated regularly according to regional practices to keep them up to date. Any changes in the data (variables updates, follow-up information, changes in diagnosis) were performed at the registry only. Finally, any results generated were reported in aggregate form with no patient-specific demographic or individual-level information included. Researchers from NN Petrov National Research Medical Centre of Oncology made sure their publications did not convey any of this information or data in any form.

The studies of cervical and breast cancer trends and productivity losses utilised publicly available secondary aggregate data. They thus did not require additional ethical approval according to the legislature at the time of publication.

4.4 Software

All analyses were conducted in `R` (R Core Team 2013) and RStudio (RStudio Team 2020). Aggregated study data are available only upon request. All figures were created with the aid of `ggplot2` (Wickham 2011). Quality assessment was performed with the aid of `Rcan` (Laversanne and Vignat 2020) and `relsurv` (Pohar and Stare 2006), trend analyses were performed with the aid of `segmented` (Muggeo, Atkins, et al. 2014), `Epi` (Carstensen and Plummer 2011) and `demography` (Hyndman, H. Booth, et al. 2019). Predictions were made with the aid of `nordpred` (Møller and Weedon-Fekjaer 2014). Data were managed and prepared with the aid of `tidyverse` (Wickham et al. 2019).

5 RESULTS

5.1 Quality of cancer registry data in the Northwest of Russia

5.1.1 Comparability

Distributions of diagnosis dates across all regions showed greater variability in certain regions. Peaks and uneven distribution in Arkhangelsk oblast, Republic of Komi, Vologda oblast, and Leningrad oblast are seen in Figure 5.1. Otherwise, distributions of diagnosis dates were generally uniform.

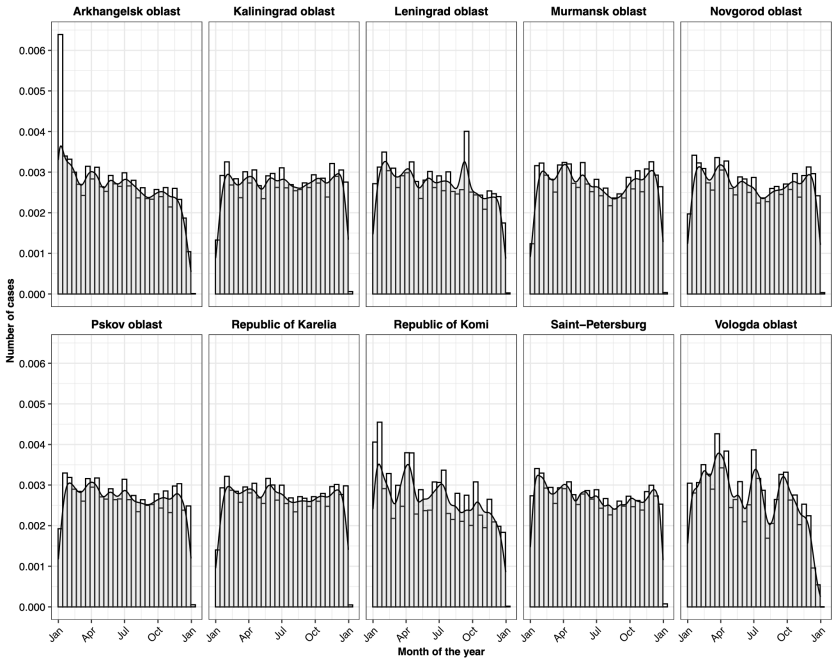

Figure 5.1 Distribution of diagnosis dates across the calendar, Northwest regions, 2008-2017.

The date when the biopsy was performed, the date of receipt by the pathologist, the date of the pathology report, the date of admission to the hospital, or the date of the first consultation were not separately available in the registry database, with a single date of diagnosis reported without specification. Examining those diagnosis dates across all regions showed greater variability in certain areas.

Between 2008 and 2017, the percentage of cases with multiple primaries in Northwest regions varied from 6.7% to 12.4% (Figure 4.2). There was slight systematic over-reporting of breast cancer cases when the initial dataset was compared to the one on which multiple primaries rules from IARC/IACR/ENCR were implemented (Figure 5.2).

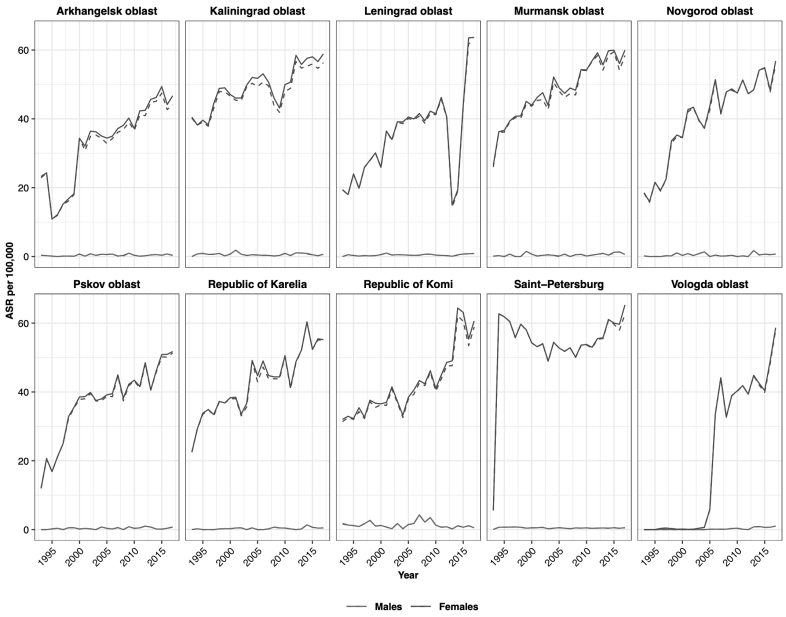

Figure 5.2 Breast cancer incidence ASRs per 100,000, before (solid line) and after (dashed line) IARC multiple primary check, Northwest regions, 1993-2017.

The recent surge in prostate cancer, as indicated by ASRs, in most regions appears to result from a similar increase in localised and advanced-stage tumour rates (Figure 5.3). A pronounced increase in early-stage thyroid cancer rates, especially in women, was also apparent in Murmansk oblast, Arkhangelsk oblast, St. Petersburg and the Republic of Komi (Figure 5.4). The incidence of breast cancer showed a persistent rise across all regions, primarily due to a surge in early-stage disease.

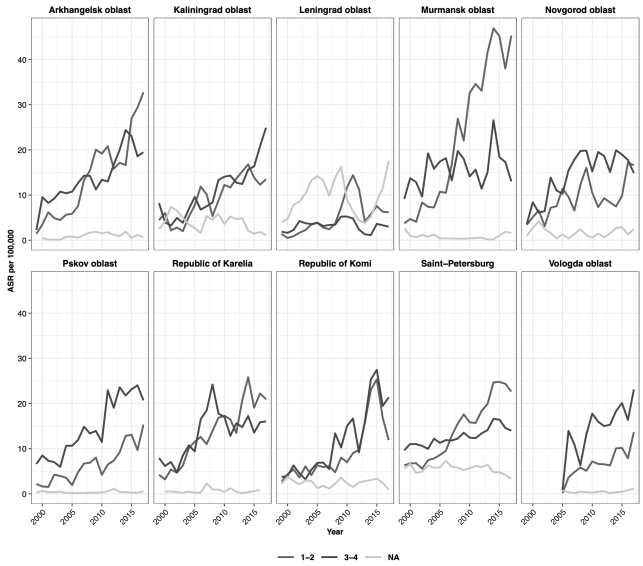

Figure 5.3 Prostate cancer incidence ASRs per 100,000 by stage (stage 1-2 and stage 3-4 combined), Northwest regions, 1993-2017.

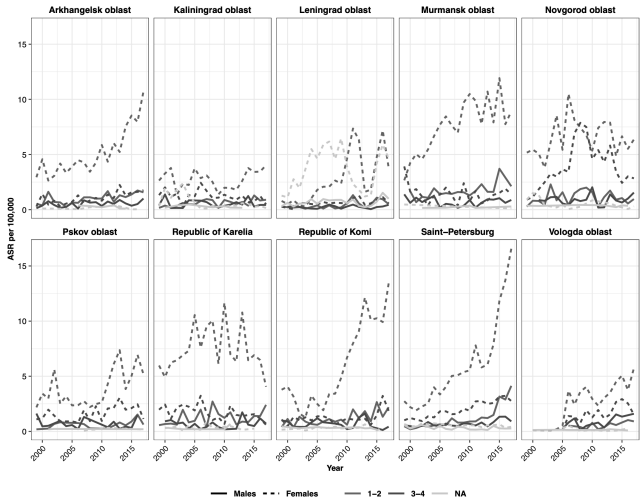

Figure 5.4 Thyroid cancer incidence ASRs per 100,000 by stage (stage 1-2 and stage 3-4 combined), Northwest regions, 1993-2017.

The percentage of deaths with documented autopsies fluctuated between regions and over time, ranging from below 10% to over 60%. The autopsy status was a predictor of DCO after adjustment for other variables (Figure 5.5).

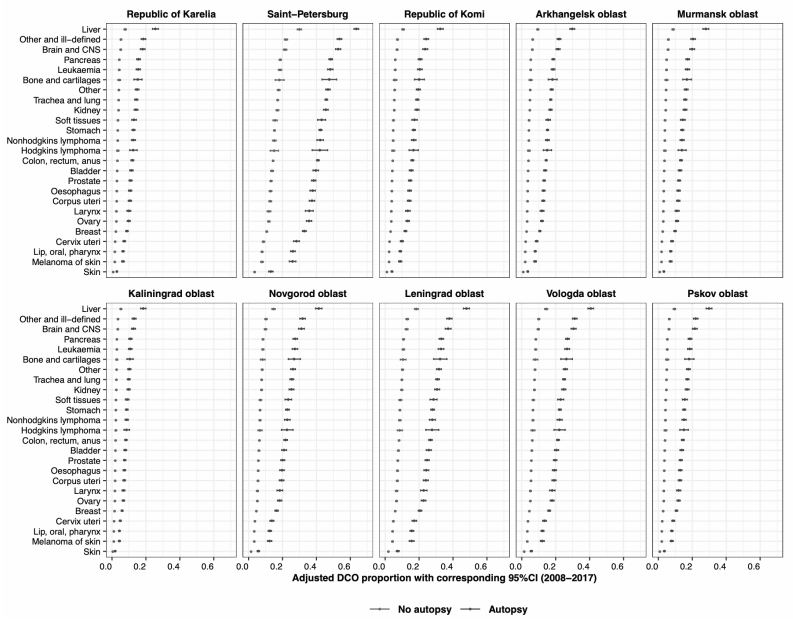

Figure 5.5 DCO proportion by autopsy status, Northwest regions, 2008-2017.

5.1.2 Validity

Tables 5.1, 5.2, 5.3, 5.4 show incidence and mortality ASRs, M:I ratios, and validity indicators (MV and DCO proportions) for men and women in 2008-2012 and 2013-2017. These indicators by cancer type for each region are presented in the supplementary material of the first paper.

Across all regions, the DCO proportion was below 14%, except in St. Petersburg, where it was higher for both men and women. Cancer types with the highest DCO% were liver, brain and CNS, and pancreas. Besides St. Petersburg, a low MV proportion was observed in Novgorod oblast and Leningrad oblast. The proportion of cases with cytological confirmation was relatively high in the Pskov oblast and Vologda oblast. Haematological malignancies, pancreas, lung, liver, and CNS tumours were reported in the registry without histological verification in all Northwestern regions. Cases registered at 60 or older were more likely to be recorded without morphological verification (Figure 5.6).

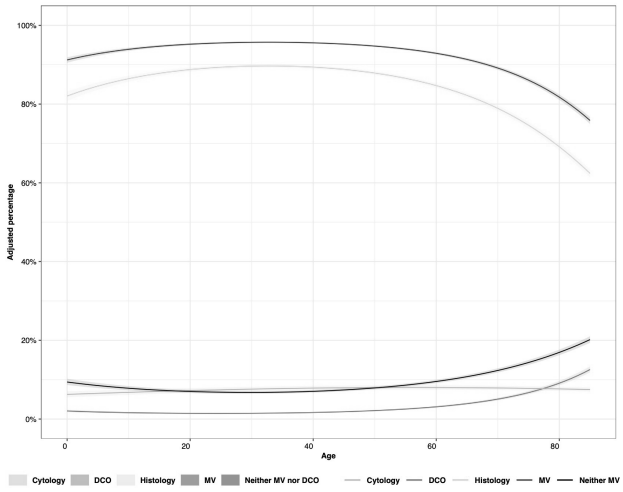

Figure 5.6 Effect of age on type of verification, with corresponding 95% CI, Northwest regions, 2008-2017.

The proportion of cases with primary site unknown was overall below 3%. The highest proportions were observed in the youngest and the oldest age groups (Figure 5.7).

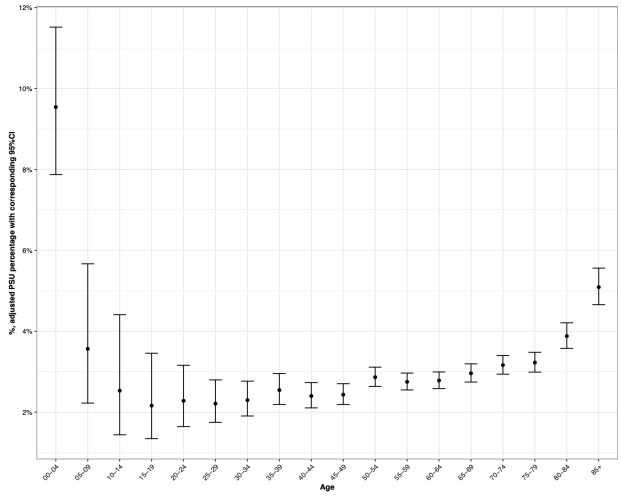

Figure 5.7 Verification proportion with the corresponding 95% CI by cancer type, Northwest regions, 2008-2017.

Over time, the proportion of cases with missing and non-specific morphology codes decreased; however, they remained high in St. Petersburg, Leningrad oblast, and Kaliningrad oblast. In Novgorod oblast, a majority of the cases recorded in

2016 and 2017 had missing morphology codes. In Vologda oblast, around 20% of the cases were recorded with non-specific morphology codes. Missing morphology codes were frequently observed for liver cancer (58%), pancreas cancer (56%), CNS cancer (41%), and lung cancer (36%). Non-specific codes were frequently noted for cancers, including other and ill-defined tumours, Non-Hodgkin lymphoma, leukaemia, and lung cancer (Figure 5.8).

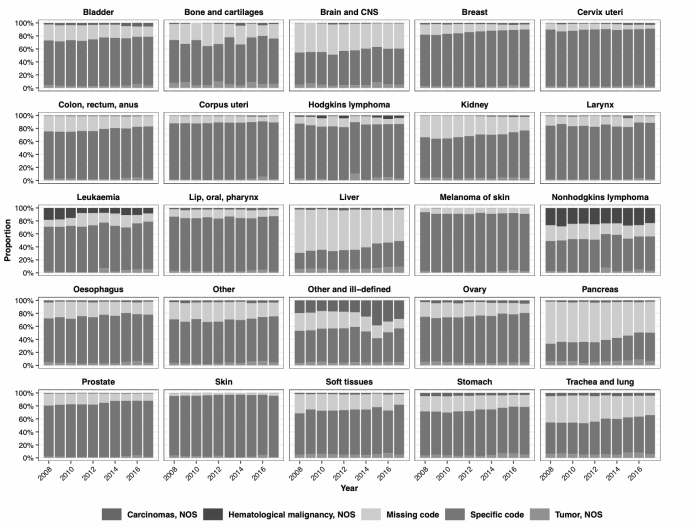

Figure 5.8 Proportion of cases with non-specific and missing codes, Northwest regions, 2008-2017.

The proportion of cases with missing information on stage varied by cancer type, with the N-stage category information being more frequently missing than T- or M-stage information. A higher proportion of missing values was observed in the younger and the older age groups (Figure 5.9). In Leningrad oblast, the proportion of cases with information on the tumour stage was the lowest, with less than 60% of the cases having such information.

The overall proportion of misclassified primary sites (comparison of ICD-10 groups in the initial databases and after the IARC conversion tool) was 0.6%. The highest misclassification proportion was seen in the Republic of Komi (1.6%, 2008-2012). The IARC tools identified 31,196 warnings (cases with an uncommon or unusual combination of variables requiring additional attention or correction) for 29,583 of the total 590,290 records (5.2%, 2008-2017). There were 12,749 grade/histology warnings, 13,294 on the basis of diagnosis/histology, and 4,180 for the his-

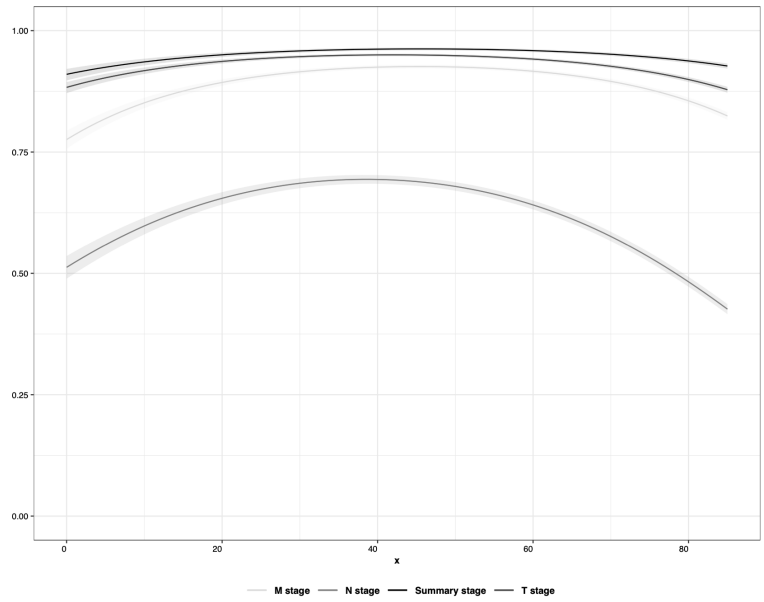

Figure 5.9 UICC/AJCC stage categories presence, Northwest regions, 2008-2017.

tology/site. Haematological malignancies were the group with the highest number of warnings.

Table 5.1 Cancer incidence, mortality and validity indicators in Northwest regions, women, 2008-2012, all sites except for non-melanoma skin cancer (C00-96 excl. C44)

	Incidence		Mortality		Indicators		
	ASR (W)	SE	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio
Arkhangelsk oblast	200.3	2.1	93.9	1.4	83.9	7.5	0.53
Kaliningrad oblast	190.6	2.3	94.6	1.6	71.4	1.0	0.55
Leningrad oblast	159.7	1.6	90.6	1.1	66.6*	4.1	0.70
Murmansk oblast	224.1	2.8	94.4	1.7	90.2	1.5	0.44
Novgorod oblast	223.0	3.1	87.4	1.8	84.8	4.8	0.46
Pskov oblast	210.4	2.0	91.8	1.7	79.4	2.5	0.57
Republic of Karelia	242.9	3.2	96.4	1.8	77.9	1.5	0.48
Republic of Komi	216.2	2.6	95.5	1.7	76.7	1.5	0.48
Saint-Petersburg	219.5	1.0	108.5	0.7	66.0*	20.5†	0.58
Vologda oblast	173.4	2.0	86.5	1.3	75.6	4.6	0.61

Lower (*) or higher (†) results are marked when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

Table 5.2 Cancer incidence, mortality and validity indicators in Northwest regions, women, 2013-2017, all sites except for non-melanoma skin cancer (C00-96 excl. C44)

	Incidence		Mortality		Indicators		
	ASR (W)	SE	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio
Arkhangelsk oblast	231.9	2.2	91.8	1.3	89.0	7.0	0.48
Kaliningrad oblast	202.1	2.3	92.6	1.5	82.2	1.8	0.52
Leningrad oblast	148.3*	1.5	88.2	1.0	77.5	6.6	0.78
Murmansk oblast	245.7	2.9	92.5	1.7	92.1	4.4	0.41
Novgorod oblast	229.8	3.1	77.9	1.6	61.7*	5.9	0.41
Pskov oblast	217.5	2.9	88.1	1.7	85.2	5.7	0.50
Republic of Karelia	247.6	3.2	93.9	1.8	85.5	3.5	0.47
Republic of Komi	263.4	2.9	95.4	1.6	81.4	6.0	0.41
Saint-Petersburg	247.1	1.1	105.5	0.7	71.9*	14.7†	0.51
Vologda oblast	207.9	2.2	84.6	1.3	80.8	9.1	0.50

Lower (*) or higher (†) results are marked when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

Table 5.3 Cancer incidence, mortality and validity indicators in Northwest regions, men, 2008-2012, all sites except for non-melanoma skin cancer (C00-96 excl. C44)

	Incidence		Mortality		Indicators		
	ASR (W)	SE	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio
Arkhangelsk oblast	299.7	3.1	198.3	2.5	80.7	8.8	0.66
Kaliningrad oblast	237.1	3.1	171.0	2.6	66.2	1.9	0.73
Leningrad oblast	177.7	1.9	177.2	1.9	57.2	6.5	1.01
Murmansk oblast	315.5	4.5	182.3	3.4	86.6	2.4	0.58
Novgorod oblast	283.9	3.9	188.7	3.2	78.1	7.3	0.67
Pskov oblast	252.2	3.5	200.5	3.1	66.7	4.0	0.81
Republic of Karelia	300.6	4.2	214.3	3.6	65.1	2.9	0.72
Republic of Komi	285.7	3.9	207.6	3.4	68.4	2.1	0.70
Saint-Petersburg	270.6	1.4	179.8	1.1	61.9*	23.1†	0.68
Vologda oblast	227.7	2.6	193.9	2.4	72.3	6.3	0.86

Lower (*) or higher (†) results are marked when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

Table 5.4 Cancer incidence, mortality and validity indicators in Northwest regions, men, 2013-2017, all sites except for non-melanoma skin cancer (C00-96 excl. C44)

	Incidence		Mortality		Indicators		
	ASR (W)	SE	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio
Arkhangelsk oblast	314.7	3.0	194.9	2.34	86.8	8.4	0.62
Kaliningrad oblast	239.2	2.9	165.5	2.37	77.1	2.4	0.70
Leningrad oblast	143.0*	1.6	169.5	1.70	68.6	9.6	1.22
Murmansk oblast	349.5	4.4	180.6	3.20	90.2	7.0	0.52
Novgorod oblast	297.3	3.9	167.8	2.90	56.4	8.2	0.57
Pskov oblast	279.2	3.6	188.3	2.94	79.8	8.4	0.69
Republic of Karelia	304.8	4.1	202.0	3.29	78.4	5.2	0.67
Republic of Komi	345.7	4.1	212.5	3.24	73.8	8.8	0.60
Saint-Petersburg	285.4	1.3	167.6	1.01	67.1*	17.2†	0.61
Vologda oblast	258.2	2.7	183.7	2.27	73.2	13.8	0.72

Lower (*) or higher (†) results are marked when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

5.1.3 Completeness

ASRs and the absolute number of case plots revealed that full-scale cancer registration with information stored in PBCRs began as early as in 1991 in the Republic of Komi and Kaliningrad oblast and in 1993 in St. Petersburg (Figures 5.11 and 5.10). All other regions started data collection in the late 1990s–early 2000s. Only Vologda oblast started data collection for solid tumours in 2005 and haematological malignancies in 2013 (Figure 5.12).

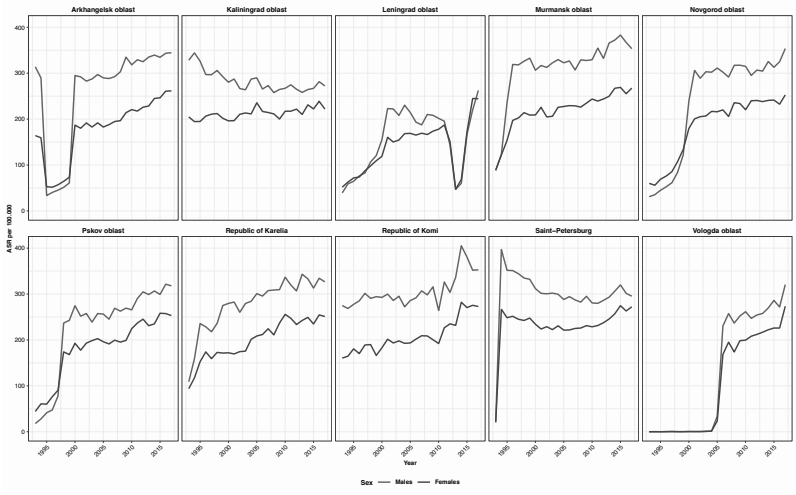

Figure 5.10 Age-standardised cancer incidence rates per 100,000 for regions in Northwest Russia (all cases with behaviour code = 3, including non-melanoma skin cancer, world population Segi-Doll, 1960).

In general, childhood cancer rates deviated only slightly from the reference range in certain regions (Figure 5.13). More specifically, for the age group 10-14 years, the rate was higher for both males and females in Novgorod oblast and only for females in Pskov oblast. Furthermore, in Novgorod oblast, the rate was above the reference range for males aged 5-9 but below the range in Leningrad oblast.

The stability of ASRs over time was generally observed, as depicted in Figure 5.14. In addition, the shape of the age-specific curves was comparable to that of other European nations, as shown in Figure 5.15, except for a decline in incidence rates among older age groups for some cancer types.

In general, M:I ratios were higher in Northwest regions compared to European countries (Figure 5.16). This disparity was particularly evident for cancers of the

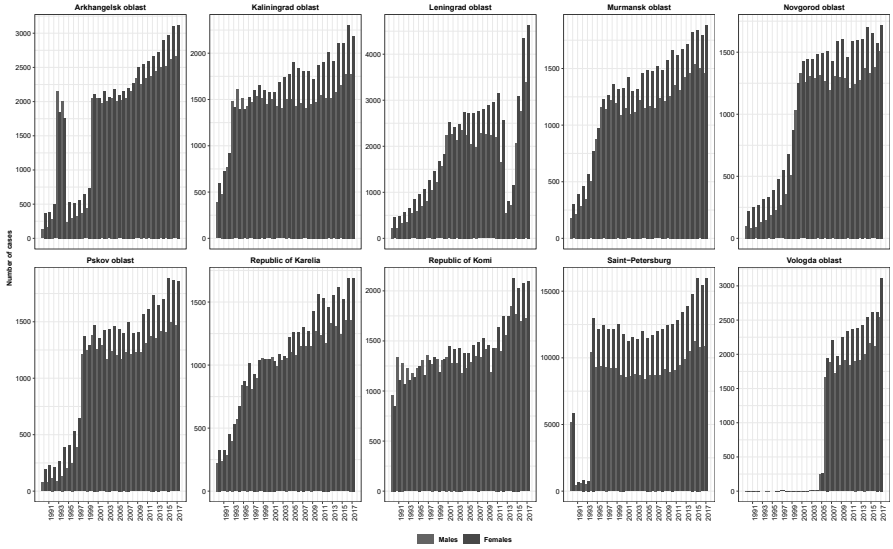

Figure 5.11 The number of cases available from cancer registry databases in Northwest regions.

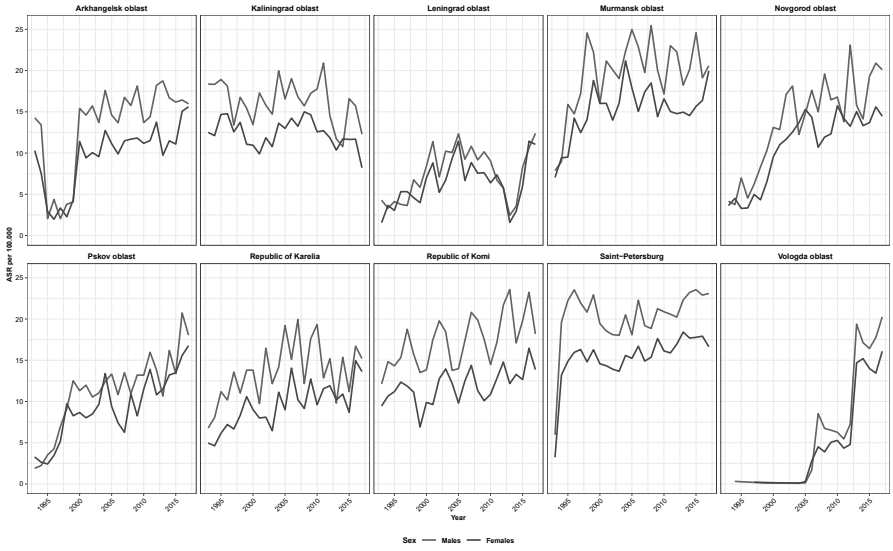

Figure 5.12 Age-standardised incidence rates per 100,000 for haematological malignancies (C81-C96), regions of Northwest Russia (world population Segi-Doll, 1960).

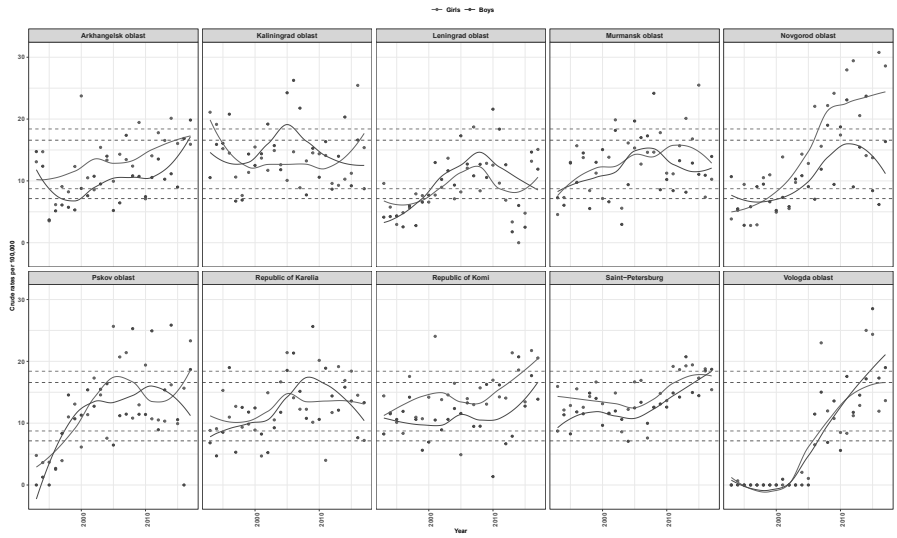

Figure 5.13 Incidence rates per 100,000 for childhood (0-14) cancer by sex in Northwest regions.

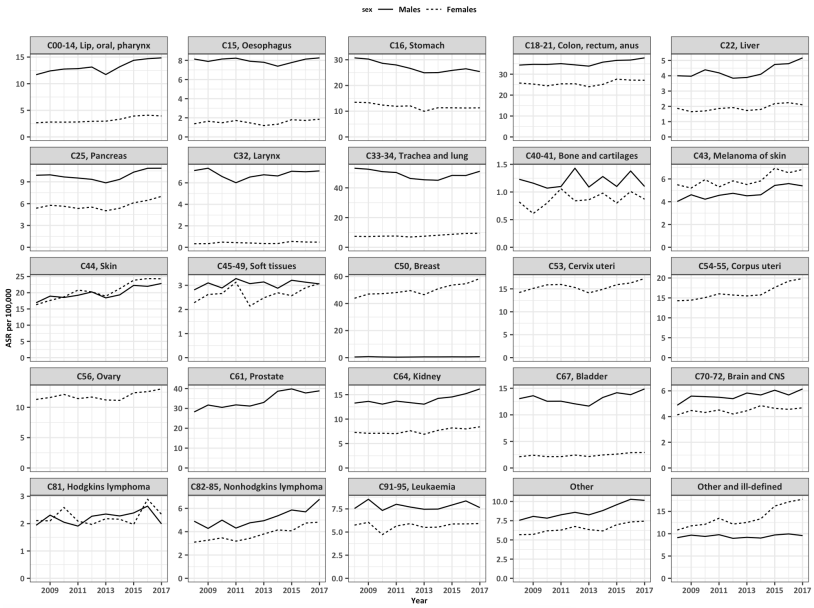

Figure 5.14 Annual trends in age-standardised (world population Segi-Doll, 1960) incidence rates for selected cancer types, in regions of Northwest Russia, 2008-2017).

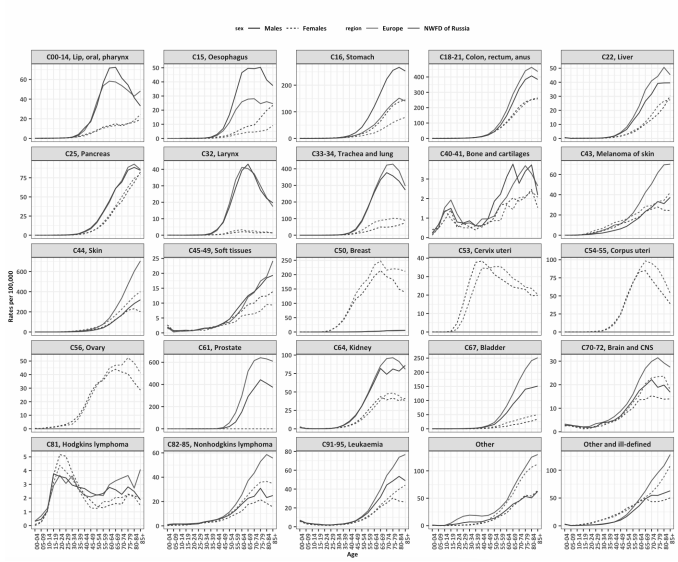

Figure 5.15 Age-specific curves for cancers in all ten regions (rates per 100,000), 2008-2017, compared to those in selected national and regional registries in Eastern Europe (Bulgaria, Czech Republic, Poland, Latvia, Lithuania, Estonia).

brain and CNS, bone, and cartilage tumours. For kidney and lung cancer M:I ratios were lower in Murmansk oblast and Novgorod oblast compared to European countries. M:I ratios were systematically higher in the Leningrad oblast for all cancer types.

Systematic deviance from the reference line was observed in Leningrad oblast and Vologda oblast when M:I ratios were plotted against one minus five-year survival (Figure 5.17 and Figure 5.18). Furthermore, in all the regions, there were instances of deviation from the trend (e.g. breast cancer in Kaliningrad oblast or other and ill-defined cancer types in all other regions). Still, for the majority of cancer types, the discrepancy was within the predetermined limit of 0.1.

Assessment of completeness using two formulas revealed low estimates in St. Petersburg. Estimates of completeness were, on the other hand, low (Lincoln-Petersen estimator) or unrealistic (Ajiki formula) for Leningrad oblast. All other regions collected data with an acceptable degree of completeness of around 90% or more. Results were similar for men (Table 5.5) and women (Table 5.6). The proportion of cases reported by different sources and completeness estimates by cancer types for all Northwest regions are represented in tables A.1, A.2, A.3, A.4, A.5, A.6,

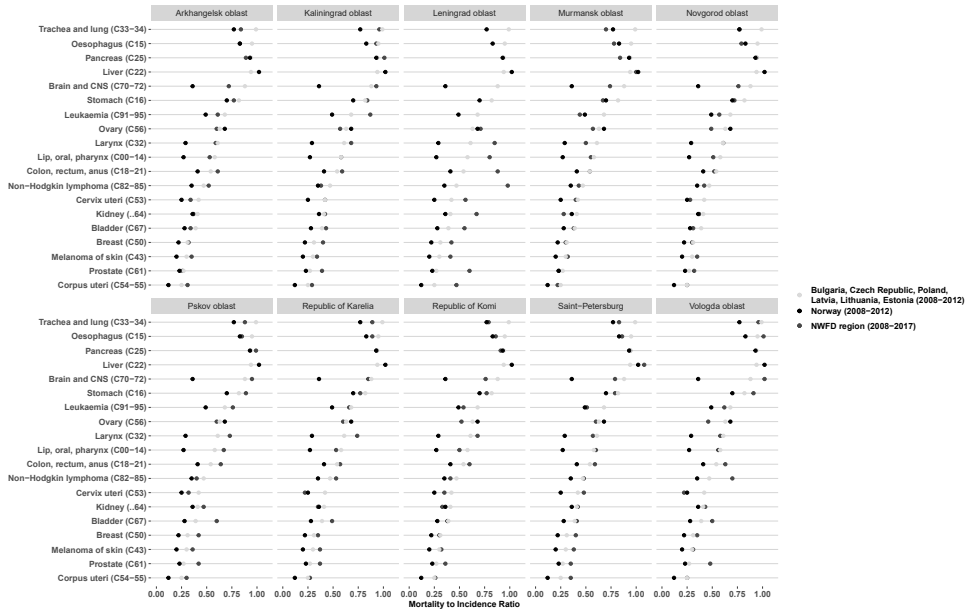

Figure 5.16 Comparison of mortality-to-incidence ratios by cancer site, regions of Northwest Russia in 2008-2017, Eastern European Countries (data from GLOBOCAN (Ervik et al. 2021)) and Norway (data from NORDCAN (Engholm et al. 2010)) in 2008–2012.

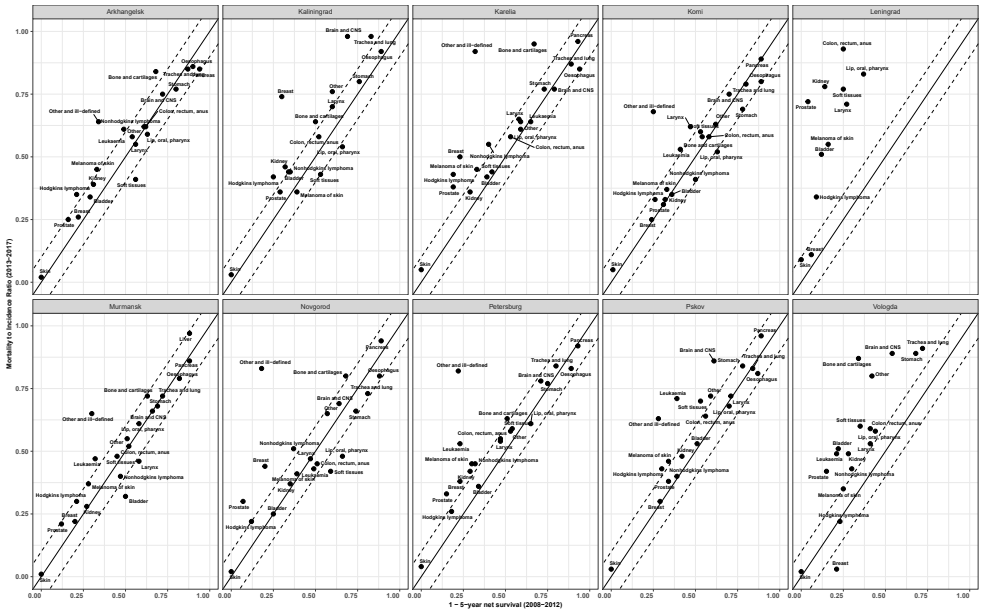

Figure 5.17 Mortality-to-incidence ratios (2013–2017) versus one minus five-year relative survival (based on diagnoses in 2008–2012) in men, regions of Northwest Russia.

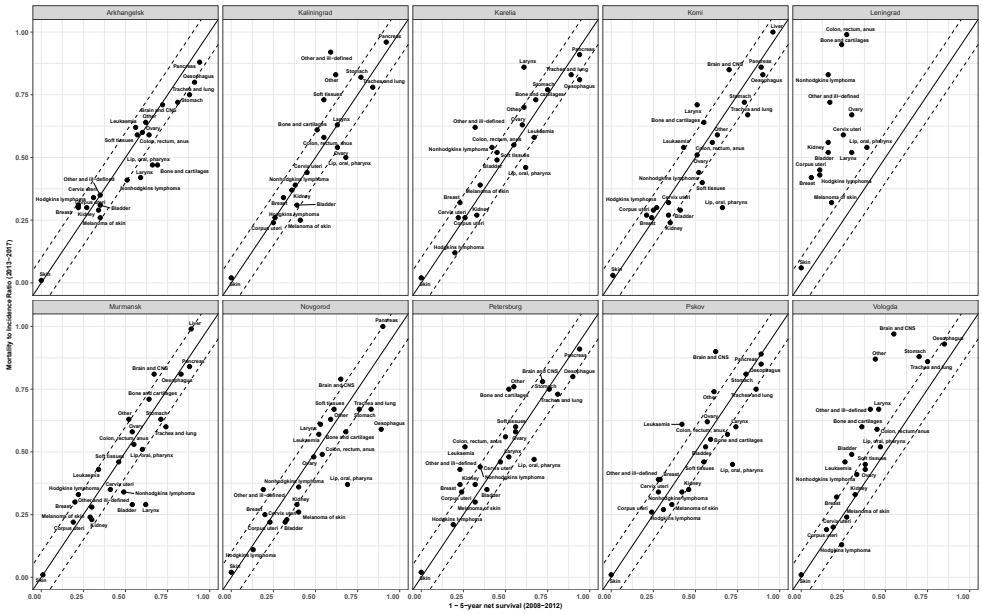

Figure 5.18 Mortality-to-incidence ratios (2013–2017) versus one minus five-year relative survival (based on diagnoses in 2008–2012) in women, regions of Northwest Russia.

A.7, A.8, A.9, A.10. Lincoln-Petersen estimator was below 90% for the following cancer types in several regions: haematological malignancies (Hodgkin lymphoma, leukaemia), skin cancer, corpus uteri and other ill-defined cancers.

Table 5.5 Data sources and completeness estimates in the regions of Northwest Russia, 2008-2017, all sites in men except non-melanoma skin (C00-C96 without C44)

Region	Data sources (%)				Completeness (%)	
	C/P	C/P and D‡	DCI	M:I ratio†	Lincoln-Petersen	Ajiki formula
Arkhangelsk oblast	36.6	54.8	8.6	0.64	95.4	94.8
Kaliningrad oblast	35.9	58.8	5.4	0.71	97.4	97.7
Leningrad oblast	54.5	33.5	11.9	1.11	80.3	101.3
Murmansk oblast	47.2	46.8	6.0	0.55	94.3	94.8
Novgorod oblast	44.2	47.9	7.9	0.62	93.4	94.8
Pskov oblast	33.2	60.2	6.7	0.74	97.2	97.6
Republic of Karelia	34.6	55.8	9.7	0.69	95.3	95.3
Republic of Komi	37.8	50.9	11.3	0.65	93.1	93.1
St. Petersburg	38.6	41.0	20.4	0.64	84.2	85.5
Vologda oblast	36.0	53.6	10.4	0.78	94.4	96.8

C/P - clinical/pathological notification only; C/P and D – clinical/pathological notification and death certificate; DCI – case initially registered based on information from the death certificate and further investigated. †– mortality-to-incidence ratio was based on the number of deaths from the civil registry. ‡– all DCI cases were excluded, including those with clinical/pathological information.

Table 5.6 Data sources and completeness estimates in the regions of Northwest Russia, 2008-2017, all sites in women except non-melanoma skin (C00-C96 without C44)

Region	Data sources (%)				Completeness (%)	
	C/P	C/P and D‡	DCI	M:I ratio†	Lincoln-Petersen	Ajiki formula
Arkhangelsk oblast	51.4	41.2	7.4	0.52	90.7	92.5
Kaliningrad oblast	52.5	44.1	3.4	0.55	95.8	97.1
Leningrad oblast	70.4	21.5	8.2	0.75	65.7	97.1
Murmansk oblast	61.3	34.8	3.8	0.44	91.6	94.9
Novgorod oblast	61.8	32.4	5.7	0.46	86.6	92.7
Pskov oblast	54.2	41.2	4.6	0.55	93.5	96.1
Republic of Karelia	55.6	37.7	6.7	0.50	89.3	92.9
Republic of Komi	58.0	34.2	7.8	0.47	85.2	90.4
St. Petersburg	49.4	32.6	18.0	0.55	75.2	82.0
Vologda oblast	56.9	35.8	7.2	0.55	87.3	93.6

C/P – clinical/pathological notification only; C/P and D – clinical/pathological notification and death certificate; DCI - case initially registered based on information from the death certificate and further investigated. †– mortality-to-incidence ratio was based on the number of deaths from the civil registry. ‡– all DCI cases were excluded, including those with clinical/pathological information.

5.1.4 Timeliness

The number of cases obtained from the national cancer report was about 10% lower than in the registry database (or about 23,300) for St. Petersburg. At the same time, Leningrad oblast PBCR lacked about 9,000 cases (Table 5.7). This difference affected most of the cancer types. Arkhangelsk oblast, Murmansk oblast, Novgorod oblast, Republic of Karelia, and Vologda oblast PBCRs had a similar number of cases in the PBCR and national cancer report (with differences in the range of 3%). Comparison of cancer cases in the registry database and the national report in Northwest Russia by cancer types for all Northwest regions are represented in tables A.11, A.12, A.13, A.14, A.15, A.16, A.17, A.18, A.19 and A.20. Liver cancer, ovarian cancer and haematological malignancies were initially overestimated in the national report, and soft tissue tumours were underestimated.

Table 5.7 Comparison of cancer cases in the registry database and the national report in Northwest Russia, 2008–2017, all sites.

Region	Cases		Difference	
	Registry	National report	Absolute	Relative (%)
Arkhangelsk oblast	51,610	50,953	657	1.3
Kaliningrad oblast	35,611	34,074	1,537	4.3
Leningrad oblast	48,535	57,556	-9,021	-18.6
Murmansk oblast	30,839	30,458	381	1.2
Novgorod oblast	29,296	29,171	125	0.4
Pskov oblast	30,144	29,169	975	3.2
Republic of Karelia	27,863	27,104	759	2.7
Republic of Komi	33,216	31,694	1,522	4.6
Saint-Petersburg	237,810	214,506	23,304	9.8
Vologda oblast	44,495	43,435	1,060	2.4

5.2 Cancer burden assessment

5.2.1 Cervical cancer trends

Between 1993 and 2013, around 12,990 cervical cancer cases were registered annually in Russia, with 7,440 estimated annual cervical cancer deaths between 1980 and 2013 (average incidence and mortality rates are reported in Table 5.8).

Table 5.8 Cervical cancer cases and deaths, average annual incidence and mortality ASRs per 100,000 women in Russia 1980-2013.

Year	Cervical cancer					
	Incidence		Mortality			
	Cases	ASRs (W)	Deaths		ASRs (W)	
			Reported	Corrected	Reported	Corrected
1980-1983	-	-	27,705	29,891	6.2	6.8
1984-1988	-	-	32,035	35,579	5.4	6.2
1989-1993	11,714*	10.6*	31,040	35,644	5.0	6.0
1994-1998	59,326	10.7	30,727	36,137	4.9	6.0
1999-2003	61,243	11.2	31,239	35,825	5.1	6.0
2004-2008	66,147	12.3	30,244	39,006	5.0	6.4
2009-2013	74,382	13.8	31,618	40,544	5.2	6.6

Cervical cancer incidence increased from 10.6 per 100,000 in 1993 to 14.2 per 100,000 in 2013. Breakpoint was detected in 2002, with an APC 0.7% (95% CI 0.1; 1.0) before and 2.3% (95% CI 2.1; 2.6) after that year (Figure 5.19). Cervical cancer mortality ASRs per 100,000 decreased before 1997 with an APC -0.8% (95% CI -1.2; -0.5) and increased after 1997 with an APC of 1% (95% CI: 0.6; 1.4) (Figure 5.20).

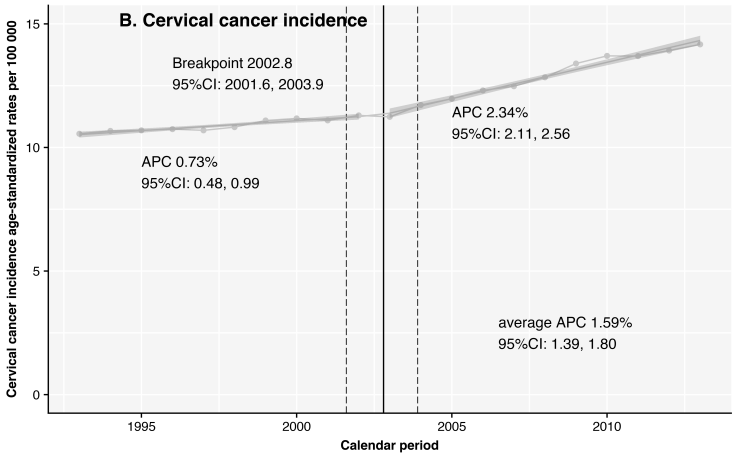

Figure 5.19 Cervical cancer incidence ASRs per 100,000 women with fitted lines from piecewise linear regression and corresponding breakpoints and APCs and average APCs, Russia, 1993–2013.

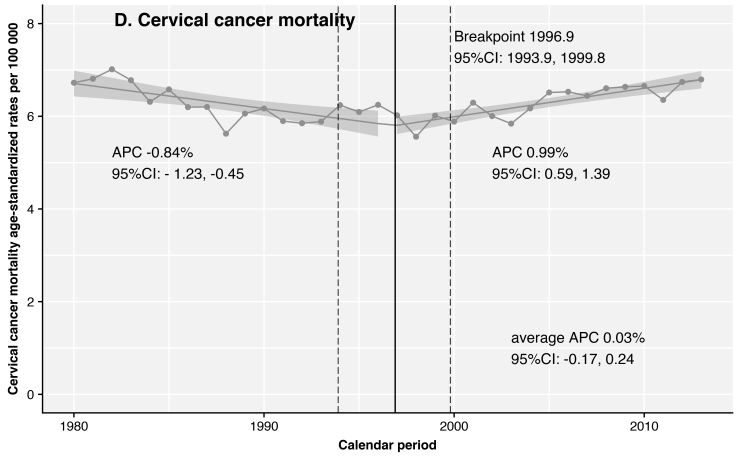

Figure 5.20 Cervical cancer mortality ASRs per 100,000 women with fitted lines from piecewise linear regression and corresponding breakpoints and APCs and average APCs, Russia, 1980–2013.

In the age-period-cohort analysis, age effects for cervical cancer plateaued between 45 and 64 years. The breakpoints in the cohort effect for cervical cancer were observed for the cohorts born between the late 1930s and early 1950s. For cervical cancer incidence and mortality, the decreasing risk among older birth cohorts was followed by rising risk among younger cohorts (Figures 5.21 and 5.22).

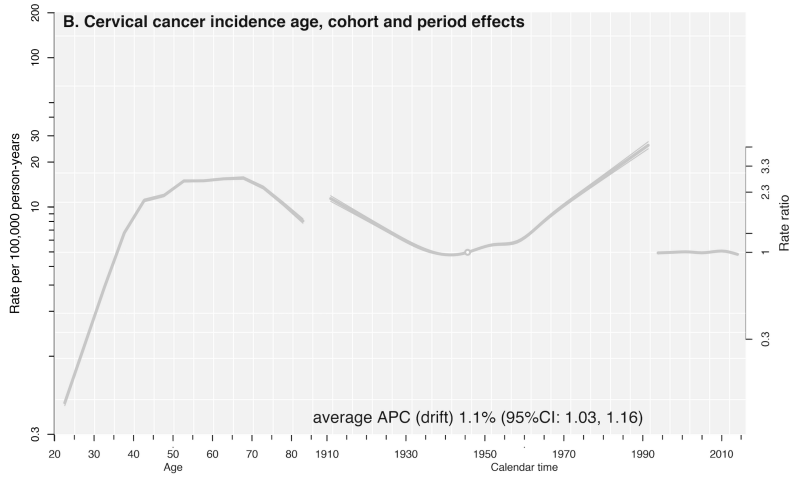

Figure 5.21 Age, cohort, and period effects for cervical cancer incidence among women, Russia, 1993-2013.

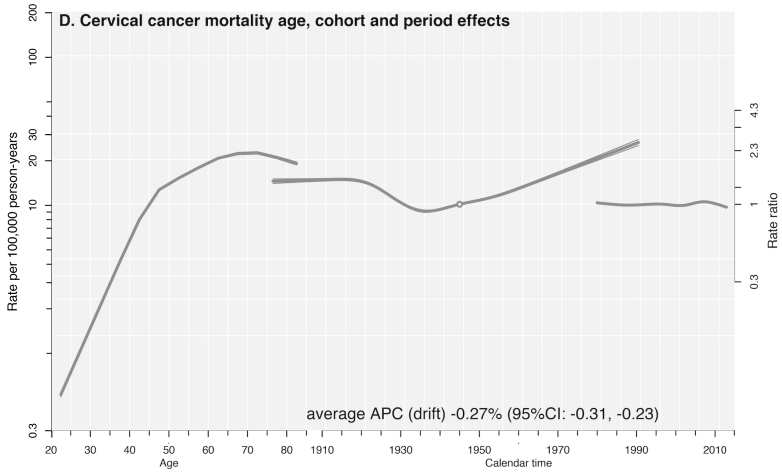

Figure 5.22 Age, cohort, and period effects for cervical cancer mortality among women, Russia, 1993-2013.

Around 22,100 cases and 10,500 deaths were predicted for 2029-2033 in the Norpred model based on the current trend (2,700 more cancer deaths than the period 2004-2008) (Figure 5.23).

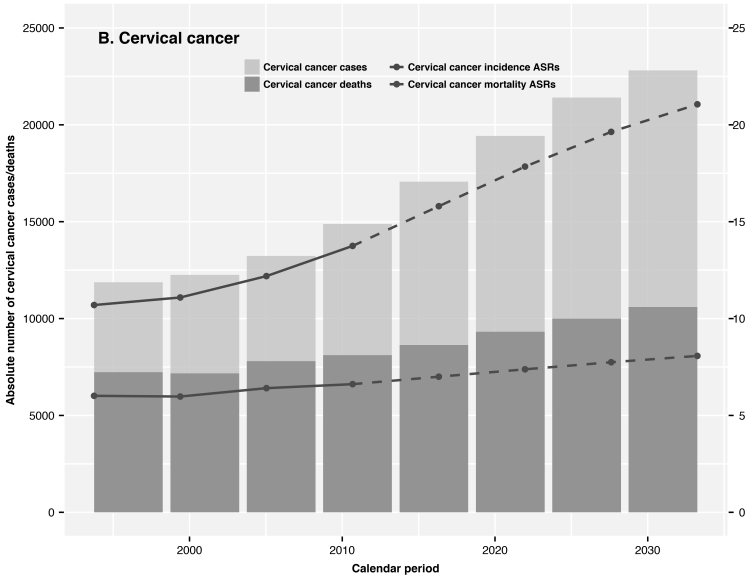

Figure 5.23 Observed and predicted cervical cancer mortality and incidence among women in Russia 2014-2032.

The number of YLL per death for cervical cancer and the overall number of YLL to cervical cancer were also expected to increase constantly over the next 30 years (Table 5.9). The overall number of YLLs was predicted to grow from around 680,000 in 1984-1988 to 1,170,000 in 2029-2033, with an overall predicted number in this period over five years of 5.9 million. YLL per death was predicted to grow from 19.1 in 1984-1988 to 22.3 in 2029-2033.

Table 5.9 Estimated overall years of life lost to cervical cancer in one-year and five-year periods and years of life lost per one cancer death (historical data and predictions based on sequential drift cut).

Period	Average overall YLL per calendar year	Overall YLL in five-year period	YLL per cancer death
1984-1988	679,508	3,397,540	19.1
1989-1993	692,477	3,462,385	19.4
1994-1998	709,777	3,548,885	19.6
1999-2003	736,448	3,682,240	20.5
2004-2008	842,712	4,213,560	21.6
2009-2013	949,120	4,745,600	23.4
2014-2018	1,046,132	5,230,660	24.2
2019-2023	1,104,646	5,523,230	23.8
2024-2028	1,149,155	5,745,775	23.1
2029-2033	1,173,614	5,868,070	22.3

5.2.2 Breast cancer trends

In the period 1993-2013, 47,680 annual breast cancer cases were registered in Russia. Between 1980 and 2013, there were 18,830 breast cancer deaths (incidence and mortality rates are reported in Table 5.10).

Table 5.10 Breast cancer cases and deaths, average annual incidence and mortality ASRs per 100,000 women in Russia 1980-2013.

Year	Breast cancer			
	Incidence		Mortality	
	Cases	ASRs (W)	Deaths	ASRs (W)
1980-1983	-	-	47,754	11.3
1984-1988	-	-	70,285	12.8
1989-1993	36,041	33.0	84,812	14.6
1994-1998	196,600	35.1	99,143	16.5
1999-2003	226,764	38.6	108,808	17.2
2004-2008	253,404	41.8	113,407	17.2
2009-2013	288,844	45.6	115,945	16.4

Breast cancer incidence ASRs increased between 1993 and 2013 without any significant breakpoint with an APC of 1.3% (95% CI: 1.0; 1.6), as illustrated in Figure 5.24. On the other hand, the breast cancer mortality ASRs were increasing until 2000 with an APC of 2.7% (95% CI 2.5; 2.8). However, after 2000, mortality APC was -0.5% (95% CI -0.7; -0.3) (Figure 5.25).

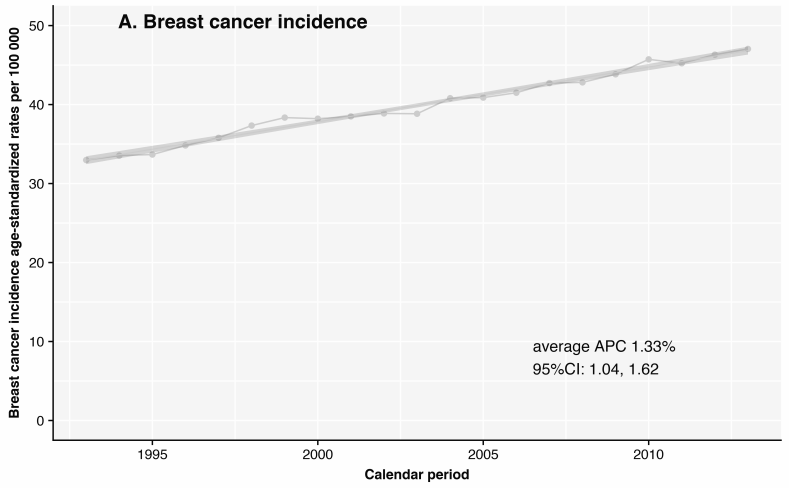

Figure 5.24 Breast cancer incidence ASRs per 100,000 women with fitted lines from piecewise linear regression and corresponding breakpoints and APCs and average APCs, Russia, 1993-2013.

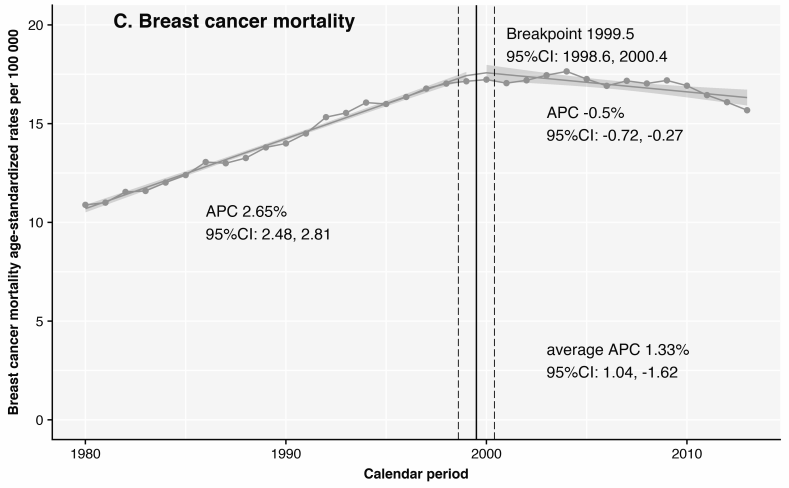

Figure 5.25 Breast cancer mortality ASRs per 100,000 women with fitted lines from piecewise linear regression and corresponding breakpoints and APCs and average APCs, Russia, 1980-2013.

Similar to cervical cancer, the change in cohort risks for breast cancer diagnosis and death was observed for the cohorts born between the late 1930s and early 1950s. Cohort risk for breast cancer diagnosis was relatively stable, and cohort risk for breast cancer death declined for younger generations (Figures 5.26 and 5.27).

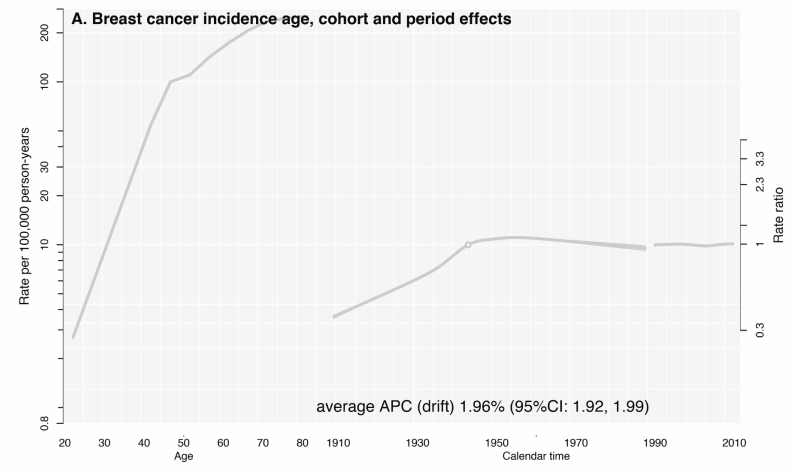

Figure 5.26 Age, cohort, and period effects for breast cancer incidence among women, Russia, 1993-2013.

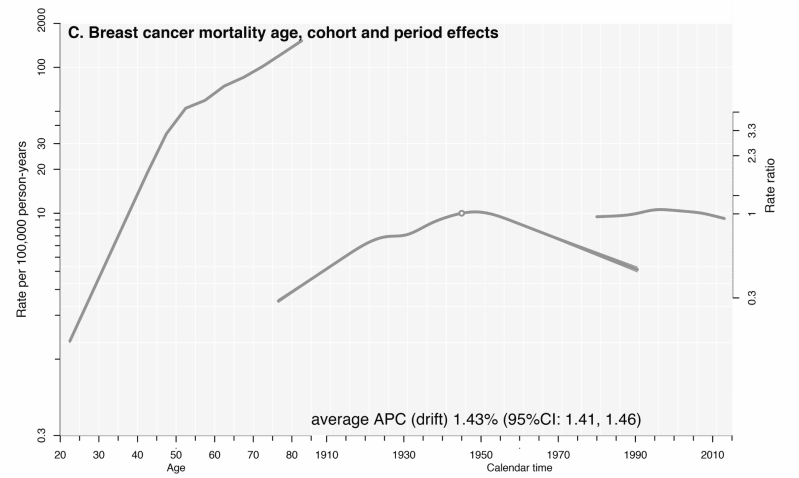

Figure 5.27 Age, cohort, and period effects for breast cancer mortality among women, Russia, 1993-2013.

The predictions for breast cancer mortality were consistent with the results of the age-period-cohort analysis. Breast cancer mortality rates were predicted to decline in future. Despite that, the absolute number of breast cancer cases and deaths was predicted to increase until 2019-2023. Only after that was the number of deaths predicted to decline, as shown in Figure 5.28.

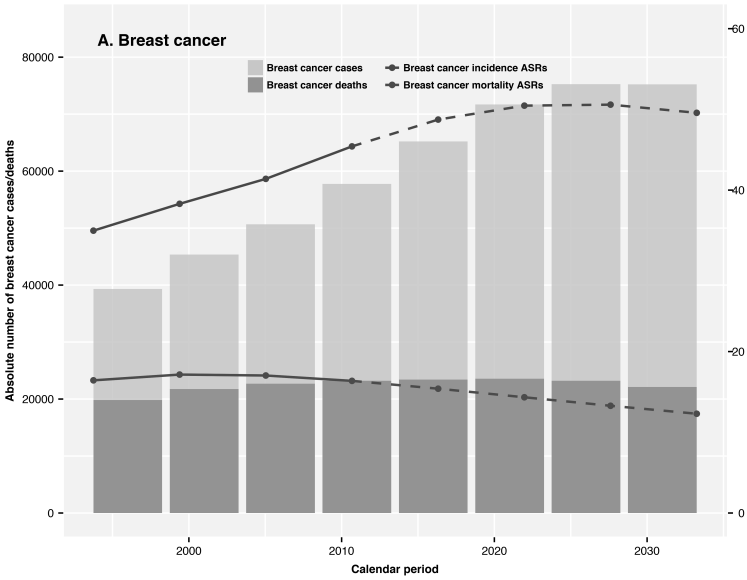

Figure 5.28 Observed and predicted breast cancer mortality and incidence among women in Russia 2014-2032.

The YLL to breast cancer peaked and declined from 2009 to 2013, whereas the YLL per cancer death decreased during the study period (Table 5.11). The 20.5 YLL per one breast cancer death in 1984-1988 was predicted to drop to 16.1 in 2029-2030. The highest overall estimate of YLL was observed in 2009-2018 – around 2.1 million per year – and this was expected to drop to 1.8 million per year in 2029-2030.

Table 5.11 Estimated overall years of life lost to breast cancer in one-year and five-year periods and years of life lost per one cancer death.

Period	Average overall YLL per calendar year	Overall YLL in five-year period	YLL per cancer death
1984-1988	1,442,419	7,212,095	20.5
1989-1993	1,696,532	8,482,660	20.0
1994-1998	1,867,630	9,338,150	18.8
1999-2003	1,950,463	9,752,315	17.9
2004-2008	2,037,226	10,186,130	18.0
2009-2013	2,144,044	10,720,220	18.5
2014-2018	2,127,327	10,636,635	18.1
2019-2023	2,023,579	10,117,895	17.1
2024-2028	1,909,143	9,545,715	16.5
2029-2033	1,775,866	8,879,330	16.1

5.2.3 Mortality and years of life lost

5.2.4 Cancer mortality and years of life lost

Overall, cancer mortality ASRs decreased both in men and women. This decrease was attributable to several common cancer types: the most prominent decrease in mortality was observed for stomach cancer, both in men and women, and lung cancer in men. Nevertheless, cancer mortality for several cancer types increased between 2001 and 2015. Lip, oral and pharynx, larynx and cervix uteri cancer mortality increased in women and prostate cancer mortality increased in men. In addition, pancreas, brain and CNS and melanoma cancer mortality increased in men and women (Figure 5.29).

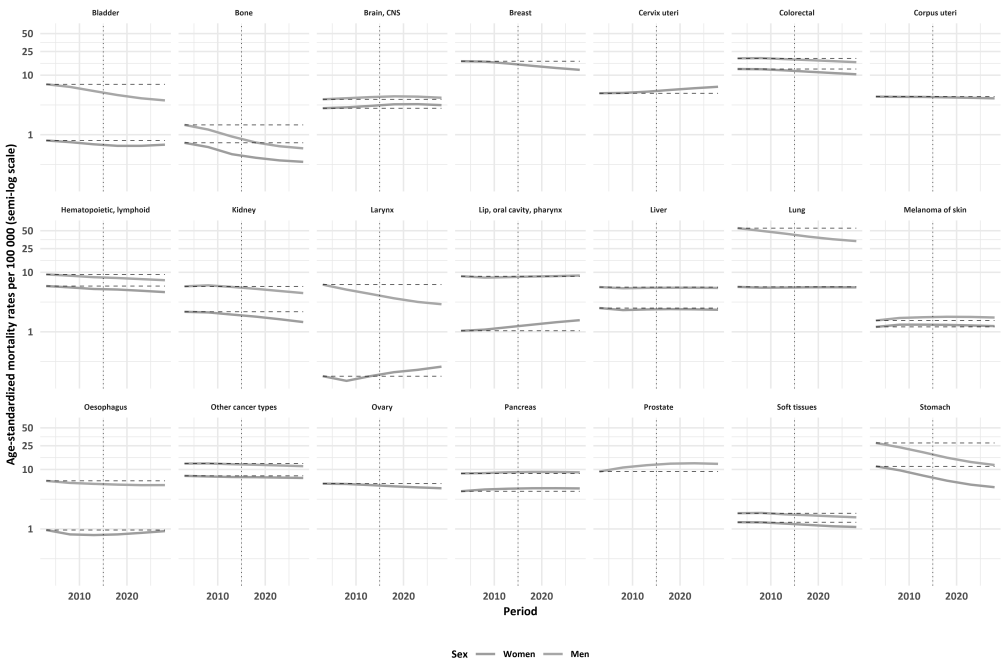

Figure 5.29 Age-standardised mortality rates per 100,000 (presented on a semi-log scale) according to cancer types and sex between 2001 and 2030 in Russia (dotted lines – corresponding reference rates from 2001).

Despite the declining trend in cancer mortality, YLL increased for most cancer types. Conversely, only a few cancer types showed a decrease in YLL. Specifically, stomach cancer was one of the cancer types that showed a consistent decrease in the

number of YLLs. In addition, a considerable relative and absolute increase in YLL was observed for prostate cancer in men and cervix uteri cancer in women (Figures 5.30 and Figures 5.30). Other cancer types that showed an increase in YLL were pancreas, colorectal and lip, oral, and pharynx.

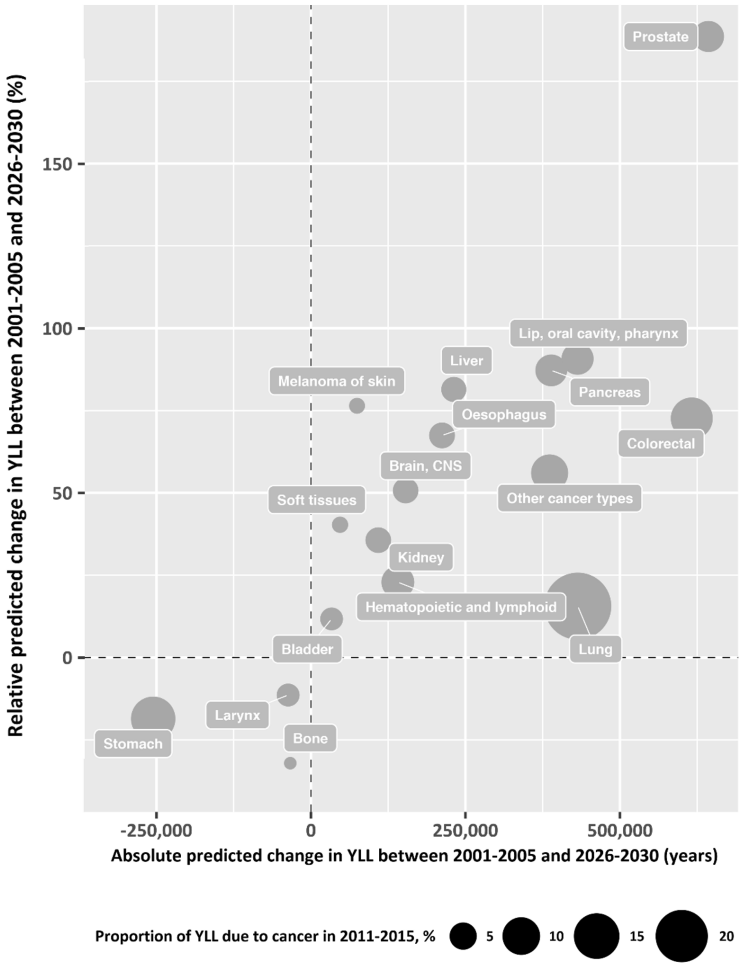

Figure 5.30 Trends in the number of YLL due to premature cancer mortality in Russia between 2001-2005 and 2026-2030, men.

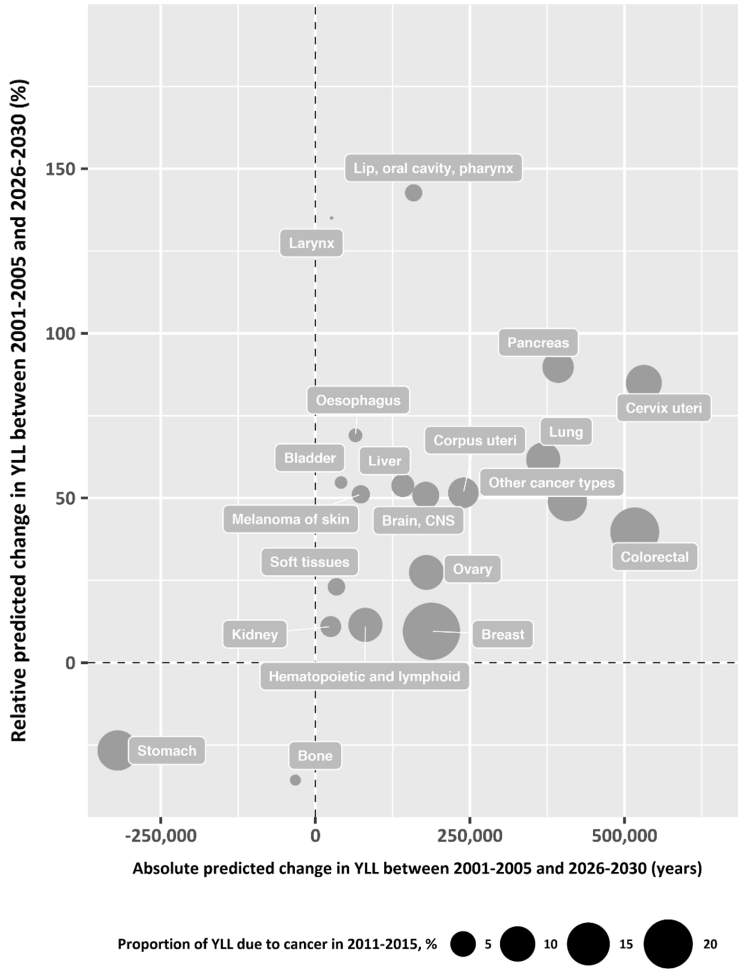

Figure 5.31 Trends in the number of YLL due to premature cancer mortality in Russia between 2001-2005 and 2026-2030, women.

5.2.5 Productivity costs of cancer

The productivity losses due to premature cancer were on average higher in men and increased overall from $6.5 billion in 2001-2005 to $8.3 billion in 2006-2010. Productivity losses were predicted to remain above $7 billion. Figure 5.32 illustrates the dynamic of overall losses in women and Figure 5.33 in men. Productivity losses as a proportion of GDP decreased from 0.28% of GDP in 2001-2005 to 0.24% in 2011-2015 and were expected to decrease to 0.14% in 2026-2030

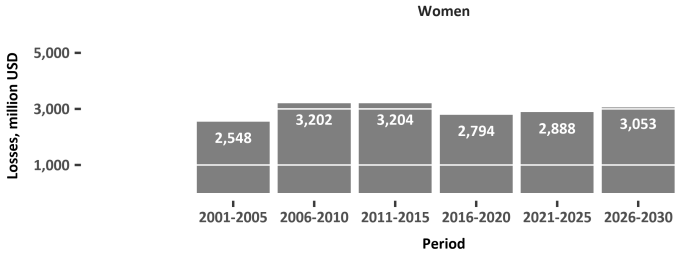

Figure 5.32 Overall annual productivity losses due to premature cancer mortality in Russia in 2001-2030 in women.

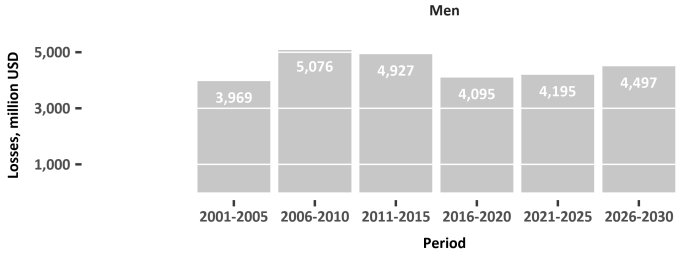

Figure 5.33 Overall annual productivity losses due to premature cancer mortality in Russia in 2001-2030 in men.

Despite the decrease in the absolute estimate, breast cancer remained the top cancer type in terms of annual productivity losses in women between 2001 and 2030. Cervical cancer surpassed stomach cancer and haematological malignancies. Cervical cancer became the second largest cause of productivity losses in women. Productivity losses from lip, oral and pharynx cancer in women has also increased from $27 to $68 million between 2001 and 2030 (Figures 5.34 and 5.35). The relative change was highest for larynx, lip, oral and pharynx, oesophagus and cervical cancer, while

absolute changes were highest for cervix uteri and lung cancer.

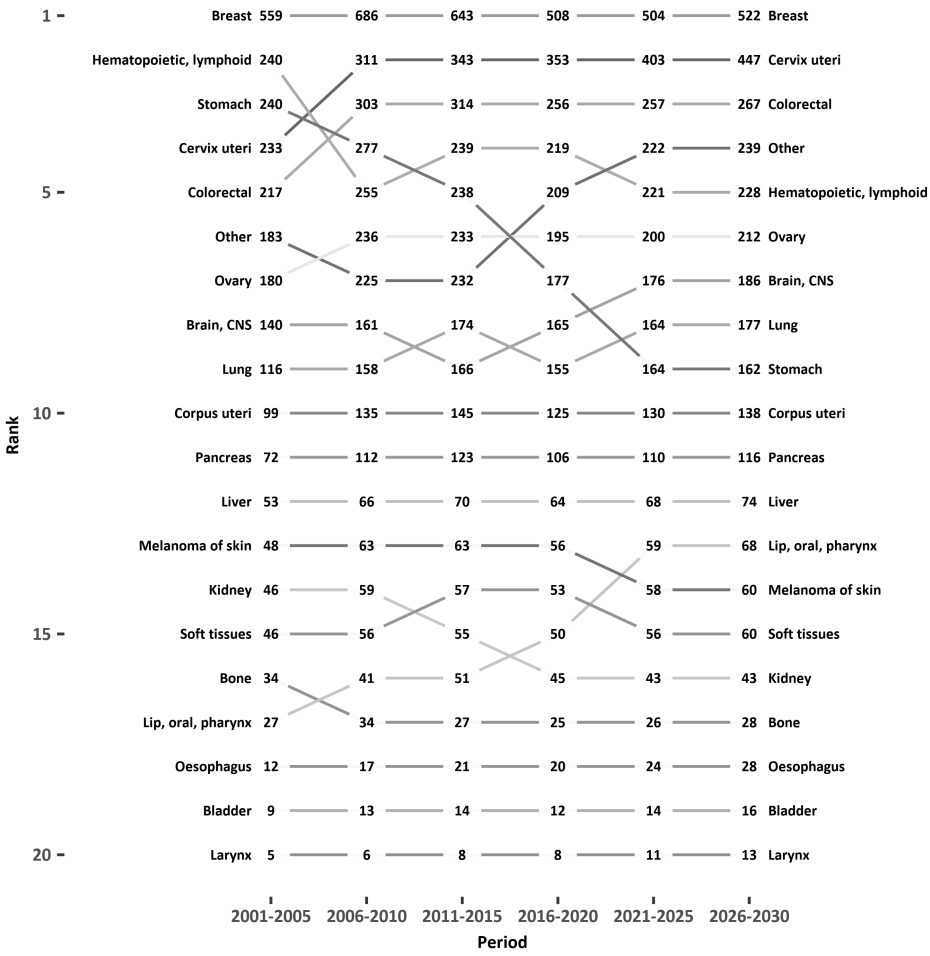

Figure 5.34 Average annual productivity losses: change in the ranking according to cancer sites, women.

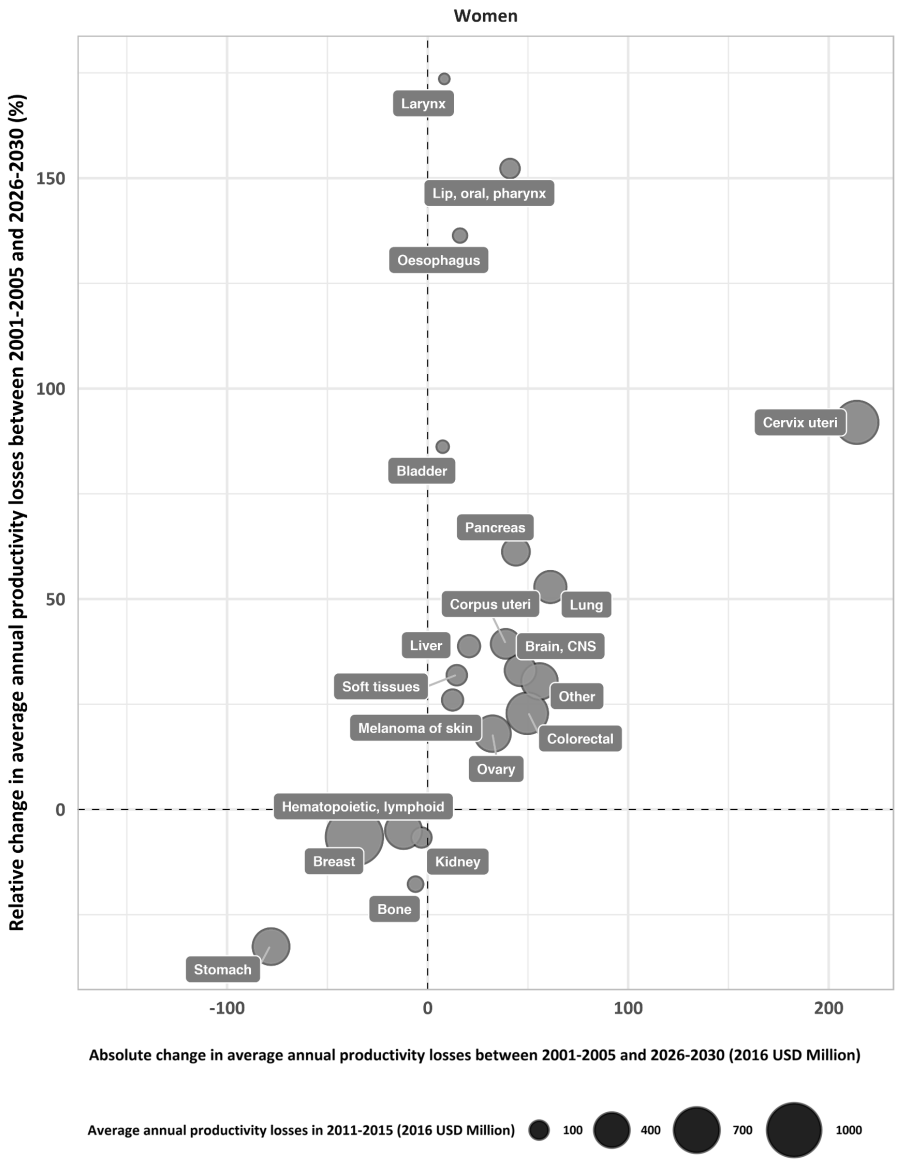

Figure 5.35 Change in annual productivity losses in Russia between 2001-2005 and 2026-2030 by cancer type, women.

Lung cancer in men was the main contributor to productivity losses over the study period, and lip, oral and pharynx cancer was predicted to surpass stomach cancer in terms of productivity losses. While the relative change was highest for prostate cancer, lip, oral and pharynx, oesophagus and liver cancer, the considerable absolute change was predicted for lip, oral and pharynx and colorectal cancer (Figures

5.36 and 5.37).

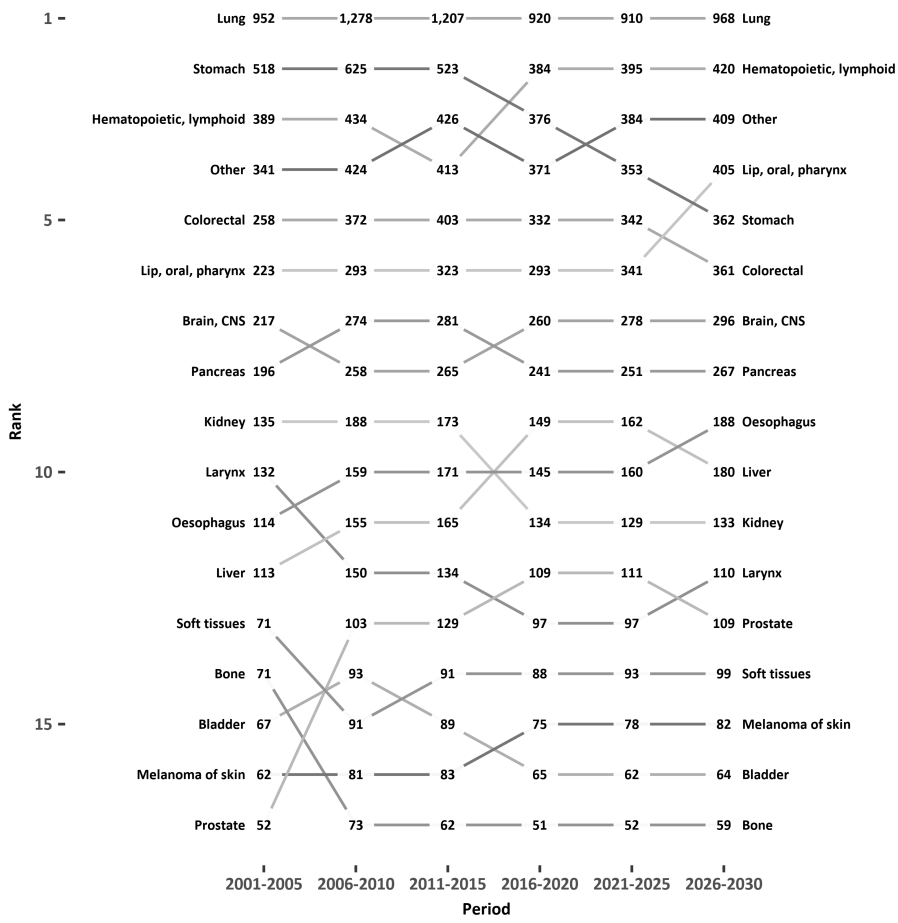

Figure 5.36 Average annual productivity losses: change in the ranking according to cancer sites, men.

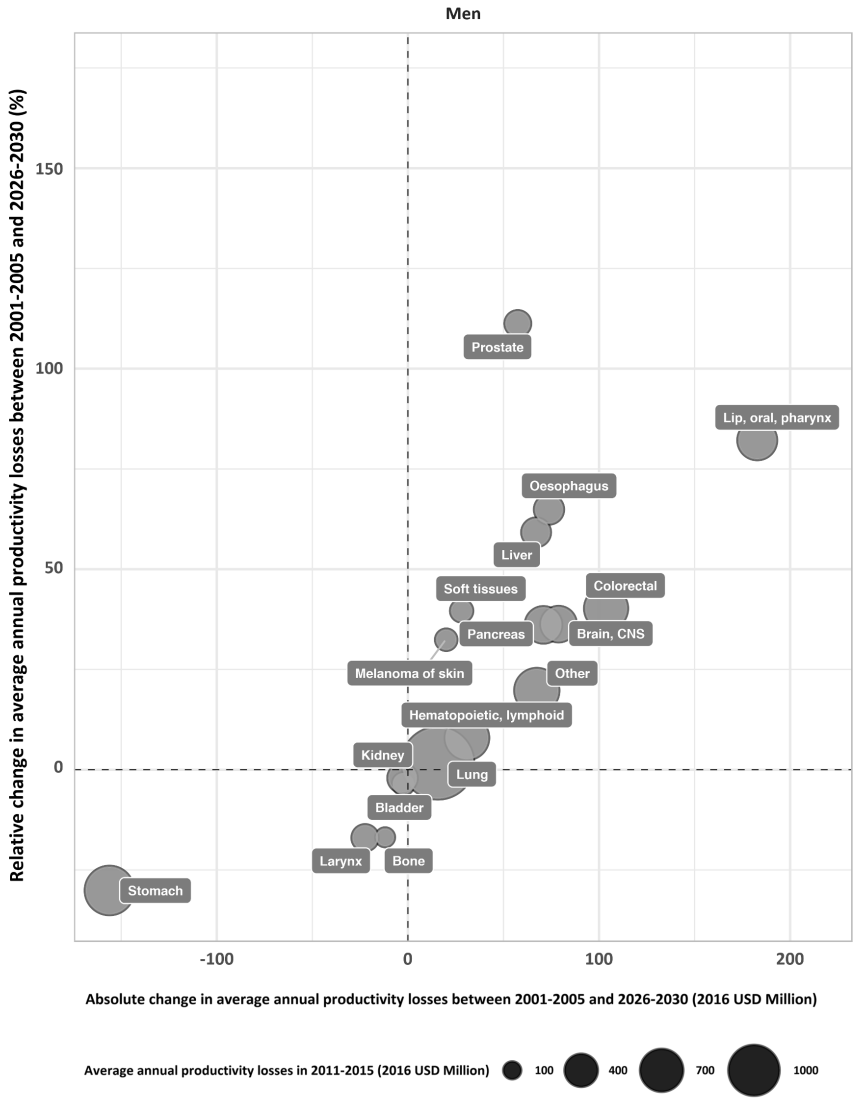

Figure 5.37 Change in annual productivity losses in Russia between 2001-2005 and 2026-2030 by cancer type, men.

6 DISCUSSION

This thesis aimed to assess the quality of population-based cancer registries as the primary source of cancer incidence data and measure the cancer burden nationally and subnationally in Northwest Russia. Establishing methods and providing a realistic path to continuous and scientifically sound cancer burden assessment in Russia, the largest country in Europe, representing about 14% of the European population, with cancer mortality above the average European rates, are relevant to the focus of international cancer epidemiologic research. Another critical issue is the absence of subnational and regional estimates to help allocate public health activities and plan cancer control at the regional level. Russia is demographically, socially and economically a highly heterogeneous country. Averaging the estimates across the country can be misleading to some aspects of policies, including cancer control, risk factor prevalence and the quality of data sources. Assessing data source quality on a regional level and providing a framework for continuous cancer burden assessment is necessary for the cancer control goals for any country.

6.1 Quality of cancer registry data in Russia

This study assessed the data quality from 10 PBCRs in Northwest Russia. It is the first systematic quantitative assessment of cancer registration in the country. Only two previous studies covered PBCR data quality in post-Soviet countries, Ukraine and Estonia (Ryzhov, Bray, et al. 2018; Lang, Mägi, and Aareleid 2003). Despite low DCO% and deviations of age-specific curves that could indicate possible underreporting, data in Ukraine were reported in a timely way and were reasonably comparable (Ryzhov, Bray, et al. 2018). Completeness in the Estonian PBCR in 2003 was about 91%. However, that study involved independent case ascertainment, a method used neither in the Ukrainian nor this study, probably making completeness in the latter overestimated. Further completeness assessments should focus on

independent case ascertainment, as with studies done in Finland and Iceland (Sigurdardottir et al. 2012; Leinonen et al. 2017).

This study revealed an evident heterogeneity in all four dimensions of the quality of cancer registry data in the ten regions of Northwest Russia, which probably reflects the situation in the country. This was the main finding of this evaluation. Despite a long history of cancer registration and nationwide legislation, implementation of cancer registration on a regional level is highly heterogeneous. A few regions have PBCR data that were comparable, accurate, complete and collected on time. Unsurprisingly, some of these regions participated in international studies, becoming the country's representatives in the global cancer burden assessment (Allemani et al. 2018; Bray, Colombet, et al. 2017).

Quite a large number of regional PBCRs by population size (10 PBCRs per approximately 13.8 million, and nine per about 8.2 million without St. Petersburg) and the relatively independent nature of PBCRs may be a reason for the organisational and qualitative heterogeneity. Establishing a more balanced organisation for cancer registration that involves regional cooperation could improve all quality elements and optimise available resources.

Maintaining consistent PBCR quality across the country is difficult due to its vast geographical, demographic and socioeconomic diversity. At the same time, pooling data of various quality levels is hardly optimal for ensuring total regional coverage. Even there, however, there are solutions to PBCR-based accurate cancer burden assessment. The Surveillance, Epidemiology, and End Results (SEER) Programme (Parkin 2008) is an example of an attempt to generate high-quality data from a non-random population sample representative of the country. However, having perfect representation (Merrill and Dearden 2004) is still difficult. Another option is to use several sources of data. Combining high-quality PBCR and mortality data could become a better and more accurate solution for measuring the cancer burden in Russia. For national estimates, though, it is not enough to have only a couple of regions that represent less than 5% of the population, as was done before (Allemani et al. 2018). So the process of quality assessment should involve more regions.

This study identified patient groups where cancer cases were systematically registered with lower quality. For example, older age at the time of diagnosis was associated with a low level of all quality indicators. That is not surprising, given that a similar situation was described in higher quality registries, e.g. in the Netherlands

(van der Willik et al. 2020). Another issue that should be addressed on the national level is the quality of data for haematological malignancies and CNS tumours, which was also behind other tumour types. Possible solutions include disease-level registries that could provide information to PBCRs, but this solution requires additional resources.

Findings related to particular quality dimension assessments require detailed discussion. Some differences in the data quality could have resulted not only from the failures of cancer registration but could have come from certain features of cancer care system organisation, diagnostic activities and cancer control interventions. Methods applied in PBCR quality assessment could provide additional insight into the future directions of cancer epidemiological research.

6.1.1 Comparability

A major drawback in cancer registration in Russia is the use of combined ICD-10/ICD-O-2 classification. The translated version of ICD-O-3 has been available in Russia since 2017. However, even if the national legislation for cancer registration is changed and the new one includes ICD-O-3, which is not the case now, implementing the new classification will probably take time. In this study, all cases were converted from ICD-O-2/ICD-10 to ICD-O-3 using the IARC conversion tool specifically designed for countries with hybrid classification (Ferlay, Burkhard, et al. 2005). This process accompanied all submissions to international studies. However, the study revealed misclassification for rare cancer types and the sites where both primary tumours and metastases are common (e.g. liver). Reporting in regional PBCRs is based on the ICD-10 code, which, at the same time, acts as the replacement for topography in hybrid ICD-10/ICD-O-2 classification, so misclassifications are expected.

The liver was previously considered a site with possible misclassification problems due to common metastases caused by other primary tumours (de Ridder et al. 2016; Rumgay et al. 2022). However, in Northwest Russia, rates mainly stayed the same after applying conversion algorithms, with only some misclassification evident. Source documentation and morphological audits are probably needed to review the correctness of liver cancer diagnosis. Liver cancer was among the sites with the lowest MV% and highest DCO% across all regions in the study. In Russia, liver cancer as a cause of death was much less consistent among the regions compared to all other can-

cer types (Danilova, V. Shkolnikov, et al. 2016), so trends and comparison between the regions should take possible misclassification into account. Studies of asbestos exposure could also be affected by the misclassification of mesothelioma (Fazzo et al. 2012). According to the analysis of registries in Northwest Russia, it was also often misclassified. An additional targeted comparability audit is warranted if registry data are used in research projects.

Based on our study results, rules for the multiple primary tumours were applied consistently. Multiple primaries proportion, which was between 6.7% and 12.4%, was reasonable in Northwestern regions. To make some comparisons, about 11% of the tumours at the Swedish cancer registry (Frödin, Ericsson, and Barlow 1997) and around 13% at the Swiss cancer Registries of Vaud and Neuchâtel were multiple primaries (Levi, Randimbison, Rafael, et al. 2015). It is worth mentioning that the proportion of multiple primaries depended on the period the PBCR has been collecting the data. It was lowest in Vologda oblast, where cancer registration started no earlier than 2005. In any case, multiple primaries research represents another possible direction of research that can be conducted using PBCR data available in Russia, as has been done in other countries (Soerjomataram, Louwman, et al. 2008; Levi, Randimbison, Te, et al. 2008).

Another critical issue in data comparability is related to diagnostic activities and cancer screening programmes, which could dramatically influence the incidence rates. In this study, thyroid and prostate cancer rates, mainly driven by early-stage disease, peaked in several regions, suggesting an increase in diagnostic activities. A dramatic increase in incidence rates was found in South Korea between 1999 and 2008, where thyroid cancer rates increased 6.4-fold. This increase was due to small tumours, which most likely constitute overdiagnosis. Authors recommended reducing unnecessary thyroid ultrasounds in the asymptomatic population at a national level (S. Park et al. 2016). Similar recommendations can be made on a regional level in Northwest Russia. Another implication of this finding relates to reporting and comparison of overall cancer rates between regions. Like skin cancer, breast and prostate cancers are sometimes excluded from reporting, and thyroid cancer should also be considered in this list.

An autopsy is still a common practice in Russia. Unlike other European countries, it is performed regularly (WHO Regional Office for Europe 2023) and could affect comparability. For example, autopsy proportions were higher than in Europe

(Bieri et al. 2015), and the DCO% was associated with the proportion of autopsies performed in the regions following the death. Still, the role of autopsies in incidental diagnosis should be further explored, but this could explain some DCO cases in regions with reasonable data quality.

6.1.2 Validity

MV% and DCO% obtained in this study were slightly lower than in the European cancer registry but still within the acceptable range, with the exception of two regions, St. Petersburg and Leningrad oblast. MV% in other regions were still lower than in Western European and USA PBCRs, with only one region reaching the threshold of 90% – Murmansk oblast. DCO% were generally slightly higher than in European PBCRs, but still within the accepted ranges for most regions and lower than in South American PBCRs, in Germany and Japan (Bray, Colombet, et al. 2017).

MV% by cancer site analysis showed that leukaemia cases are registered predominantly based on "cytology" verification, as registries were probably miscoding the bone marrow biopsy (which should be labelled as code 7, "Histology") (Fritz et al. 2013). This issue can be corrected with registry training. However, that was probably not the only reason for low MV% for haematological malignancies. Relatively high DCO% and low MV% reflected overall difficulties with data flow for haematological patients, who are often admitted to federal institutions beyond the network of regional cancer hospitals.

The proportions of cases with primary site unspecified were comparable with the registries in Eastern Europe (Dimitrova and Parkin 2015). As with many other validity indicators, older age was associated with a higher proportion of primary site unspecified cases. A much higher proportion of cases with the primary site unspecified in the youngest age group was surprising. Tumours detected at early ages outside the regional oncology network are probably much less accurately reported. IARC recently started an initiative to improve global childhood cancer registration (ChildGICR) in partnership with St. Jude Children's Research Hospital in the United States. This thesis only partially touched on childhood cancer registration quality and required detailed analysis in line with this initiative.

Overall, the proportion of missing information was highest in St. Petersburg, Leningrad oblast and Vologda oblast. Haematological tumours were recorded with

the highest proportion of missing or non-specific codes, supporting other findings about this disease group. IARC check analysis also revealed a higher proportion of mistakes in haematological malignancies registration.

Finally, stage information was available in the cancer registry and was supposed to include categories recorded following the 5th AJCC/UICC TNM classification for staging (Sobin and Fleming 1997). However, it was unclear if registries followed this exact version of TNM classification and if they were collecting information from the clinical records, as newer versions of this classification were probably used by clinicians in recent periods. Information on stages is extremely useful in interpreting the trends and survival analysis. However, the quality of staging information can limit the interpretation of study results. For example, the patterns of missing information in this study were probably related to diagnostic challenges and poor prognosis (e.g. soft tissue, bone, and cartilage tumours) (Merrill, Sloan, et al. 2011). Therefore, the primary limitation for studies that will utilise staging information is how to deal with these gaps, as exclusion of these cases will bias the result, and imputation requires additional assumptions about the patterns of absence (Eisemann, Waldmann, and Katalinic 2011).

6.1.3 Completeness

Semiquantitative completeness assessment is closely linked to epidemiological studies and requires additional knowledge of risk factors and the prevalence of diagnostic practices. One of the possible signs of incomplete data is the lack of an upward trend in the number of new cases in the registry. In general, the ageing of the population, diagnostic developments and screening implementation are leading to more cases being registered every following year. The obvious example of data incompleteness is the drop in incident cases in Leningrad oblast in 2014-1016. However, a downward trend is not always a sign of incomplete data. For example, rapid changes in certain risk factor prevalence can influence this general upward trend. In St. Petersburg, the absolute numbers of cases and rates decreased till the late 1990s, and only in the early 2000s did the number of cases start to grow. The quality of cancer registry data in the late 1990s–early 2000s could be one explanation for this phenomenon. However, the cancer incidence patterns have changed dramatically during the same period. Until the late 1990s, lung and stomach cancer were the most common. However, they rapidly decreased and were replaced by colorectal cancer, breast cancer in women

and prostate cancer in men. The drop in lung and stomach cancer rates in St. Petersburg was similar to the global trends related to changes in risk factor prevalence (tobacco smoking, Helicobacter pylori infection) (Islami, Torre, and Jemal 2015; Luo et al. 2017). It is worth mentioning that, despite the same trend, the magnitude of changes in cancer rates were different in St. Petersburg and other regions of Northwest Russia, suggesting regional differences in risk factor prevalence, and probably the drop in lung cancer rates is yet to be observed in other regions.

The childhood cancer rates were generally within limits; however, they slightly increased in a few regions, especially in the late 2010s. Additional studies are needed to explore whether this was a registration issue (e.g. duplicate registrations) or a true epidemiological phenomenon (Parkin and Bray 2009).

Age-specific curves showed that incidence rates were decreasing in older age groups for several sites in Northwest regions, as in several Eastern European countries. This could also indicate the lack of completeness in older age but can be the consequence of the population selection due to competing risks (Tanskanen et al. 2021).

Regional differences in M:I ratios can be partly attributed to data completeness and diagnostic and screening practices, which are closely linked to comparability. In this study, M:I for lung cancer were lower in Murmansk oblast and Arkhangelsk oblast compared to Norway. In a global comparison, lung cancer survival in several Russian registries was similar to European estimates, in contrast to other cancer types, where survival was much lower (Allemani et al. 2018).

This study revealed completeness above 90% in eight regions out of ten. The Lincoln-Petersen estimator performed much better at detecting incomplete data in the Leningrad oblast. The assumption behind the estimate obtained using the Ajiki formula estimate is that fatality is similar for both registered and unregistered, which was not realistic for the Leningrad oblast.

Finally, despite early reporting, our timeliness assessment showed that the national annual report provided accurate statistics for smaller regions. However, it did not include about 10% of cases probably collected later in St. Petersburg. With a population of around five million, one month is not enough to collect information on all the cases that occurred during the previous year. Certain cancer types statistics suffered from early reporting in all the regions (e.g. liver, haematological malignancies, soft tissues). These findings point to the lack of reliability of the national estimates for certain cancer types.

6.2 Measuring cancer burden

Apart from the regional PBCR data quality assessment, the study analysed the burden of cervical and breast cancer on the national level. It also focused on the productivity losses associated with premature mortality from all major cancer types in Russia. Study findings can be used in shaping cancer-specific control policies but also represent opportunities for cancer data analysis and can be extended to other cancer types and research hypotheses. At the time of publication, the study of cervical and breast cancer burden was the first comprehensive assessment combining incidence and mortality estimates.

6.2.1 Cervical cancer

The study demonstrated a higher overall burden of cervical cancer in Russia than in other European countries and a modest increase in cervical cancer incidence and mortality ASRs. At the same time, the changes in cohort risks were more substantial. Rising cervical cancer cohort-specific incidence and mortality in Russia probably reflected the increased prevalence of human papillomavirus (HPV) infections against a continued absence of effective national screening programmes. This result is consistent with previous research exploring period and cohort effects on cervical cancer incidence risks in Russia. A previous study focused on preventable fractions of cervical cancer via screening in six Baltic, central, and eastern European countries, including Russia (Vaccarella et al. 2016). The study suggested that the generational risk of HPV exposure was a decisive factor in predicting cervical cancer incidence and cervical cancer screening was suggested to be visible through the period effect. The results indicated that risk was substantially higher in eastern European and Baltic countries, likely due to the lack of screening programmes in these regions.

The published results on cervical cancer incidence risks in Russia became a basis for justifying the implementation of screening and prevention programmes, despite the absence of more reliable data on HPV prevalence. Unfortunately, high-quality information on HPV burden in Russia is unavailable, and several reports suggest a wide range of prevalence for high-risk HPV – between 0 and 48% (Rogovskaya et al. 2013; Shipitsyna et al. 2011).

Another possible risk factor that could influence the generational risk of cervi-

cal cancer is smoking. A recent study examined trends and patterns of smoking in Russia from 1975 to 2016 (V. Shkolnikov, Churilova, et al. 2020). Results showed that between 1975 and 2005, male smoking prevalence was relatively stable at 60%, while female smoking prevalence more than doubled after age 55 and increased significantly among younger women and those with lower educational levels. However, after 2008, smoking prevalence declined among men and women of all ages and educational levels.

The prediction based on the modified age-period-cohort model in the study showed the expected rise in cancer incidence rates and the need for public health policies that include population-based screening and HPV vaccination. The predicted trend was similar to that observed between 2013 and 2018, but long-term prediction overestimated the true cervical cancer incidence. Cervical cancer incidence rate growth slowed down in 2018-2019 in Russia. Additional studies are needed to explore the reasons behind these changes, and whether these are changes in the prevalence of risk factors or the effect of possible interventions.

Several studies examined the potential impact of both cytology-based and HPV detection methods, along with primary prevention through vaccination, on cervical cancer burden (Bespalov et al. 2021). Results of the simulation studies indicated that cervical cancer burden could be dramatically reduced when vaccination is combined with screening (K. Tay and S. K. Tay 2011). Despite multiple studies showing its effectiveness (Anttila and Nieminen 2000), cancer screening remains opportunistic in Russia.

Finally, this study found that cervical cancer rates differ across regions of the country, probably displaying heterogeneity in the quality of the cancer registry, prevalence of risk factors, and uptake of diagnostic interventions. Additional studies are needed to explore these differences.

6.2.2 Breast cancer

This study showed that breast cancer mortality rates in Russia had decreased recently and among younger cohorts. Concurrently, the incidence of breast cancer was increasing. The findings indicated that the breast cancer trends in Russia were mainly comparable to other countries in Europe (Dimitrova, Znaor, et al. 2017). The study assessed the burden of breast cancer in South-Eastern European countries based on data from 14 PBCRs in 2000-2010. The results showed an increase in incidence and

a decrease in mortality rates in nearly all age groups. However, in Russia, mortality rates were higher than in most developed countries.

This study results for breast cancer trends were also in line with previous reports (V. Shkolnikov, McKee, et al. 1999; Hirte et al. 2007), but added information about the most recent period. Results of previous study (Hirte et al. 2007) suggested that breast cancer mortality rates may either stabilise or decrease. This report provided evidence of the decrease in mortality rates in the most recent period.

Increasing breast cancer incidence rates can be explained by different factors, such as decreasing fertility rates, increasing obesity prevalence and changing dietary habits, and also improved diagnostics and opportunistic efforts at early detection. The role of opportunistic mammography screening in breast cancer incidence trends in Russia seems to be minimal. The stage distribution and stage-specific trends in breast cancer incidence do not suggest the presence of large-scale diagnostic or screening intervention (Ryzhov, Corbex, et al. 2021). The decrease in breast cancer mortality (observed mainly in younger cohorts) should probably be attributed to new treatment options, e.g. adjuvant therapy (Semiglazov et al. 1994). Population-based breast cancer screening programmes are not implemented in Russia, and organised programmes could help maintain the decreasing mortality trend (Sarkeala, Heinävaara, and Anttila 2008). Monitoring incidence is also essential for population-based screening as it is a proxy for screening uptake at the start of the programme implementation.

Similar to cervical cancer, changes in breast cancer rates were not uniform across the country's regions, suggesting inequalities in access to diagnostics and cancer care. This issue should also be explored in subsequent studies.

6.2.3 Productivity costs of cancer in Russia

The study is not the first assessment of productivity losses in Russia (Pearce et al. 2018). The previous cross-sectional report estimated productivity losses from cancer-related premature mortality in the BRICS countries. However, our study was the first to analyse trends and predict productivity losses in Russia up to 2030. Apart from productivity costs related to premature mortality, the study also assessed national trends in cancer mortality and estimated the YLL for each cancer type. Cross-sectional reports can be used for international comparisons, e.g. productivity costs in Europe in 2008 were, on average, 0.36% of total GDP (Luengo-Fernandez et al.

2013), in the US, about 1.11% of GDP in 2000 (Bradley et al. 2008). Productivity costs for Russia were 0.24% of GDP for the most recent observed period. The findings also indicated lung cancer was the biggest contributor to productivity losses in men and breast cancer in women. In particular, lung cancer accounted for 24% of the total loss, equivalent to $1.2 billion, while breast cancer accounted for 20% of the total loss, or $0.6 billion.

Another possible application of these results is quantifying overall cancer costs in Russia, which is relevant in the absence of data on direct and indirect medical costs. In our estimation, Russia experienced a productivity loss of approximately $8.1 billion per annum in the most recent period. One systematic literature review explored the methodological differences and global relevance of estimating productivity costs for cancer. The authors included 27 articles in the qualitative analysis, and results showed that the weight of cost productivity could be considerable, up to 50% of the total costs. The most common estimation method is HCA. However, there was considerable heterogeneity in the estimation methods and results (Gol-Montserrat et al. 2017). Given the results of our study, which were obtained using HCA, it is safe to assume that overall costs are likely to be more than $15 billion.

In addition to the cross-sectional results mentioned above, the study provided additional insight into the dynamics of productivity losses, highlighting not only the cancer types that are a common cause of premature death at the moment but the changes in the distribution of these causes in the future. The major findings were related to the growing burden of HPV-related cancer types, which almost exclusively drove productivity losses up in absolute and relative terms. These results are highly relevant for cost-effectiveness studies that are often conducted to estimate the benefits and costs of cancer control activities focused on HPV-related cancer types (e.g. vaccination).

Cost-benefit studies apply different methods when estimating the benefits of interventions. A study conducted to assess HPV vaccination in the UK applied eight methods for monetising health and economic benefits (M. Park, Jit, and Wu 2018). These approaches varied significantly in the total benefits reported and the threshold vaccine cost. The authors conclude that greater convergence on methodological approaches is needed to ensure consistency and comparability when using cost-benefit analysis to inform priority settings in public health. Our study used HCA, which resulted in much more significant benefits for HPV vaccination than in the UK

study. This should be considered when our study results are applied for cost-benefit analysis. As an example, cost-effectiveness analyses of potential HPV vaccine introduction in Ghana that took into account productivity losses suggested it would be cost-effective in Ghana under any strategy (Vodicka et al. 2022).

Besides productivity losses, our study assessed overall changes in cancer-specific mortality in Russia. While an overall decline was observed and projected, mortality rates from specific cancer types were still rising. In addition to HPV-related cancers (e.g. cervix uteri, oral and pharynx), the following cancer types showed an upward mortality trend: larynx cancer in women, prostate cancer in men, and melanoma, pancreas, brain and CNS both in men and women. Several reasons for those trends can be identified, but additional studies are needed to explore whether changes in registration and diagnostic practices or risk factor prevalence stand behind them. The overall trend in the number of YLL was in the opposite direction to the mortality ASR trends. The increase in YLL for most cancer types was mainly due to changes in life expectancy in Russia. Life expectancy was increasing in Russia, but the progress was modest. Despite the substantial economic gains made in Russia since 2005, there is a noticeable gap between actual life expectancy and what should be expected, given its level of wealth (V. Shkolnikov, Andreev, et al. 2019). The life expectancy gap for Russia was 6.5 years in 2015. It had narrowed from 8.9 years in 2005. The largest contributors to the life expectancy deficit were external causes of death.

The decrease in overall cancer mortality and productivity losses was mostly attributed to smoking-related cancer types in men. Changes in smoking prevalence were the main reason behind those changes, especially in men (V. Shkolnikov, Churilova, et al. 2020). However, lung cancer mortality in women was relatively low in all the periods, in line with the low smoking prevalence reported in women (V. Shkolnikov, Andreev, et al. 2019).

Finally, despite decreasing mortality ASRs, obesity-related cancer types were becoming a new public health issue due to the growing number of deaths and productivity losses. According to a recent assessment, Russia and the USA were two countries with the most obese residents (Boutari and Mantzoros 2022), so the expected number of obesity-related cancer types will probably continue to grow.

6.3 Limitations

Several limitations of the study are worth mentioning and discussing.

The quality assessment of PBCR data focused on Northwest regions and could only represent part of the country. At least three PBCRs in the Northwest represented Russia in the "Cancer in five continents" volumes (St. Petersburg, Arkhangelsk oblast and the Republic of Karelia). For a long period, St. Petersburg was the only PBCR represented there. One can argue that the quality of PBCRs in Northwest Russia is exceptional compared to all other regions. Without comprehensive data quality assessments in other regions, it is difficult to confirm this statement. Still, recent international studies included data from PBCR outside the Northwest. Chelyabinsk oblast and Samara oblast PBCRs were included in the "Cancer Incidence in Five Continents (CI5)" volume XI (Bray, Colombet, et al. 2017) and Samara oblast, Omsk oblast and Tomsk oblast PBCRs data were included in CONCORD-3 survival analysis (Allemani et al. 2018). This study identified at least two more PBCRs that could be considered good candidates for international studies (Murmansk oblast and Komi oblast), and it seems that the data quality is not the only reason so few registries from Russia are not involved in international research.

Other limitations of the quality assessment are related to the methods applied for analyses. Validity assessment could benefit from re-abstracting and recoding audits that were not part of this study. Our study only partly touched on the problem of staging information validity. However, additional studies are needed to explore the role of changing staging classification in case registration. In addition, the AJCC/UICC staging system is not the only staging classification used for different cancer types (e.g. haematological malignancies and childhood cancers). At the same time, staging information is important for survival analysis as it sometimes helps distinguish between treatment and diagnostics progress.

The lack of independent sources of cancer registrations is an essential limitation for completeness assessment. Pathology laboratories do not provide independent notification, they first report to clinicians, and then pathological information becomes part of the clinical notification. If we check the data sources, the situation in Russia is similar to Bulgarian PBCR. There were zero notifications from pathologists only in Bulgaria (Dimitrova and Parkin 2015). At the same other PBCRs were success-

fully using capture-recapture models with several sources to estimate completeness (Larsen et al. 2009). Independent case ascertainment was used in the completeness assessment in Finland (Leinonen et al. 2017). Comparing the PBCR database with truly independent case sources may provide a less biased assessment of completeness. However, finding and linking such a source to the PBCR database is only sometimes realistic. Large representative population-based cohort studies are probably the best tool to assess the completeness of cancer registration (van der Willik et al. 2020). Unfortunately, cohort studies are rare in Russia. However, our completeness assessment can be complemented by the independent case ascertainment using hospital databases of national medical research cancer centres with a long history of hospital-based registration or regional databases of insurance funds that have recently started collecting claims data.

The death certificate method applied to estimate data completeness requires assumptions. The definition of DCI proportion was based on our assumption about PBCR procedures, which may differ across regions and require additional testing. For example, low DCO in some regions may indicate failures in data linkage with the civil registry.

The national data used in the breast and cervical cancer burden assessment was collected before any quality assessment was performed. The DCO proportion provided in the national report from breast and cervical cancer was between 1-2% in 2007-2013, and the MV proportion was 97% for the same period. It is similar to the estimates obtained in Northwest regions; however, several regions across the country may need more data, like in Leningrad oblast. This limitation supports the conclusion that quality assessment is needed across the country. Fortunately, sudden changes in incidence and mortality rates indicative of changes in registration practices were not observed over the study period.

Mortality correction using proportions from other countries is not the only way to account for the bias in death registration of uterine cancers. Individual-level data studies are preferable, though rarely conducted. Another possible source of underestimation of cervical cancer incidence and mortality is the lack of information about hysterectomies in Russia. In some settings, it may influence the disease and mortality rates (Hammer et al. 2017).

A few additional limitations were also present in the assessment of productivity losses. First, quality issues are relevant to this study as well. Mortality data quality

was discussed in several publications, and it is probably not much worse for cancer mortality than in other countries (Danilova, V. Shkolnikov, et al. 2016). Population size could also be biased, and our study did not consider it. Still, double registrations during the census and under-registration between censuses could influence the population estimates, and there is no clear consensus on the extent of this bias in Russia (Andreev 2012).

Second, there is a rich methodological diversity in calculating productivity and other losses caused by a cancer diagnosis and death. For example, productivity losses estimated through HCA are considerably higher than the alternative friction cost approach. Nevertheless, most studies exploring the societal burden of cancer utilise HCA. At the same time, many other payments and financial losses are not included in productivity losses (e.g. unpaid work for caring for cancer patients, losses due to disability). Individual-level data would help account for all direct and indirect losses from both healthcare and societal perspective. Still, collecting data like this is often impossible outside high-quality, thoroughly planned studies, and this approach is hardly feasible in Russia.

Despite these limitations, the study included analysis of regional individual-level and national data from several sources and applied almost all available methods for PBCR data quality and cancer burden assessment. It is the first study to examine the quality of PBCR data in Russia. In addition, it used the combination of economic and epidemiological data available to estimate cancer burden on a national level. Therefore, the limitations are not likely to considerably influence the findings and conclusions of the study.

6.4 Priorities for cancer control

This study is devoted to cancer burden assessment and the quality of data sources. Still, it is difficult to avoid discussing the cancer control activities implied in any cancer burden measurement (Parkin 2008). Therefore, our study touches on several aspects of cancer control activities when discussing the observed estimates and provides some perspectives on cancer control planning.

Russia signed the WHO's Framework Convention on Tobacco Control in 2008. Studies show the effect of anti-smoking policies on smoking prevalence (V. Shkolnikov, Churilova, et al. 2020). The effect on lung cancer mortality and productivity

losses associated with premature lung cancer deaths was also seen in our study. Still, more studies are needed to assess the effect of smoking on cervical cancer rates in Russia. More recent data showed a decrease in cervical cancer incidence and mortality in Russia not predicted in our study of cervical cancer trends. This decrease could be due to changes in HPV prevalence, diagnostic activities, changes in registration practices or decreasing smoking prevalence in younger generations. In addition, despite seemingly succesful smoking cessation measures, tobacco remains one of the leading preventable causes of cancer deaths in Russia. Changes in tobacco consumption practices can also affect the cancer burden, so continuous monitoring of smoking-related cancer burden is instrumental in tobacco control.

Obesity is another important risk factor for several cancer types and requires additional activities in cancer control planning (Kyrgiou et al. 2017; Rtveladze et al. 2012). Our study provided some evidence of the increase in productivity losses from the oesophagus, liver and pancreas cancer mortality and the increase in breast cancer incidence, cancer types that could be associated with obesity. Some of these cancer types were traditionally associated with alcohol consumption in Russia (Zaridze, Brennan, et al. 2009). More epidemiological studies are warranted to explore the changes in subtypes of those cancers that would indicate changes in risk factors patterns (Lindblad, Rodriguez, and Lagergren 2005).

HPV primary prevention through vaccination is vital in reaching the proposed cervical cancer elimination goal (Singh et al. 2022). Still, HPV vaccination is not included in the national vaccination schedule in Russia. Our study highlights the need for such a step, providing evidence of the growing HPV-related cancer burden (which includes cervical cancer in women and oral and pharynx cancers in both sexes). Unfortunately, the COVID-19 pandemic revealed a grim attitude towards vaccination in Russia, which requires additional studies and efforts to improve vaccine uptake (Lazarus et al. 2023).

Second, cancer screening implemented in several countries changes the patterns of both incidence and mortality trends (Anttila, Sarkeala, et al. 2008; P. Basu et al. 2018). Our study did not provide any results showing the start of population-based screening activities, and none were reported in Russia. The national "dispanserization" programme, launched in 2012, provided some guidance for implementing cancer screening but never expanded beyond opportunistic diagnostic activities that lacked proper uptake and quality control. By contrast, the increase in the incidence

of cancer types for which evidence of effective screening is absent (e.g. thyroid cancer) suggests opportunistic and unorganised early detection activities in some regions (S. Park et al. 2016). The results of our study can support the recommendation against such activities.

Third, access to effective cancer treatment is essential to cancer control planning. The decrease in breast cancer mortality observed from the late 1990s could be attributed to the changes in breast cancer management and the introduction of adjuvant therapy. Without screening programmes, new treatment options should be considered as possible explanations for the reduction in colorectal cancer mortality observed nationally. Therefore, methods for cancer burden monitoring presented in this thesis could help monitor changes in cancer burden related to treatment. Regional cancer survival analyses could provide additional information on treatment effectiveness absent in Russia (Goss et al. 2014). In conclusion, this thesis provides the foundation for future studies that could assist cancer control monitoring and planning.

7 CONCLUSIONS AND RECOMMENDATIONS

7.1 Quality assessment

As a result of this study, the first comprehensive quantitative assessment of the quality of PBCRs from the Russian Federation was completed. The study focused on the data from 10 PBCRs in Northwest Russia, covering a population of approximately 13 million and thus representing the most extensive systematic assessment of the quality of cancer registration in Russia. Considerable heterogeneity was observed for most quality indicators by region, cancer site, and age. Validity indicators varied by region, age and cancer type (haematological malignancies), providing additional insight into deficiencies in cancer diagnostics and registration. Additional studies are needed to explore the sources of these differences, as they could potentially point to problems in cancer diagnostics and care. In terms of comparability, the study provided insight into the possible population-based effects of diagnostic and opportunistic screening activities (mainly skin, breast, and thyroid), that could be further investigated, as some of them may represent an artificial diagnostic epidemic (Miranda-Filho et al. 2021).

Our study showed that completeness was above 90% in most regions (except the two largest regions, St. Petersburg and Leningrad oblast). Compared to other regions, there was also a 10% difference in the number of cases in the PBCR database and the national report for St. Petersburg. These results support the hypothesis that the population size and access to multiple cancer diagnostics and care facilities are the reasons for data collection deficiencies in the regions mentioned above. Approaches to cancer registration implementation cannot be universal across the country. They should probably be differentiated based on the population size and the cancer care system.

Another important conclusion of the study is related to the local instructions for cancer registration, which need to be updated and implemented in line with international standards. This project has already improved some aspects of PBCR data collection in Northwest Russia. However, the translation of ICD-O-3 into Russian was completed only in 2017. Therefore, further implementation of this classification is warranted in future.

The seminal paper on PBCR quality assessment (Bray and Parkin 2009) mentioned an earlier report (Skeet 1991): "registries should be able to quote some objective measure of [ascertainment] rather than relying on received wisdom and pious hope". This thesis points to the importance of a systematic approach to quality assessment in the country, which has a long history of cancer registration. Still, cancer registration remains largely unexplored inside and outside the country. It is unclear whether a similar study for other regions would be possible soon. This thesis did at least take the opportunity to assess the country's most recent developments related to cancer burden assessment.

For cancer control planning, a country does not need PBCR data from the whole country to prepare nationwide estimates. However, a sample representative of the whole country's population can be used for this (Parkin 2008). In some aspects, Russia's PBCR system is similar to the United States, where a successful SEER programme covers only a part of the country's population. At the moment, national cancer burden estimates are calculated using data from all the Russian regions. Nonetheless, one cannot assume similar quality across the highly varied cancer registration practices. While attempts should be made to assess and improve cancer registration in all the regions where it is already functioning, nationwide estimates can be produced using the data from PBCR with reasonable quality. Excluding regions with low data quality will certainly make the cancer burden estimates more accurate. According to our study results, the overall quality of PBCR data in some regions meets international standards. However, differences between the regions of Northwest Russia are substantial. Data of reasonable quality are probably available for other Russian regions. We suggest it is representative of the general population. In that case, these registries can form a basis for cancer estimates in the country, providing more accurate estimates compared to the national report.

Considering some Northwestern regions, cancer registry data from several PBCRs are sufficient for epidemiological research. Unfortunately, only two regions provide

data to international studies; Arkhangelsk oblast and the Republic of Karelia. Data from at least two more regions, Murmansk oblast and the Republic of Komi, could represent the country in international studies.

One of the principles of cancer registration was formulated in the paper covering the work of the Finnish cancer registry: "the better the quality of data of a cancer registry, the better the possibilities for effective use of these data in planning and research. Conversely, the more active and research-oriented the registry, the better the possibilities of maintaining good coverage and accuracy" (Teppo, Pukkala, and Lehtonen 1994). The cancer burden assessment conducted in this study supplemented the assessment for the data sources.

7.2 Cancer burden assessment

This study is the first broad assessment of cancer mortality, incidence, and cancer mortality-related productivity cost patterns in Russia. Trend analysis focused on cervical and breast cancer in this study.

First, the results showed substantial and contrasting changes in breast and cervical cancer trends during the past decades. For cervical cancer, it was an alarming increase in incidence and mortality rates. In contrast, for breast cancer, trends were similar to many European countries: increasing incidence and recent downward mortality trend. The study was the first to include a combined analysis of incidence and mortality trends and incorporate years of life lost and future predictions of the burden.

The increasing trends in cervical cancer incidence and mortality in younger generations should be used for setting priorities for cancer control. There is a clear need for effective screening and prevention (vaccination) programmes in Russia. Unfortunately, population-based cervical screening is not implemented in Russia, despite clear evidence of its effectiveness in other countries (Anttila and Nieminen 2000).

A similar analysis for other cancer types is undoubtedly warranted and feasible in the presence of available data. Another approach to cancer burden assessment should consider the recommendation for pooling reasonably high-quality cancer registry data in these assessments.

The productivity costs of cancer obtained in this study can also be applied to cancer control planning. The cost-effectiveness assessment of different public health interventions should consider the overall cost of cancer deaths in Russia, which was

found to amount to more than $8 billion or 0.24% of GDP in 2011-2015. The productivity cost assessments identified major contributors to these losses (lung and breast cancer) and assessed the rising losses linked to cancers related to human papillomavirus (HPV). The study points to the direction of cancer control activities, including primary prevention (tobacco and HPV control) and population-based cancer screening (cervical, breast and colorectal).

Finally, despite clear regional implications, Russia is not the only country struggling with establishing a high-quality cancer registration system that would be instrumental in cancer control planning and monitoring. This study provides an example of conducting an epidemiological registry-based project in a hostile environment that is not open to research activities. Nevertheless, without such an approach, it is impossible to help people suffering from largely avoidable severe health outcomes related to cancer.

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APPENDIX A COMPLETENESS AND TIMELINESS ESTIMATES BY REGION

Table A.1 Data sources and completeness estimates in Arkhangelsk oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	1,529	2.8	98.2	97.4
Oesophagus	C15	1,391	8.9	99.0	98.0
Stomach	C16	4,806	8.9	97.7	97.1
Colon, rectum, anus	C18-21	6,527	8.4	94.7	94.1
Liver	C22	464	26.3	97.4	110.6
Pancreas	C25	1,702	15.9	98.7	97.7
Larynx	C32	551	4.7	95.6	96.5
Trachea and lung	C33-34	5,796	12.2	98.0	97.4
Bone and cartilages	C40-41	118	5.1	97.6	97.7
Melanoma of skin	C43	986	1.2	95.8	97.7
Skin	C44	5,091	0.4	67.1	77.4
Soft tissues	C45-49	488	6.1	94.4	92.8
Breast	C50	4,623	1.7	90.0	96.2
Cervix uteri	C53	1,441	1.7	94.4	96.8
Corpus uteri	C54-55	1,718	4.7	82.1	89.0
Ovary	C56	1,045	5.7	96.0	96.0
Prostate	C61	2,912	5.4	77.5	84.1
Kidney	C64	2,197	7.6	80.3	85.6
Bladder	C67	1,367	4.7	86.2	90.4
Brain and CNS	C70-72	985	16.1	93.3	92.4
Hodgkins lymphoma	C81	242	4.1	72.5	92.6
Nonhodgkins lymphoma	C82-85	783	6.8	92.6	93.4
Leukaemia	C91-95	952	12.3	90.2	90.9
Other	a)	1,599	9.9	93.1	94.3
Other and ill-defined	b)	2,297	11.5	81.0	87.2
All sites	C00-C96	51,610	7.2	92.1	92.8

DCI - case initially registered based on information from the death certificate.

Table A.2 Data sources and completeness estimates in Kaliningrad oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%) Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	1,009	2.8	98.7	97.9
Oesophagus	C15	408	11.5	98.7	99.0
Stomach	C16	2,444	6.4	98.7	98.7
Colon, rectum, anus	C18-21	4,059	5.0	96.2	96.4
Liver	C22	366	19.1	97.7	109.2
Pancreas	C25	960	10.6	99.2	100.2
Larynx	C32	514	3.5	98.0	98.3
Trachea and lung	C33-34	3,161	7.6	98.8	99.6
Bone and cartilages	C40-41	160	4.4	96.4	97.9
Melanoma of skin	C43	835	0.4	99.2	99.3
Skin	C44	4,647	0.2	87.5	93.7
Soft tissues	C45-49	399	4.8	95.9	95.2
Breast	C50	4,523	0.8	97.2	98.8
Cervix uteri	C53	1,236	1.4	98.2	98.1
Corpus uteri	C54-55	1,465	1.0	96.2	97.6
Ovary	C56	928	3.2	97.9	97.5
Prostate	C61	1,818	1.3	97.8	98.0
Kidney	C64	1,357	3.2	93.4	95.4
Bladder	C67	1,083	1.8	97.5	97.6
Brain and CNS	C70-72	467	10.5	96.1	99.1
Hodgkins lymphoma	C81	256	2.0	91.0	95.6
Nonhodgkins lymphoma	C82-85	578	2.6	96.5	95.6
Leukaemia	C91-95	584	9.4	91.8	98.4
Other	a)	970	4.3	97.1	98.9
Other and ill-defined	b)	1,384	5.6	96.8	99.4
All sites	C00-C96	35,611	3.7	95.7	96.8

DCI - case initially registered based on information from the death certificate.

Table A.3 Data sources and completeness estimates in Leningrad oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	1,650	5.8	87.6	98.4
Oesophagus	C15	872	15.8	91.2	105.4
Stomach	C16	3,695	13.4	88.7	103.3
Colon, rectum, anus	C18-21	6,106	10.6	74.4	98.4
Liver	C22	449	43.4	82.4	150.9
Pancreas	C25	1,279	23.1	92.0	114.4
Larynx	C32	677	6.2	77.8	98.8
Trachea and lung	C33-34	4,000	20.8	89.2	111.3
Bone and cartilages	C40-41	161	11.2	65.4	99.8
Melanoma of skin	C43	1,098	3.5	74.3	94.7
Skin	C44	4,440	0.9	26.2	85.3
Soft tissues	C45-49	455	5.9	77.8	98.4
Breast	C50	6,721	3.3	56.6	95.3
Cervix uteri	C53	1,633	3.1	83.4	97.6
Corpus uteri	C54-55	2,208	5.0	46.1	94.0
Ovary	C56	1,410	5.7	73.6	97.5
Prostate	C61	2,474	7.0	55.9	95.0
Kidney	C64	1,831	7.4	62.5	96.1
Bladder	C67	1,588	4.5	70.4	96.2
Brain and CNS	C70-72	543	25.8	71.4	114.9
Hodgkins lymphoma	C81	243	2.9	47.1	95.7
Nonhodgkins lymphoma	C82-85	635	11.2	58.3	99.7
Leukaemia	C91-95	582	18.6	64.3	107.1
Other	a)	1,451	13.4	66.3	100.1
Other and ill-defined	b)	2,334	5.1	63.2	97.1
All sites	C00-C96	48,535	8.9	70.4	97.9

DCI - case initially registered based on information from the death certificate.

Table A.4 Data sources and completeness estimates in Murmansk oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	938	2.3	98.3	98.1
Oesophagus	C15	545	4.4	98.9	98.7
Stomach	C16	2,198	5.2	97.7	97.3
Colon, rectum, anus	C18-21	3,749	5.1	94.8	95.5
Liver	C22	313	28.1	94.9	100.1
Pancreas	C25	891	15.2	98.1	96.7
Larynx	C32	323	3.4	95.1	96.4
Trachea and lung	C33-34	3,224	7.7	97.0	96.5
Bone and cartilages	C40-41	86	3.5	97.5	97.5
Melanoma of skin	C43	625	1.0	94.8	98.0
Skin	C44	2,380	0.3	64.9	79.0
Soft tissues	C45-49	294	6.5	92.0	93.0
Breast	C50	3,739	0.8	93.6	98.2
Cervix uteri	C53	884	1.5	96.2	97.8
Corpus uteri	C54-55	1,250	1.8	83.3	93.6
Ovary	C56	755	2.9	96.9	97.7
Prostate	C61	1,906	3.0	78.2	89.3
Kidney	C64	1,563	6.4	75.9	82.4
Bladder	C67	708	3.4	92.1	94.2
Brain and CNS	C70-72	438	7.1	96.6	97.3
Hodgkins lymphoma	C81	244	2.9	74.6	93.5
Nonhodgkins lymphoma	C82-85	479	5.6	89.7	92.1
Leukaemia	C91-95	879	5.3	86.4	92.9
Other	a)	911	6.8	93.6	94.9
Other and ill-defined	b)	1,517	4.3	87.4	94.8
All sites	C00-C96	30,839	4.5	92.0	94.3

DCI - case initially registered based on information from the death certificate.

Table A.5 Data sources and completeness estimates in Novgorod oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	861	1.9	98.1	98.2
Oesophagus	C15	577	7.8	98.2	97.7
Stomach	C16	2,575	8.4	96.3	96.5
Colon, rectum, anus	C18-21	3,412	6.8	91.6	93.2
Liver	C22	294	39.5	92.1	115.8
Pancreas	C25	888	20.2	96.9	98.5
Larynx	C32	363	5.0	93.3	96.6
Trachea and lung	C33-34	3,246	11.2	95.9	96.3
Bone and cartilages	C40-41	73	8.2	93.8	99.2
Melanoma of skin	C43	497	2.4	91.5	95.4
Skin	C44	3,351	0.4	54.8	79.2
Soft tissues	C45-49	244	4.5	95.7	96.3
Breast	C50	3,093	1.1	90.3	97.5
Cervix uteri	C53	876	1.3	93.5	96.8
Corpus uteri	C54-55	1,182	2.4	81.6	92.8
Ovary	C56	736	3.4	94.8	96.3
Prostate	C61	1,340	4.0	82.3	91.1
Kidney	C64	1,063	6.2	81.6	88.9
Bladder	C67	897	4.2	78.3	90.0
Brain and CNS	C70-72	417	18.7	87.2	92.7
Hodgkins lymphoma	C81	161	3.7	55.6	83.8
Nonhodgkins lymphoma	C82-85	448	3.8	90.9	94.6
Leukaemia	C91-95	600	6.8	89.2	94.4
Other	a)	883	7.2	91.9	95.7
Other and ill-defined	b)	1,219	5.7	76.3	93.5
All sites	C00-C96	29,296	6.0	88.7	92.9

DCI - case initially registered based on information from the death certificate.

Table A.6 Data sources and completeness estimates in Pskov oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	861	0.8	99.7	99.6
Oesophagus	C15	481	5.8	99.3	98.9
Stomach	C16	2,440	7.0	98.7	99.1
Colon, rectum, anus	C18-21	3,340	5.4	96.2	96.8
Liver	C22	358	24.9	97.4	107.8
Pancreas	C25	887	15.9	98.2	99.8
Larynx	C32	585	3.2	98.9	98.7
Trachea and lung	C33-34	3,214	9.2	98.2	98.7
Bone and cartilages	C40-41	94	1.1	99.4	99.9
Melanoma of skin	C43	477	0.6	98.0	98.9
Skin	C44	4,493	0.1	84.5	95.0
Soft tissues	C45-49	296	4.1	97.1	97.0
Breast	C50	2,990	1.0	95.9	98.6
Cervix uteri	C53	973	0.3	98.8	99.3
Corpus uteri	C54-55	1,292	2.1	87.2	94.9
Ovary	C56	760	2.4	98.1	98.4
Prostate	C61	1,395	2.7	95.1	96.2
Kidney	C64	1,054	4.2	92.1	95.0
Bladder	C67	749	3.9	95.2	97.4
Brain and CNS	C70-72	428	17.5	93.6	98.8
Hodgkins lymphoma	C81	227	4.4	81.5	91.2
Nonhodgkins lymphoma	C82-85	387	4.9	92.2	92.2
Leukaemia	C91-95	481	16.2	81.0	94.0
Other	a)	791	8.1	93.7	97.4
Other and ill-defined	b)	1,091	4.4	95.2	96.7
All sites	C00-C96	30,144	4.7	94.2	95.9

DCI - case initially registered based on information from the death certificate.

Table A.7 Data sources and completeness estimates in the Republic of Karelia, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	838	2.3	98.9	98.0
Oesophagus	C15	661	8.8	99.0	98.8
Stomach	C16	2,463	10.1	97.0	96.6
Colon, rectum, anus	C18-21	3,517	8.7	92.7	93.0
Liver	C22	289	41.5	95.4	114.9
Pancreas	C25	854	17.2	98.6	98.4
Larynx	C32	307	5.9	95.0	97.8
Trachea and lung	C33-34	3,028	13.3	98.1	98.2
Bone and cartilages	C40-41	66	7.6	93.8	100.5
Melanoma of skin	C43	537	1.1	97.8	98.1
Skin	C44	2,315	0.2	87.1	95.4
Soft tissues	C45-49	294	5.8	93.9	92.8
Breast	C50	3,058	1.5	90.7	97.2
Cervix uteri	C53	1,176	1.4	89.6	94.8
Corpus uteri	C54-55	1,066	2.9	83.3	92.1
Ovary	C56	717	6.7	94.8	95.1
Prostate	C61	1,366	2.0	95.2	96.6
Kidney	C64	1,153	3.6	88.2	93.0
Bladder	C67	707	4.5	91.4	95.1
Brain and CNS	C70-72	411	19.0	93.0	95.8
Hodgkins lymphoma	C81	114	8.8	30.7	74.3
Nonhodgkins lymphoma	C82-85	332	6.0	91.1	94.4
Leukaemia	C91-95	514	18.7	86.9	87.9
Other	a)	828	14.4	89.8	94.5
Other and ill-defined	b)	1,252	11.7	86.1	92.8
All sites	C00-C96	27,863	7.4	91.6	93.3

DCI - case initially registered based on information from the death certificate.

Table A.8 Data sources and completeness estimates in the Republic of Komi, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	1,107	5.4	96.7	94.4
Oesophagus	C15	794	11.7	98.5	97.9
Stomach	C16	2,480	11.8	96.3	95.9
Colon, rectum, anus	C18-21	4,002	10.5	91.4	92.4
Liver	C22	419	42.2	94.5	115.3
Pancreas	C25	956	23.3	97.6	96.8
Larynx	C32	400	7.0	92.9	96.4
Trachea and lung	C33-34	3,977	13.9	96.6	95.6
Bone and cartilages	C40-41	86	15.1	82.2	94.6
Melanoma of skin	C43	596	1.8	92.4	96.0
Skin	C44	2,292	0.6	66.5	87.9
Soft tissues	C45-49	375	9.3	86.3	89.8
Breast	C50	3,719	1.9	87.3	95.5
Cervix uteri	C53	1,150	3.5	87.6	93.4
Corpus uteri	C54-55	1,122	5.3	69.8	83.9
Ovary	C56	907	7.4	91.4	92.6
Prostate	C61	1,385	4.6	87.4	91.3
Kidney	C64	1,712	6.2	78.8	86.3
Bladder	C67	907	5.5	86.0	90.4
Brain and CNS	C70-72	526	27.0	83.1	88.2
Hodgkins lymphoma	C81	252	4.8	75.9	87.7
Nonhodgkins lymphoma	C82-85	494	4.7	93.8	92.9
Leukaemia	C91-95	809	13.7	76.8	86.7
Other	a)	947	12.6	88.6	93.9
Other and ill-defined	b)	1,802	8.4	78.5	89.3
All sites	C00-C96	33,216	8.8	88.5	91.0

DCI - case initially registered based on information from the death certificate.

Table A.9 Data sources and completeness estimates in St. Petersburg, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	6,097	12.5	92.6	90.4
Oesophagus	C15	3,221	24.6	95.8	94.6
Stomach	C16	17,175	25.5	91.8	90.9
Colon, rectum, anus	C18-21	34,128	19.5	82.1	82.9
Liver	C22	3,523	50.6	92.3	107.2
Pancreas	C25	9,271	35.0	96.4	96.6
Larynx	C32	2,295	16.3	81.1	85.4
Trachea and lung	C33-34	21,483	28.5	92.0	91.9
Bone and cartilages	C40-41	640	20.9	81.6	90.8
Melanoma of skin	C43	5,384	7.6	79.4	86.5
Skin	C44	18,217	1.6	42.2	56.5
Soft tissues	C45-49	2,332	23.1	82.7	81.9
Breast	C50	28,609	9.2	66.4	85.0
Cervix uteri	C53	5,225	12.3	83.8	85.1
Corpus uteri	C54-55	9,493	11.8	64.8	75.1
Ovary	C56	6,452	18.5	85.6	84.9
Prostate	C61	13,624	11.0	69.1	77.4
Kidney	C64	9,158	17.2	64.4	71.5
Bladder	C67	6,518	14.7	70.6	75.0
Brain and CNS	C70-72	4,467	28.5	86.7	89.6
Hodgkins lymphoma	C81	1,390	8.0	47.7	78.6
Nonhodgkins lymphoma	C82-85	4,804	17.1	69.4	77.3
Leukaemia	C91-95	6,274	19.3	64.0	77.4
Other	a)	8,164	25.9	79.0	85.4
Other and ill-defined	b)	9,866	15.3	48.5	86.1
All sites	C00-C96	237,810	17.7	77.1	82.1

DCI - case initially registered based on information from the death certificate.

Table A.10 Data sources and completeness estimates in Vologda oblast, 2008–2017, by cancer site.

Site	ICD-10	Cases	DCI (%)	Completeness (%)	
				Lincoln-Petersen	Ajiki
Lip, oral, pharynx	C00-14	1,249	3.6	97.8	97.1
Oesophagus	C15	847	9.9	98.8	100.1
Stomach	C16	4,036	14.8	95.8	98.2
Colon, rectum, anus	C18-21	5,461	8.0	93.0	94.9
Liver	C22	464	26.1	97.1	113.9
Pancreas	C25	1,178	23.1	98.9	104.5
Larynx	C32	549	2.9	97.0	97.9
Trachea and lung	C33-34	4,570	14.0	96.9	99.3
Bone and cartilages	C40-41	167	10.2	85.9	98.9
Melanoma of skin	C43	918	2.0	94.4	95.5
Skin	C44	5,540	0.3	83.7	89.8
Soft tissues	C45-49	423	4.7	93.5	95.6
Breast	C50	4,539	3.0	85.4	94.1
Cervix uteri	C53	1,688	1.4	86.1	95.0
Corpus uteri	C54-55	1,656	2.6	77.4	91.9
Ovary	C56	1,170	3.7	93.1	95.5
Prostate	C61	1,851	4.5	90.9	95.0
Kidney	C64	1,745	4.4	92.0	94.0
Bladder	C67	1,258	6.7	90.1	92.9
Brain and CNS	C70-72	681	19.4	88.2	100.5
Hodgkins lymphoma	C81	192	3.1	57.1	92.9
Nonhodgkins lymphoma	C82-85	446	5.6	87.6	97.4
Leukaemia	C91-95	901	8.9	78.0	94.1
Other	a)	1,128	9.1	90.3	100.1
Other and ill-defined	b)	1,838	15.9	85.6	96.7
All sites	C00-C96	44,495	7.7	89.5	94.0

DCI - case initially registered based on information from the death certificate.

Table A.11 Comparison of cancer cases in the registry database and reported the national report in Arkhangelsk oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	1,529	1,458	71	4.6
Oesophagus	C15	1,391	1,374	17	1.2
Stomach	C16	4,806	4,740	66	1.4
Colon, rectum, anus	C18-21	6,527	6,468	59	0.9
Liver	C22	464	666	-202	-43.5
Pancreas	C25	1,702	1,680	22	1.3
Larynx	C32	551	541	10	1.8
Trachea and lung	C33-34	5,796	5,743	53	0.9
Bone and cartilages	C40-41	118	105	13	11.0
Melanoma of skin	C43	986	935	51	5.2
Skin	C44	5,091	5,087	4	0.1
Soft tissues	C45-49	488	267	221	45.3
Breast	C50	4,623	4,668	-45	-1.0
Cervix uteri	C53	1,441	1,404	37	2.6
Ovary	C56	1,045	1,169	-124	-11.9
Prostate	C61	2,912	2,870	42	1.4
Kidney	C64	2,197	2,121	76	3.5
Bladder	C67	1,367	1,337	30	2.2
Brain and CNS	C70-72	985	932	53	5.4
Haematological malignancies	C81-C95	1,977	2,220	-243	-12.3

Table A.12 Comparison of cancer cases in the registry database and reported the national report in Kaliningrad oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	1,009	885	124	12.3
Oesophagus	C15	408	408	0	0.0
Stomach	C16	2,444	2,378	66	2.7
Colon, rectum, anus	C18-21	4,059	3,923	136	3.4
Liver	C22	366	425	-59	-16.1
Pancreas	C25	960	942	18	1.9
Larynx	C32	514	501	13	2.5
Trachea and lung	C33-34	3,161	3,011	150	4.7
Bone and cartilages	C40-41	160	124	36	22.5
Melanoma of skin	C43	835	762	73	8.7
Skin	C44	4,647	4,630	17	0.4
Soft tissues	C45-49	399	221	178	44.6
Breast	C50	4,523	4,379	144	3.2
Cervix uteri	C53	1,236	1,197	39	3.2
Ovary	C56	928	927	1	0.1
Prostate	C61	1,818	1,675	143	7.9
Kidney	C64	1,357	1,234	123	9.1
Bladder	C67	1,083	1,047	36	3.3
Brain and CNS	C70-72	467	420	47	10.1
Haematological malignancies	C81-C95	1,418	1,460	-42	-3.0

Table A.13 Comparison of cancer cases in the registry database and reported the national report in Leningrad oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	1,650	1,883	-233	-14.1
Oesophagus	C15	872	1,106	-234	-26.8
Stomach	C16	3,695	4,728	-1,033	-28.0
Colon, rectum, anus	C18-21	6,106	7,561	-1,455	-23.8
Liver	C22	449	766	-317	-70.6
Pancreas	C25	1,279	1,870	-591	-46.2
Larynx	C32	677	746	-69	-10.2
Trachea and lung	C33-34	4,000	6,186	-2,186	-54.6
Bone and cartilages	C40-41	161	219	-58	-36.0
Melanoma of skin	C43	1,098	1,114	-16	-1.5
Skin	C44	4,440	5,379	-939	-21.1
Soft tissues	C45-49	455	260	195	42.9
Breast	C50	6,721	6,705	16	0.2
Cervix uteri	C53	1,633	1,704	-71	-4.3
Ovary	C56	1,410	1,459	-49	-3.5
Prostate	C61	2,474	3,065	-591	-23.9
Kidney	C64	1,831	2,075	-244	-13.3
Bladder	C67	1,588	1,521	67	4.2
Brain and CNS	C70-72	543	733	-190	-35.0
Haematological malignancies	C81-C95	1,460	1,984	-524	-35.9

Table A.14 Comparison of cancer cases in the registry database and reported the national report in Murmansk oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	938	906	32	3.4
Oesophagus	C15	545	543	2	0.4
Stomach	C16	2,198	2,179	19	0.9
Colon, rectum, anus	C18-21	3,749	3,715	34	0.9
Liver	C22	313	348	-35	-11.2
Pancreas	C25	891	875	16	1.8
Larynx	C32	323	310	13	4.0
Trachea and lung	C33-34	3,224	3,220	4	0.1
Bone and cartilages	C40-41	86	65	21	24.4
Melanoma of skin	C43	625	617	8	1.3
Skin	C44	2,380	2,283	97	4.1
Soft tissues	C45-49	294	196	98	33.3
Breast	C50	3,739	3,737	2	0.1
Cervix uteri	C53	884	872	12	1.4
Ovary	C56	755	740	15	2.0
Prostate	C61	1,906	1,881	25	1.3
Kidney	C64	1,563	1,520	43	2.8
Bladder	C67	708	703	5	0.7
Brain and CNS	C70-72	438	418	20	4.6
Haematological malignancies	C81-C95	1,602	1,817	-215	-13.4

Table A.15 Comparison of cancer cases in the registry database and reported the national report in Novgorod oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	861	833	28	3.3
Oesophagus	C15	577	584	-7	-1.2
Stomach	C16	2,575	2,581	-6	-0.2
Colon, rectum, anus	C18-21	3,412	3,386	26	0.8
Liver	C22	294	322	-28	-9.5
Pancreas	C25	888	908	-20	-2.3
Larynx	C32	363	363	0	0.0
Trachea and lung	C33-34	3,246	3,282	-36	-1.1
Bone and cartilages	C40-41	73	66	7	9.6
Melanoma of skin	C43	497	490	7	1.4
Skin	C44	3,351	3,352	-1	0.0
Soft tissues	C45-49	244	156	88	36.1
Breast	C50	3,093	3,050	43	1.4
Cervix uteri	C53	876	860	16	1.8
Ovary	C56	736	750	-14	-1.9
Prostate	C61	1,340	1,306	34	2.5
Kidney	C64	1,063	1,072	-9	-0.8
Bladder	C67	897	888	9	1.0
Brain and CNS	C70-72	417	397	20	4.8
Haematological malignancies	C81-C95	1,209	1,403	-194	-16.0

Table A.16 Comparison of cancer cases in the registry database and reported the national report in Pskov oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	861	802	59	6.9
Oesophagus	C15	481	463	18	3.7
Stomach	C16	2,440	2,357	83	3.4
Colon, rectum, anus	C18-21	3,340	3,144	196	5.9
Liver	C22	358	411	-53	-14.8
Pancreas	C25	887	867	20	2.3
Larynx	C32	585	581	4	0.7
Trachea and lung	C33-34	3,214	3,066	148	4.6
Bone and cartilages	C40-41	94	118	-24	-25.5
Melanoma of skin	C43	477	457	20	4.2
Skin	C44	4,493	4,451	42	0.9
Soft tissues	C45-49	296	218	78	26.4
Breast	C50	2,990	2,957	33	1.1
Cervix uteri	C53	973	1,070	-97	-10.0
Ovary	C56	760	735	25	3.3
Prostate	C61	1,395	1,323	72	5.2
Kidney	C64	1,054	1,014	40	3.8
Bladder	C67	749	695	54	7.2
Brain and CNS	C70-72	428	406	22	5.1
Haematological malignancies	C81-C95	1,095	1,160	-65	-5.9

Table A.17 Comparison of cancer cases in the registry database and reported the national report in the Republic of Karelia, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	838	830	8	1.0
Oesophagus	C15	661	649	12	1.8
Stomach	C16	2,463	2,437	26	1.1
Colon, rectum, anus	C18-21	3,517	3,413	104	3.0
Liver	C22	289	302	-13	-4.5
Pancreas	C25	854	847	7	0.8
Larynx	C32	307	300	7	2.3
Trachea and lung	C33-34	3,028	2,961	67	2.2
Bone and cartilages	C40-41	66	60	6	9.1
Melanoma of skin	C43	537	501	36	6.7
Skin	C44	2,315	2,278	37	1.6
Soft tissues	C45-49	294	185	109	37.1
Breast	C50	3,058	3,004	54	1.8
Cervix uteri	C53	1,176	1,122	54	4.6
Ovary	C56	717	711	6	0.8
Prostate	C61	1,366	1,314	52	3.8
Kidney	C64	1,153	1,104	49	4.2
Bladder	C67	707	684	23	3.3
Brain and CNS	C70-72	411	384	27	6.6
Haematological malignancies	C81-C95	960	1,003	-43	-4.5

Table A.18 Comparison of cancer cases in the registry database and reported the national report in the Republic of Komi, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	1,107	977	130	11.7
Oesophagus	C15	794	780	14	1.8
Stomach	C16	2,480	2,427	53	2.1
Colon, rectum, anus	C18-21	4,002	3,810	192	4.8
Liver	C22	419	537	-118	-28.2
Pancreas	C25	956	930	26	2.7
Larynx	C32	400	378	22	5.5
Trachea and lung	C33-34	3,977	3,855	122	3.1
Bone and cartilages	C40-41	86	70	16	18.6
Melanoma of skin	C43	596	545	51	8.6
Skin	C44	2,292	2,026	266	11.6
Soft tissues	C45-49	375	234	141	37.6
Breast	C50	3,719	3,539	180	4.8
Cervix uteri	C53	1,150	1,092	58	5.0
Ovary	C56	907	869	38	4.2
Prostate	C61	1,385	1,313	72	5.2
Kidney	C64	1,712	1,618	94	5.5
Bladder	C67	907	854	53	5.8
Brain and CNS	C70-72	526	511	15	2.9
Haematological malignancies	C81-C95	1,555	1,637	-82	-5.3

Table A.19 Comparison of cancer cases in the registry database and reported the national report in the St. Petersburg, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	6,097	5,303	794	13.0
Oesophagus	C15	3,221	2,956	265	8.2
Stomach	C16	17,175	15,524	1,651	9.6
Colon, rectum, anus	C18-21	34,128	30,974	3,154	9.2
Liver	C22	3,523	3,255	268	7.6
Pancreas	C25	9,271	8,262	1,009	10.9
Larynx	C32	2,295	2,061	234	10.2
Trachea and lung	C33-34	21,483	19,149	2,334	10.9
Bone and cartilages	C40-41	640	556	84	13.1
Melanoma of skin	C43	5,384	4,838	546	10.1
Skin	C44	18,217	17,148	1,069	5.9
Soft tissues	C45-49	2,332	1,136	1,196	51.3
Breast	C50	28,609	25,640	2,969	10.4
Cervix uteri	C53	5,225	4,722	503	9.6
Ovary	C56	6,452	6,124	328	5.1
Prostate	C61	13,624	11,753	1,871	13.7
Kidney	C64	9,158	8,216	942	10.3
Bladder	C67	6,518	5,846	672	10.3
Brain and CNS	C70-72	4,467	3,988	479	10.7
Haematological malignancies	C81-C95	12,468	12,814	-346	-2.8

Table A.20 Comparison of cancer cases in the registry database and reported the national report in Vologda oblast, 2008–2017, by cancer site.

Cancer site	ICD-10	Cases		Difference	
		Registry	National report	Absolute	Relative (%)
Lip, oral, pharynx	C00-14	1,249	1,199	50	4.0
Oesophagus	C15	847	800	47	5.5
Stomach	C16	4,036	3,813	223	5.5
Colon, rectum, anus	C18-21	5,461	5,217	244	4.5
Liver	C22	464	495	-31	-6.7
Pancreas	C25	1,178	1,114	64	5.4
Larynx	C32	549	527	22	4.0
Trachea and lung	C33-34	4,570	4,337	233	5.1
Bone and cartilages	C40-41	167	172	-5	-3.0
Melanoma of skin	C43	918	823	95	10.3
Skin	C44	5,540	5,525	15	0.3
Soft tissues	C45-49	423	315	108	25.5
Breast	C50	4,539	4,318	221	4.9
Cervix uteri	C53	1,688	1,582	106	6.3
Ovary	C56	1,170	1,111	59	5.0
Prostate	C61	1,851	1,893	-42	-2.3
Kidney	C64	1,745	1,641	104	6.0
Bladder	C67	1,258	1,193	65	5.2
Brain and CNS	C70-72	681	597	84	12.3
Haematological malignancies	C81-C95	1,539	2,146	-607	-39.4

PUBLICATIONS

PUBLICATION
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ORIGINAL ARTICLE

Comparability and validity of cancer registry data in the northwest of Russia

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ABSTRACT

Background: Despite the elaborate history of statistical reporting in the USSR, Russia established modern population-based cancer registries (PBCR) only in the 1990s. The quality of PBCRs data has not been thoroughly analyzed. This study aims at assessing the comparability and validity of cancer statistics in regions of the Northwestern Federal District (NWFD) of Russia.

Material and methods: Data from ten Russian regional PBCRs covering ~13 million (~5 million in St. Petersburg) were processed in line with IARC/IACR and ENCR recommendations. We extracted and analyzed all registered cases but focused on cases diagnosed between 2008 and 2017. For comparability and validity assessment, we applied established qualitative and quantitative methods.

Results: Data collection in NWFD is in line with international standards. Distributions of diagnosis dates revealed higher variation in several regions, but overall, distributions are relatively uniform. The proportion of multiple primaries between 2008 and 2017 ranged from 6.7% in Vologda Oblast to 12.4% in Saint-Petersburg. We observed substantial regional heterogeneity for most indicators of validity. In 2013–2017, proportions of morphologically verified cases ranged between 61.7 and 89%. Death certificates only (DCO) cases proportion was in the range of 1–14% for all regions, except for Saint-Petersburg (up to 23%). The proportion of cases with a primary site unknown was between 1 and 3%. Certain cancer types (e.g., pancreas, liver, hematological malignancies, and CNS tumors) and cancers in older age groups showed lower validity.

Conclusion: While the overall level of comparability and validity of PBCRs data of four out of ten regions of NWFD of Russia meets the international standards, differences between the regions are substantial. The local instructions for cancer registration need to be updated and implemented. The data validity assessment also reflects pitfalls in the quality of diagnosis of certain cancer types and patient groups.

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KEYWORDS
Cancer registry; data quality; comparability; validity; northwest of Russia

Background

In Russia, the national cancer surveillance system relies on a network of regional population-based cancer registries (PBCRs) that register all *in situ* and malignant neoplasms [1]. Despite the long history of statistical reports in the Soviet Union, automated individual-level data collection by PBCRs did not start until the early 1990s. Russia introduced definitions for Regional and National Cancer Registries in 1996, and the most recent international description of cancer registration in Russia was given in 1998 [2,3]. At least two former USSR countries (Estonia and Ukraine) have published reports on the quality of cancer registration since 1998 [4,5]. Despite substantial advances through national legislative acts introduced in 1996 and 1999, information on cancer registration practices and data quality in the Russian Federation has not been systematically compiled and published until only recently [6].

For cancer registration procedures and practices to be nationally and internationally comparable, PBCRs should follow well-defined international recommendations and standards, but in reality, they vary [7]. The quality of data from PBCRs is traditionally assessed with reference to four standard dimensions: comparability, validity, completeness, and timeliness [8,9]. Qualitative, semi-quantitative, and quantitative methods can be applied to individual-level databases to assess quality indicators and gauge data quality.

Our report focuses on data from PBCRs in the Northwestern Federal District (NWFD) of Russia, which encompasses eleven regions with a population of around 13 million (~9.5% of the country's total population). The Ministry of Healthcare tasked three national cancer centers

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Supplemental data for this article can be accessed here.

to implement and monitor cancer control policies across the country in 2018. The National Research Medical Center of Oncology, named after N. N. Petrov (NRMCO), located in Saint-Petersburg, was responsible for assessing and improving the cancer surveillance system in the NWFD. The present report focuses on the data comparability and validity of PBCRs in the region.

Material and methods

Instructions for cancer registration and classifications are provided in The Order by the Ministry of Health of Russia #135 issued in 1999 [1]. In Russia, the cancer registration system can be formally described as passive and exhaustive, with paper-based notification forms used to report cases. PBCRs collect personal information, tumor characteristics, information about the treatment type, and follow-up data. All data are stored in the electronic databases of regional PBCRs, usually part of regional cancer hospitals – 'dispensaries'. PBCRs regularly perform linkage with the death certificates available in regional civil registries.

According to Order #135, PBCRs use adapted ICD-10 (similar to 5-digit ICD-10-CM (Clinical Modification) to code topography, ICD-O-2 for morphology, and the 5th AJCC/UICC TNM classification for staging. The exact version TNM of classification is not available from the registry database. A detailed description of the history and current status of cancer registration is available in a recently published report [6].

In our analyses, we use data from ten PBCRs databases of eleven regions of the NWFD (the Arkhangelsk Oblast (including the Nenets Autonomous Okrug), the Murmansk Oblast, the Republic of Komi, the Republic of Karelia, the Pskov Oblast, the Kaliningrad Oblast, the Leningrad Oblast, the Novgorod Oblast, the Vologda Oblast, Saint-Petersburg) extracted in December 2019 (Figure 1).

Data

We extracted data for all cases of malignant neoplasms (C00-C96 codes in ICD-10) and selected variables according to the essential variables list recommendations for PBCRs [7]. We performed the multistep conversion and cleaning procedure using 'IARC/IACR Tools for Cancer Registries' software (IARC tools). We assigned ICD-O-3 codes to all registered cases and applied IARC/IACR/ENCR multiple primary rules to delete duplicates [10]. Data processing is summarized in Figure 2. Cases diagnosed between 2008 and 2017 were selected for primary analysis (576,705 cases).

Age-standardized rates (ASRs) per 100,000 (Segi-Doll world standard [11]) were calculated for cancer incidence and mortality using mid-year population estimates by region, cause, sex, and five-year age groups from the Russian Fertility and Mortality Database (the RFMD) [12].

In tables similar to IARC 'Cancer Incidence in Five Continents' (CI5) volumes, we summarized the number of cases, deaths, rates, and the basic quality indicators for two periods (2008–2012 and 2013–2017): the proportion of morphologically verified cases (MV%), the proportion of cases registered with information available from death certificates only (DCO%), and the mortality to incidence ratio (M:I). We compared estimates with 12 East European cancer registries from CI5 volume X (2003–2007): [Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia] using recommended statistical tests. An overdispersion parameter, corresponding to excess variation between registries, is added to models – Poisson for rates and binomial for DCO% and MV% The regional dynamics is assumed to be homogeneous. Then rates and proportions were flagged as unusual based on test statistics if rates were greater than three times or <0.3 times of the value in the comparison population [13]. Detailed tables for individual regions are provided in Supplementary Material.

We produced plots to preliminary assess overall cancer (C00–C96) incidence ASRs per 100,000 per calendar year (Figure S1). Additional plots were produced for incidence ASRs of hematological malignancies (Figure S2). The rates in the Leningrad Oblast dropped dramatically in 2012–2014, suggesting problems with acquiring complete data from that period. Mortality to incidence ratios is also suggesting the lack of completeness in the Leningrad oblast. The Republic of Komi is the only region with data available from 1991, while Vologda Oblast started cancer registration only around 2005–2006. PBCR in Vologda Oblast has also begun data collection for hematological malignancies later (in 2012) than for solid tumors (in 2006).

Comparability

We evaluated the definitions used for incidence dates, handling multiple primary tumors, and incidental diagnosis (screening and autopsy diagnosis) [8]. We analyzed the distribution of incidence dates, temporal changes in stage-specific ASRs and reported autopsy proportions along with DCO percentage to explore patterns in the incidental diagnoses. We adjusted autopsy and DCO proportions among patients who died using logistic models with age, region, cancer type, and period as covariates.

Validity

To assess validity, we applied diagnostic criteria methods, missing information, and internal consistency checks. Along with MV% and DCO%, we reported the proportions of missing or uncertain information for different variables in the database. We also reported cases with primary site unknown (PSU%) – unknown primary site (C80), malignant neoplasms of ill-defined organs of the digestive system (C26), malignant neoplasms of ill-defined organs of the respiratory system (C39), peritoneal and retroperitoneal neoplasms (C48) and Other and ill-defined sites (C76). We assessed the proportions of cases with summary stage unknown (SU%), missing TNM coding, and non-specific morphology codes [10]. We used regression analysis using logistic models to obtain the adjusted effects of covariates (age, gender, region, and period) on the reported data quality indicators. We also

Figure 1. Map of the Northwestern Federal District of Russia with bordering regions and countries and corresponding population as of 1 January 2019. Nenets Autonomous Okrug is an autonomous region of Arkhangelsk Oblast with a population of ~44,000 people included in the Arkhangelsk oblast population.

assessed ASRs for major cancer types based on initial ICD-10 coding and reverse conversion based on ICD-O-3 coding performed with IARC tools software to detect any systematic deviations [10].

For our report, we aggregated all cancer sites in groups to match national mortality statistics (Table S1).

Results

Comparability

Only one date of diagnosis for each cancer case was available from the registry database. The distribution of diagnosis dates across the year revealed higher variation in several regions (Figure S3). Peaks and uneven distribution in Arkhangelsk oblast, Republic of Komi, Vologda oblast, and Leningrad Oblast are observed, but overall, distributions are relatively uniform.

The proportion of multiple primaries between 2008 and 2017 ranged from 6.7% in Vologda Oblast to 12.4% in Saint-Petersburg (Figure 2). After applying IARC/IACR/ENCR multiple primaries rules, we found only minor systematic over-reporting of breast cancer incidence in most regions (Figure S4).

Breast cancer incidence ASRs demonstrated a consistent increase in all the regions of the NWFD, primarily due to a rise in localized stage lesions (Figure 3). A similar but more extreme increase in localized stage thyroid cancer rates was evident (Figure S5). The recent increase in prostate cancer rates in most regions appeared attributable to both localized and advanced-stage tumors (Figure S6).

The proportion of deaths with reported autopsies varied between the regions and periods from $<$10% in Kaliningrad and Novgorod oblast to more than 60% in Arkhangelsk oblast in 2017. Autopsy status predicted DCO diagnosis among deceased patients regardless of cancer type, region, age, and period (Figure S7).

Validity

The proportions of MV and DCO cases along with incidence and mortality ASRs and M:I ratios are summarized in Table 1

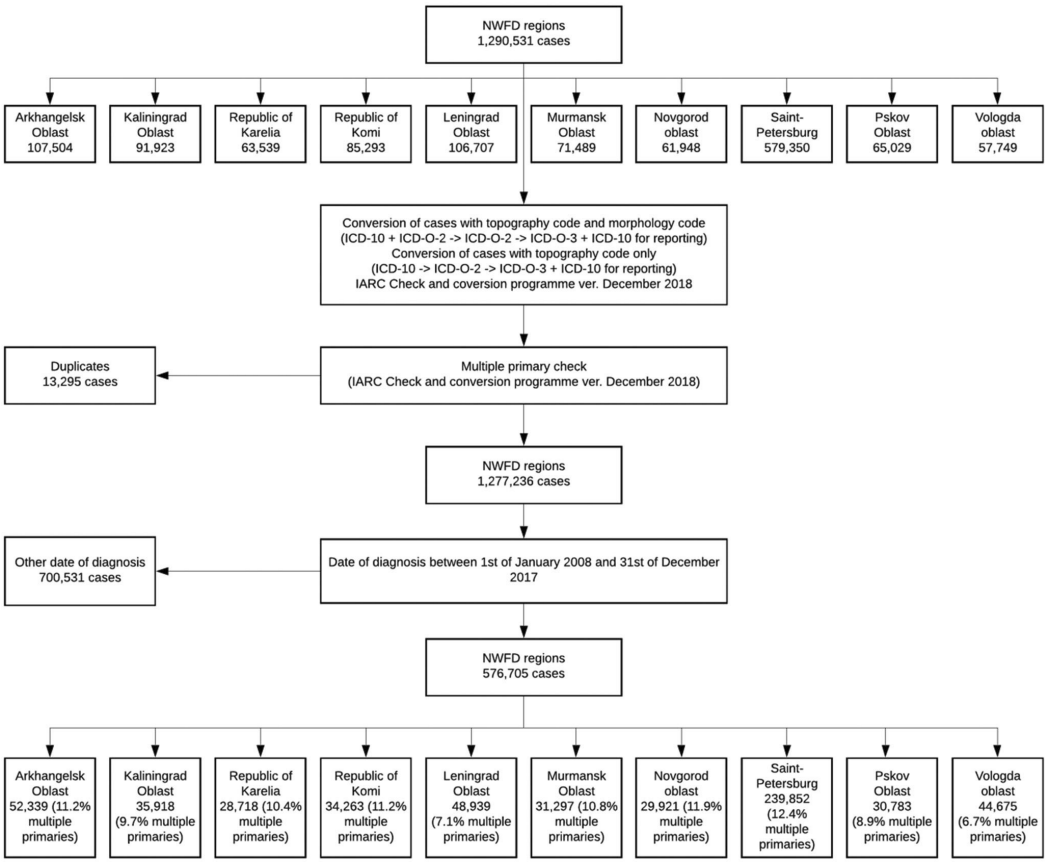

Figure 2. Processing of the cancer registry data.

and by cancer type in Tables S2–S21. DCO% was in the range of 1–14% for all regions, except for Saint-Petersburg where DCO% was high in both men and women in both periods and for all cancer types. Liver, CNS, and pancreas cancer cases were most frequently registered based on death certificates only. As a result of high DCO%, Saint-Petersburg exhibited the lowest MV%. MV% was also relatively low in Novgorod Oblast and Leningrad Oblast. Pskov and Vologda oblast PBCRs registered an unusually high proportion of cases with cytological confirmation of diagnosis (43 and 35%, respectively) (Figure S8). Proportions of cases with the cytological diagnosis were below 15% in all other regions and were common only for skin cancer and leukemia. Hematological malignancies, pancreas, lung, liver, and CNS tumors were commonly registered without morphological verification in all the regions of NWFD. Additionally, older age (particularly 60+) was an independent predictive factor for DCO and the absence of MV (Figure S9).

The proportion of cases with a PSU was between 1 and 3%. Age was the independent factor for a higher proportion of cases with the PSU. The relationship was not linear with higher adjusted proportions in very young (0–4 age group – 8.1%) and older age groups (85+ age group – 4.3%) (Figure S10).

The proportions of cases with missing and non-specific morphology codes decreased over the analyzed period but remain high in some regions (e.g., Saint-Petersburg, Leningrad, and Kaliningrad oblast). In Novgorod Oblast, most of the cases registered in 2016 and 2017 still had missing morphology codes. In Vologda oblast, the proportion of cases with non-specific morphology was around 20%. Missing morphological codes were common in the following cancer groups: liver (58%), pancreas (56%), CNS (41%), lung (36%), non-specific codes were most common in other and ill-defined tumors (28%), Non-Hodgkin's lymphoma (28%), leukemia (14%), and lung (11%) (Figure S11).

The lowest proportion of cases with information on tumor stage was in Leningrad Oblast (<60%). The proportion of cases with missing information on stage varies by cancer type (Figure 4). N stage category information was more often missing than T or M stage in most cancer types in all regions of the NWFD. Age younger than 20 or older than 60 was associated with a higher proportion of missing values (Figure S12).

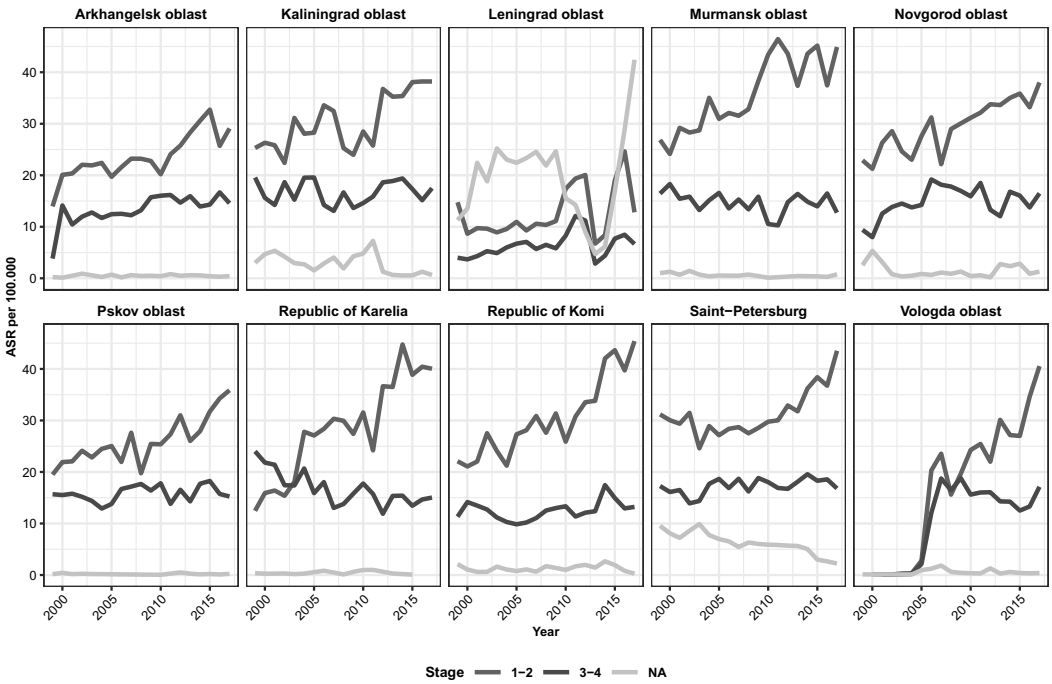

Figure 3. Breast cancer incidence ASRs per 100,000 by stage [localized (1–2) and advanced (3–4) stage], regions of the NWFD, 1999–2017.

Table 1. Comparison of incidence and mortality rates (ASRs), the proportion of morphological verification (MV%), proportion of cases registered with information from death certificates only (DCO%), and mortality to incidence (M:I) ratios, regions of the NWFD of Russia, 2008–2012 and 2013–2017, all sites except for non-melanoma skin cancer (C00-96 excl. C44).

	2008–2012									2013–2017								
	Incidence			Mortality			Quality indicators			Incidence			Mortality			Quality indicators		
Region	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV (%)	DCO (%)	M:I ratio
Men																		
Arkhangelsk oblast	11,421	200.3	2.1	6057	93.9	1.4	83.9	7.5	0.53	13,304	231.9	2.2	6326	91.8	1.3	89.0	7.0	0.48
Kaliningrad oblast	8103	190.6	2.3	4524	94.6	1.6	71.4	1.0	0.55	9241	202.1	2.3	4803	92.6	1.5	82.2	1.8	0.52
Leningrad oblast	12,947	159.7	1.6	9103	90.6	1.1	**66.6***	4.1	0.70	12,875	**148.3***	1.5	10,044	88.2	1.0	77.5	6.6	0.78
Murmansk oblast	7487	224.1	2.8	3320	94.4	1.7	90.2	1.5	0.44	8362	245.7	2.9	3459	92.5	1.7	92.1	4.4	0.41
Novgorod oblast	7034	223.0	3.1	3259	87.4	1.8	84.8	4.8	0.46	7424	229.8	3.1	3063	77.9	1.6	**61.7***	5.9	0.41
Pskov oblast	6709	210.4	2.0	3794	91.8	1.7	79.4	2.5	0.57	7415	217.5	2.9	3671	88.1	1.7	85.2	5.7	0.50
Republic of Karelia	7102	242.9	3.2	3431	96.4	1.8	77.9	1.5	0.48	7550	247.6	3.2	3533	93.9	1.8	85.5	3.5	0.47
Republic of Komi	7710	216.2	2.6	3704	95.5	1.7	76.7	1.5	0.48	9681	263.4	2.9	3956	95.4	1.6	81.4	6.0	0.41
Saint-Petersburg	59,082	219.5	1.0	34,146	108.5	0.7	**66.0***	**20.5†**	0.58	69,873	247.1	1.1	35,816	105.5	0.7	**71.9***	**14.7†**	0.51
Vologda oblast	9512	173.4	2.0	5778	86.5	1.3	75.6	4.6	0.61	11,436	207.9	2.2	5659	84.6	1.3	80.8	9.1	0.50
Women																		
Arkhangelsk oblast	10,684	299.7	3.1	7059	198.3	2.5	80.7	8.8	0.66	11,839	314.7	3.0	7389	194.9	2.34	86.8	8.4	0.62
Kaliningrad oblast	6570	237.1	3.1	4778	171.0	2.6	66.2	1.9	0.73	7357	239.2	2.9	5126	165.5	2.37	77.1	2.4	0.70
Leningrad oblast	9863	177.7	1.9	9970	177.2	1.9	57.2	6.5	1.01	8813	**143.0***	1.6	10,708	169.5	1.70	68.6	9.6	1.22
Murmansk oblast	6023	315.5	4.5	3481	182.3	3.4	86.6	2.4	0.58	7045	349.5	4.4	3638	180.6	3.20	90.2	7	0.52
Novgorod oblast	5833	283.9	3.9	3911	188.7	3.2	78.1	7.3	0.67	6276	297.3	3.9	3589	167.8	2.90	56.4	8.2	0.57
Pskov oblast	5743	252.2	3.5	4646	200.5	3.1	66.7	4.0	0.81	6423	279.2	3.6	4411	188.3	2.94	79.8	8.4	0.69
Republic of Karelia	5664	300.6	4.2	4054	214.3	3.6	65.1	2.9	0.72	6087	304.8	4.1	4065	202.0	3.29	78.4	5.2	0.67
Republic of Komi	6426	285.7	3.9	4522	207.6	3.4	68.4	2.1	0.70	8154	345.7	4.1	4896	212.5	3.24	73.8	8.8	0.60
Saint-Petersburg	42,848	270.6	1.4	28,913	179.8	1.1	**61.9***	**23.1†**	0.68	49,832	285.4	1.3	30,170	167.6	1.01	**67.1***	**17.2†**	0.61
Vologda oblast	8376	227.7	2.6	7180	193.9	2.4	72.3	6.3	0.86	9810	258.2	2.7	7076	183.7	2.27	73.2	13.8	0.72

Lower (*) or higher (†) results are marked in bold when compared with that from 12 cancer registries in CI5X 2003–2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia. All statistical tests are described in Cancer Incidence in Five Continents Volume VIII [13]. Tests are performed for incidence ASRs, MV(%), and DCO(%).

The number of cases reported for different primary sites (ICD-10 groups) in the original databases was similar to those reported after the conversion and cleaning. The proportion of misclassified primary sites overall was 0.6% – it was highest in the Republic of Komi in 2008–2012, at 1.6%, and lowest in Saint-Petersburg in the same period, at 0.2%. The IARC

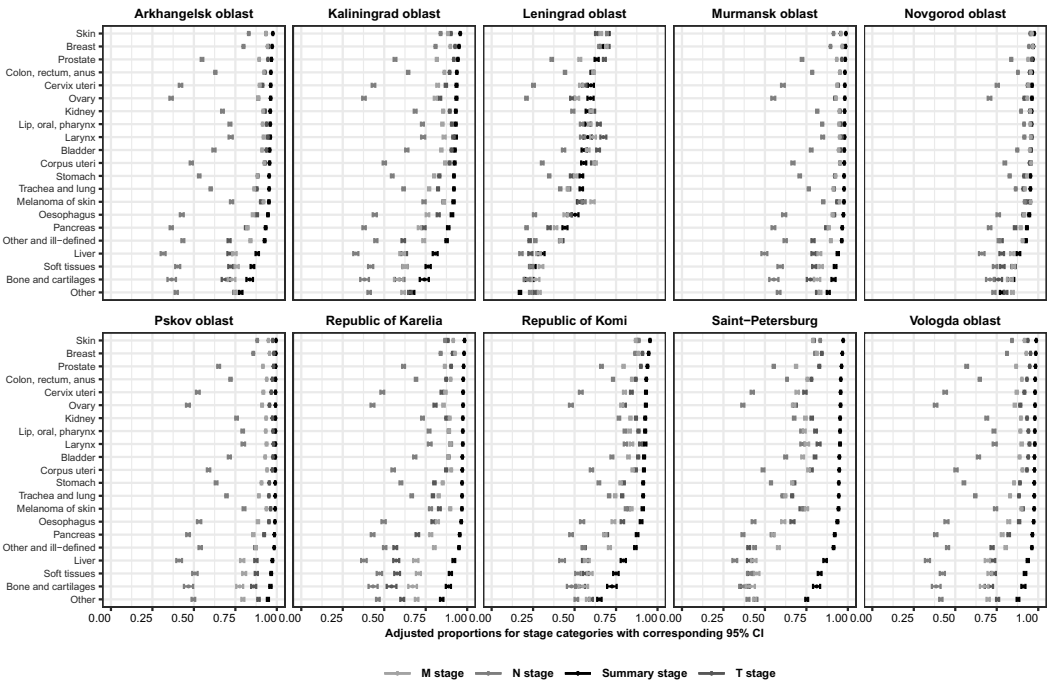

Figure 4. Estimated proportions for the presence of UICC/AJCC stage categories with corresponding 95% CI values by cancer type and regions of the Northwestern Federal District, 2008–2017 (hematological malignancies, lymphomas, CNS tumors, and DCO cases excluded).

tools revealed 31,196 warnings for 29,583 individual records of the total of 576,705 cases (5.1%) registered in 2008–2017. The majority of the warnings were related to grade/histology, the basis of diagnosis/histology, and histology/site combinations (12,749; 13,294; and 4,180 warnings, respectively) with the highest rates for hematological malignancies.

Discussion

This study is the first comprehensive quantitative assessment of the comparability and validity of ten PBCRs from the Russian Federation. Thus, it represents the largest and most systematic assessment of the quality of cancer registration in Russia. We observed notable heterogeneity for most quality indicators by region, cancer site, and age. Older age and hematological malignancies were associated with lower data validity. We also observed the effects of diagnostic and screening activities on cancer incidence (mainly skin, breast, and thyroid), which should be considered when comparing cancer burdens in different populations. Our findings are in line with previous quality assessments of other Eastern European PBCRs [5,14].

Comparability

The findings highlight the differences between national and international recommendations that can lead to apparent problems with comparability. Even though PBCRs in Russia use a combination of modified ICD-10 and ICD-O-2 morphology, the apparent differences from ASRs reported using ICD-O-3 were seen only in liver cancer and some rare cancers (mesothelioma, thymus, endocrine cancers). This issue was most apparent for sites, where metastases are common, and diagnosis is challenging (e.g., liver, pancreas, lung, endocrine tumors, and mesothelioma) [15].

The analysis of diagnosis dates revealed certain dates assigned more frequently than expected, which may reflect a practice of entering a standard date for cases where the date or month is missing. We revealed quite reasonable proportions of multiple primaries (from 6.7 to 12.4%). These findings were similar to other cancer registries [16–18].

Analysis of stage-specific incidence ASRs of breast, cervical, prostate, and thyroid cancer indicates that changes in diagnostic practice and early detection programs may significantly affect the trends in the regions, making a comparison across years difficult [19,20]. Russia started nationwide opportunistic screening in 2012, and regional healthcare officials were responsible for implementing this program. The range of free diagnostic procedures offered to target age groups included but was not limited to mammography, PSA, fecal occult blood test, cervical cytology. Besides that, thyroid exams and ultrasound became available and easily accessible to a healthy population.

Autopsy practices appear to be different across the regions, which may have an impact on comparability. An autopsy followed more than 60% of deaths in the Arkhangelsk Oblast PBCR. However, this proportion was not

more than 30% in Novgorod Oblast, which is still materially higher than in most other parts of Europe [21]. The proportion of DCO cases increased with the number of autopsies in the Republic of Karelia, suggesting that at least some DCO diagnoses could be latent cases revealed only at autopsy. Autopsy proportions did not vary greatly across different cancer types, but DCO diagnoses were more common among cases with an autopsy. Audits are needed to explore further and explain the role of autopsy practices [22].

Validity

The proportions of DCO cases in Saint-Petersburg and Leningrad Oblast were larger than expected for high-quality cancer registration. The reasons are not clear and require further analysis. MV and DCO proportions in other regional PBCRs were similar to the corresponding estimates for Eastern European countries in the CI5-X [23]. However, MV proportions are usually higher in high-quality Western European PBCRs [14].

Age at diagnosis was a significant independent predictor of the quality of cancer registration. The quality of cancer registration is partially linked to the quality of cancer diagnosis and cancer care. A study based on Dutch cancer registry data showed that cancer registries are more likely to miss older patients' information [24]. Although we did not include completeness assessment in this report, higher DCO proportions in older age groups may indicate a lack of completeness. Still, misclassification of diagnosis and stage might become an issue as well. This finding is also essential for cancer control programs in light of population aging and the growing number of older patients.

PSU proportions were below 3%, which is comparable to some Southern and Eastern European countries [14]. Our analysis suggests a quite encouraging decline in the proportion of cases with missing morphological code in the most recent period. The lowest proportions of missing and nonspecific codes were in the Murmansk Oblast and the Republic of Komi. The proportion of hematological malignancies with missing morphological codes is surprisingly high in the registries of NWFD, especially for Leukemia and Non-Hodgkin's lymphoma. This pattern reflects the lack of communication between PBCRs and facilities responsible for managing hematological malignancy outside regional cancer networks.

PBCRs collect information on the clinical stage providing greater research opportunities, but this data quality is also crucial. Overall, the N stage category was more likely to be missing than T and M categories. This pattern may reflect not only registration but also diagnostic issues. Soft tissue, bone, and cartilage tumors represent the greatest challenge for diagnosis and staging; similar findings on stage completeness were observed in the Mallorca cancer registry [25].

The IARC check analysis showed that training in coding needs a particular focus on hematological malignancies that are being treated outside the oncology centers.

Limitations

This PBCRs data quality assessment focused on the comparability and validity of the data. The analysis of completeness and timeliness should supplement it. The validity of PBCR data needs to be further analyzed using re-abstracting and recoding audits, as some issues in cancer registration cannot be detected in the database analysis. Quality of staging information also requires an additional in-depth quality audit. AJCC/UICC staging system may not be relevant for certain cancer types (especially hematological malignancies and cancers in children).

Arkhangelsk Oblast and the Republic of Karelia PBCRs are included in the latest CI5 Volume XI [26]. According to our analysis, at least two more PBCRs (Murmansk Oblast and the Republic of Komi) have data quality meriting inclusion in CI5 at the moment, and other regions can be considered future candidates. A similar analysis of PBCRs across all the regions could help identify more registries with reasonable data quality.

Conclusions

While the overall level of comparability and validity of PBCRs data in some but not all regions of NWFD of Russia fulfills the international PBCR standards, differences between the regions of the NWFD of Russia are substantial. Probably, cancer registry data of a quality sufficient for surveillance and cancer research are also available for other Russian regions. However, the local instructions for cancer registration need to be updated and implemented in line with international standards, and a similar quality assessment process should be started for each PBCR in the whole of Russia. After completion of data quality analyses and implementation of any recommendations that may arise in updated guidelines and registration practices, PBCRs could then be more reliably used to guide and monitor cancer control activities. The validity of data from PBCRs may also reflect pitfalls in the quality of diagnosis and treatment, in particular for certain cancer types (e.g., hematological malignancies and CNS tumors) and older patients.

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Ethical approval

This research is a part of a collaborative effort of the NRMCO in Saint-Petersburg, Russia, Tampere University, Tampere, Finland, and the International Agency for Research on Cancer, Lyon, France. All data

analysis was performed in NN Petrov National Research Medical Center of Oncology. In Russia ethical review is not required for registry-based research. According to the Russian national regulation (The Order of the Ministry of Health #420 12/23/96), anonymized cancer registry data from the NWFD are collected and maintained in NRMCO for various purposes, including epidemiological analyses and international cooperation.

Author contributions

ABa conceived and designed the study. ABa, RT, ABe, and YK acquired the data. ABa, RT, and JN analyzed the data. ABa, AAn, AAu, NM, AR, and AZ drafted the manuscript. All authors critically reviewed, edited, and approved the manuscript.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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Supplementary material

Comparability and validity of cancer registry data in the Northwest of Russia

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Figures

Tables

Figures

Figure S1. Age-standardized cancer incidence rates per 100,000 for regions of the Northwestern Federal District (all cases with behavior code = 3 including non-melanoma skin cancer, world standard population Segi-Doll, 1960).

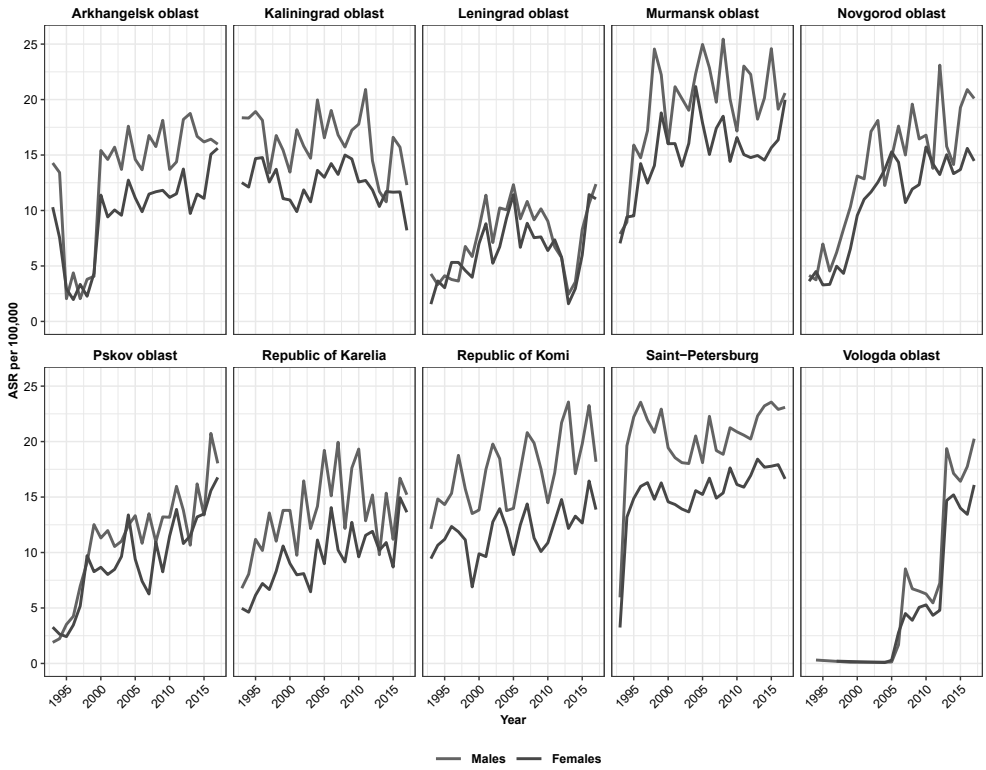

Figure S2. Age-standardized incidence rates per 100,000 for hematological malignancies (C81-C96), regions of the Northwestern Federal District (world standard population Segi-Doll, 1960).

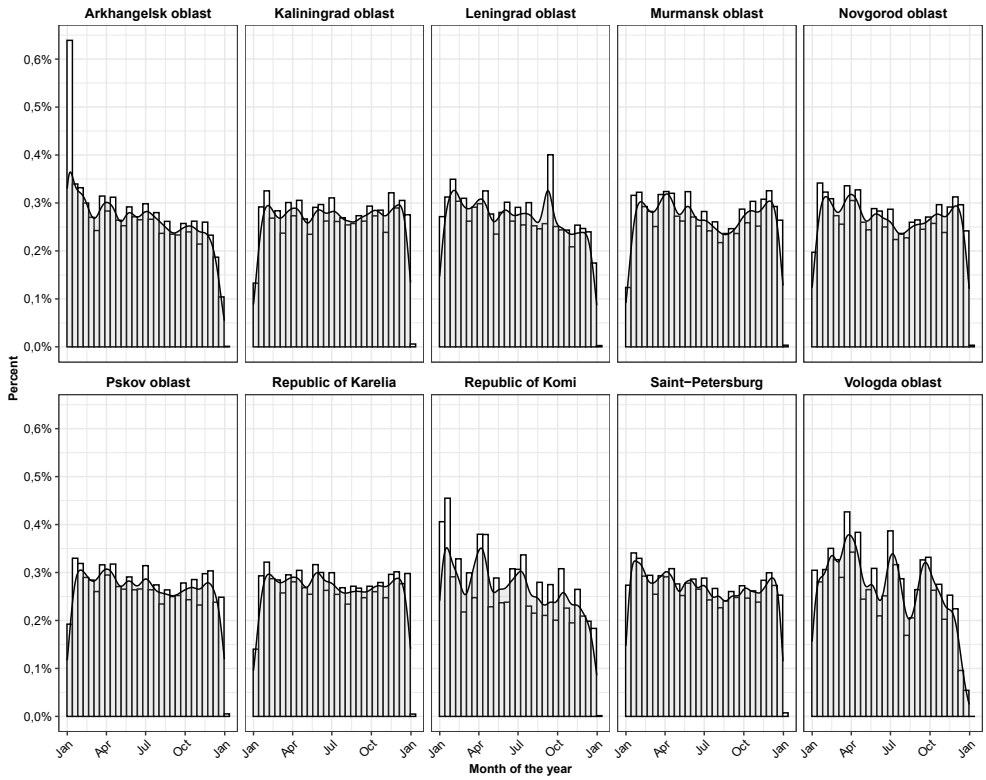

Figure S3. Distribution of dates of diagnosis across the calendar, regions of the NWFD, 2008-2017 (smooth curve refers to probability density functions fitted to data).

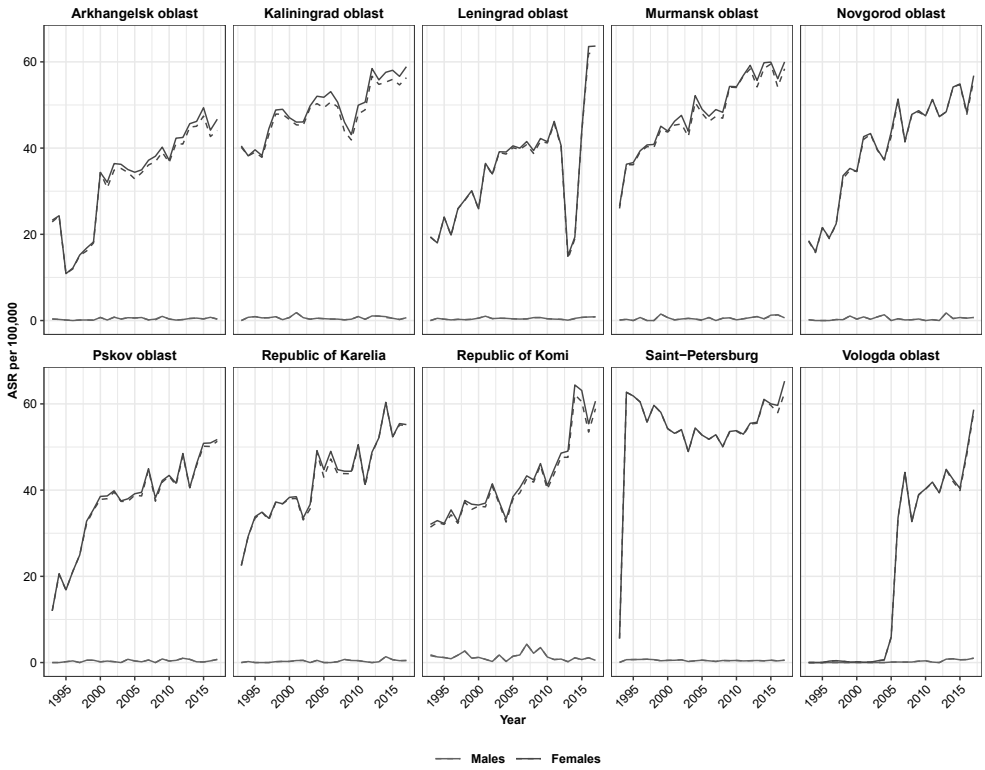

Figure S4. Breast cancer incidence ASRs per 100,000, before (solid line) and after (dashed line), IARC multiple primary check, regions of the NWFD, 1993-2017.

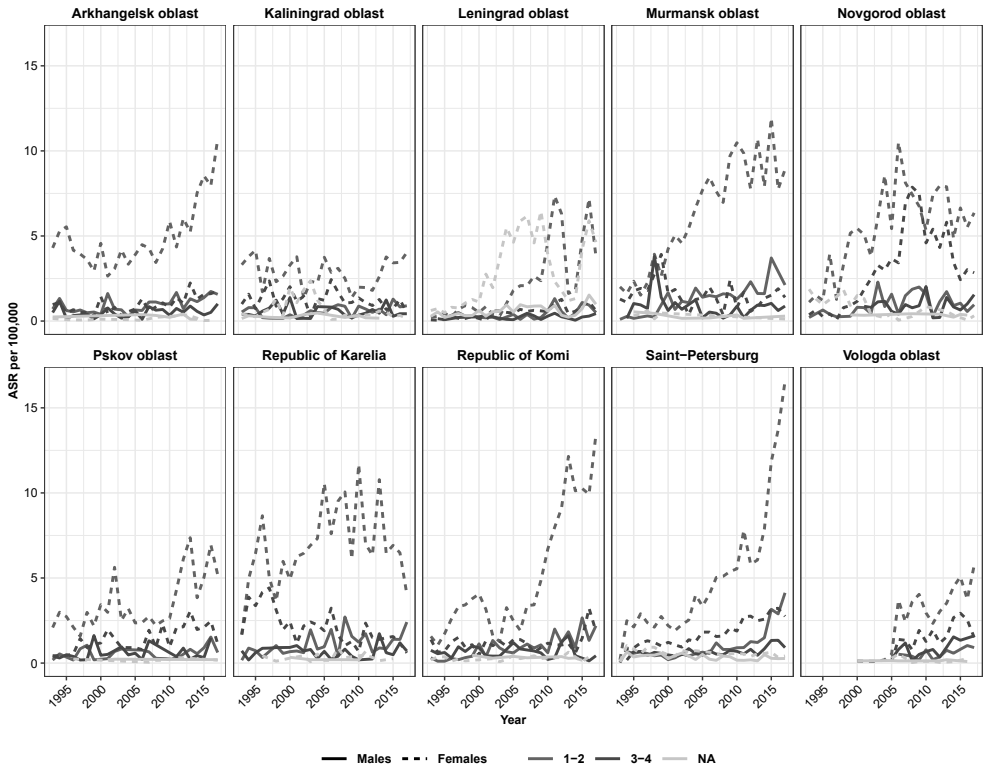

Figure S5. Thyroid cancer incidence ASRs per 100,000 by stage (stage 1-2 and stage 3-4 combined), sex and region of the Northwestern Federal District, 1993-2017.

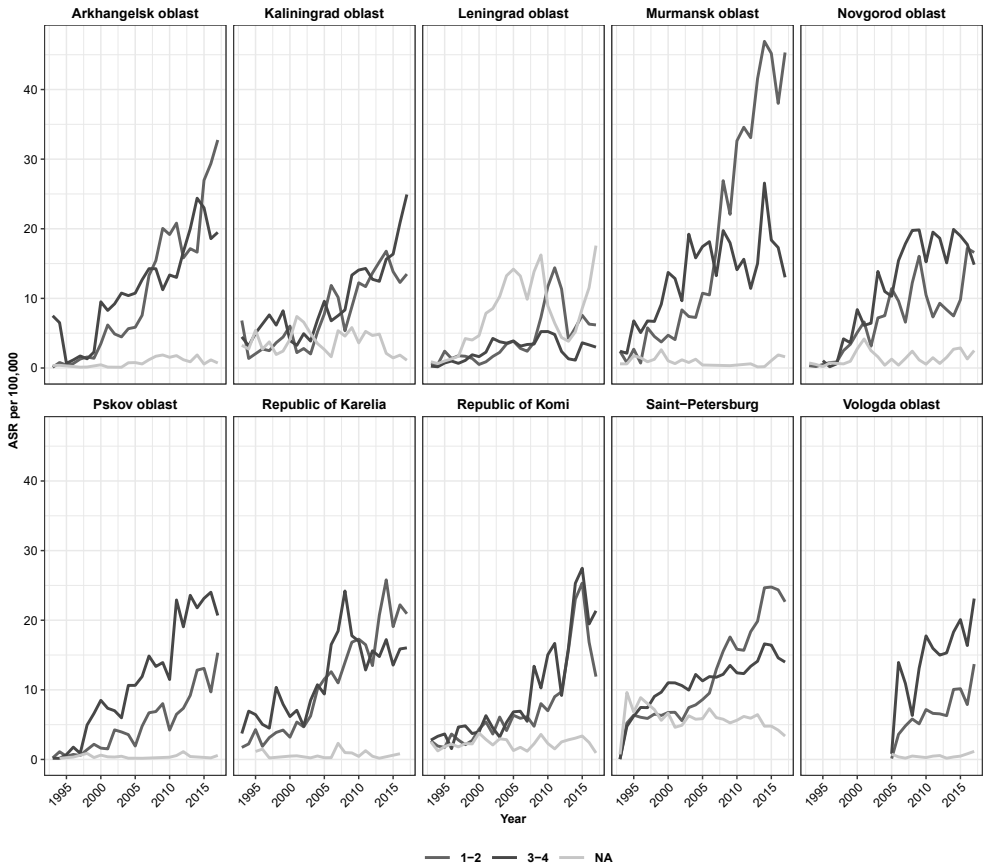

Figure S6. Prostate cancer incidence ASRs per 100,000 by stage (stage 1-2 and stage 3-4 combined), regions of the NWFD, 1993-2017.

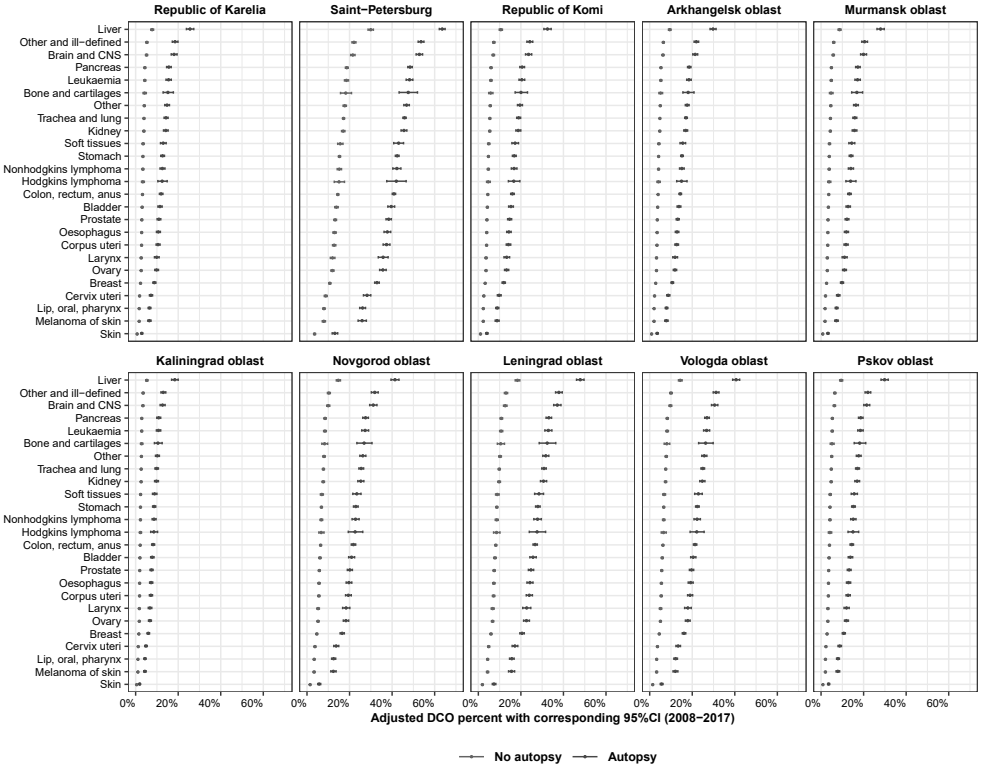

Figure S7. Adjusted estimated percent of DCO (deaths registered with information from death certificate only) by autopsy status, regions of the NWFD, 2008-2017.

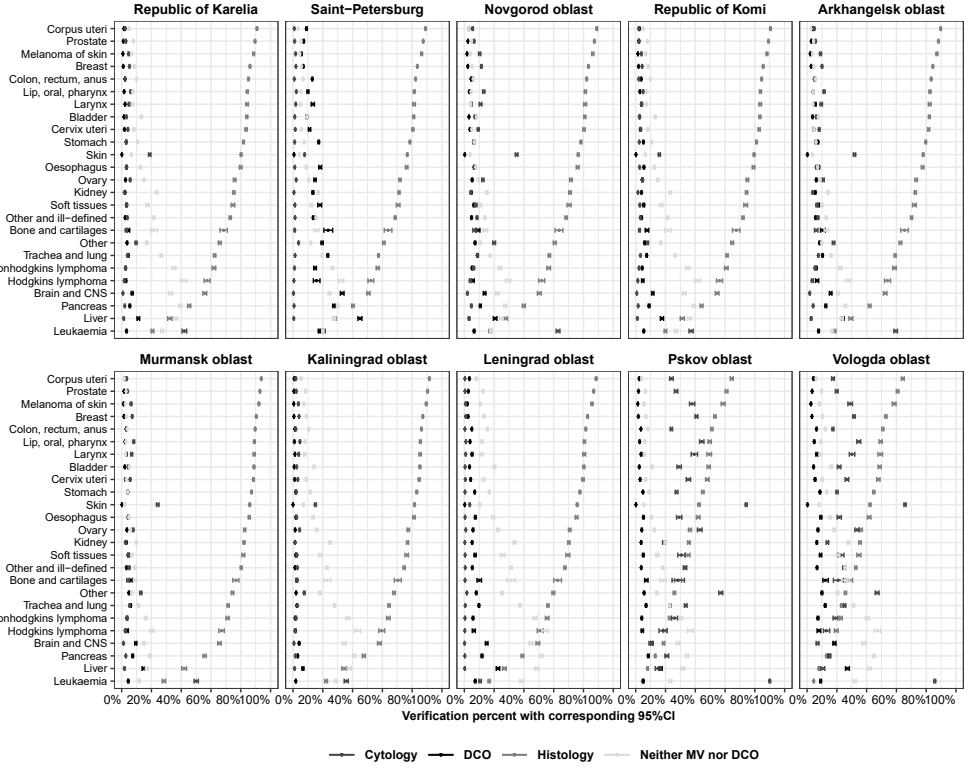

Figure S8. Observed verification percent with corresponding 95%CI sorted by histological verification by cancer type and region of the Northwestern Federal District, 2008-2017.

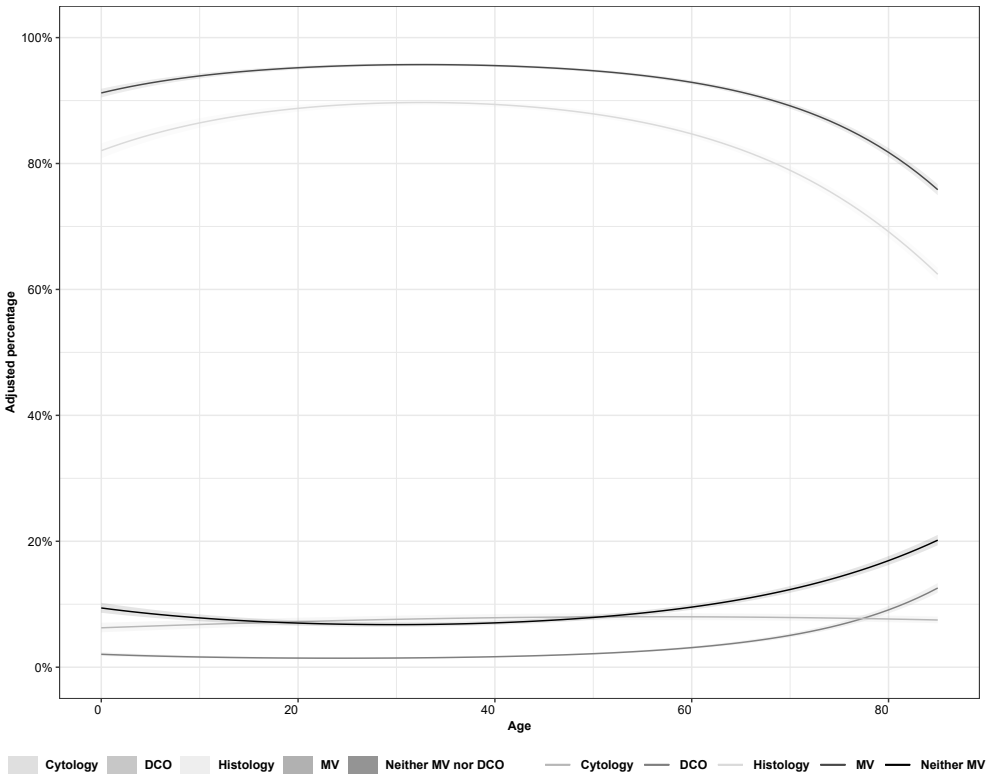

Figure S9. Adjusted (gender, cancer type, region) effect of age on percentage of verification groups, with corresponding 95% CI, regions of the NWFD, 2008-2017.

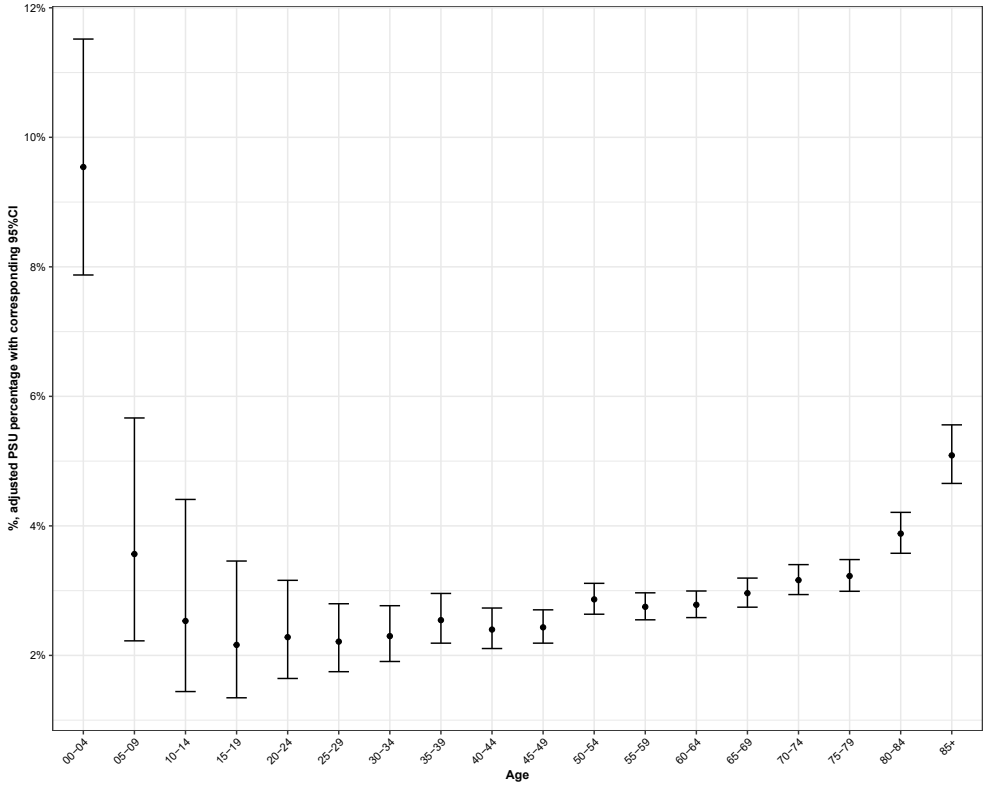

Figure S10. Adjusted (gender, region) effect of age on PSU (primary site unknown) percentage with corresponding 95%CI, regions of the NWFD, 2008-2017.

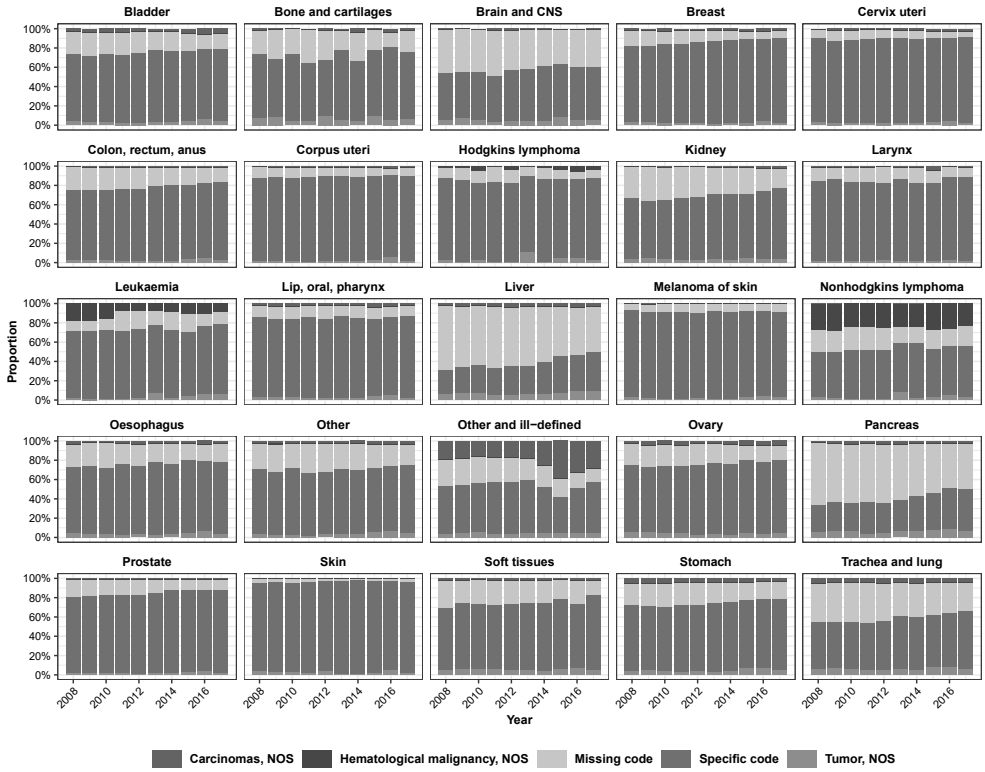

Figure S11. Adjusted (age, gender, period, region) proportion of non-specific and missing codes, regions of the NWFD, 2008-2017.

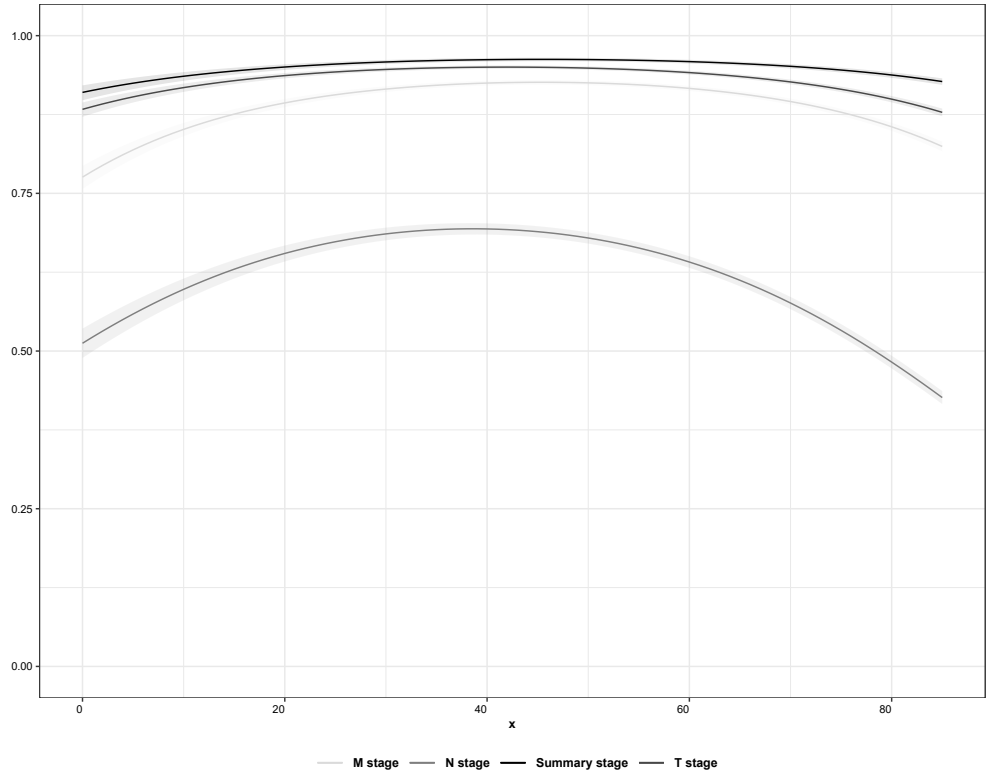

Figure S12. Adjusted (gender, cancer type, region) effect of age on the presence of UICC/AJCC stage categories with corresponding 95% CI, regions of the NWFD, 2008-2017 (hematological malignancies, CNS tumors and DCO cases excluded).

Tables

Table S1. Cancer site labels (short list to match national mortality statistics).

ICD-10	Site label
C00-14	Lip, oral and pharynx
C15	Oesophagus
C16	Stomach
C18-21	Colorectal
C22	Liver
C25	Pancreas
C32	Larynx
C33-34	Trachea, bronchus, and lung
C40-41	Bone and cartilages
C43	Melanoma of skin
C44	Skin (non-melanoma)
C50	Breast
C45-49	Soft tissues
C53	Cervix uteri
C54-55	Corpus uteri, Uterus, parts unspecified
C56	Ovary
C61	Prostate
C64	Kidney
C67	Bladder
C70-72	Brain, central nervous system
C81	Hodgkin lymphoma
C82-85	Non-Hodgkin lymphoma
C91-95	Leukaemia
C69, C73-80, C88, C96	Other and ill-defined
C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90	Other
C00-C96	All sites
C00-C96 without C44	All sites but non-melanoma skin

Table S2. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Arkhangelsk oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	189	3.1	0.24	75	1.2	0.15	**87.3** >	1.1	0.40	207	3.4	0.27	97	1.4	0.16	**97.6** >	3.4	0.47
Oesophagus	C15	211	**2.8** >	**0.22**	158	2.0	0.18	79.6	10.4	0.75	203	**2.8** >	**0.21**	162	2.0	0.18	**90.6** >	12.8	0.80
Stomach	C16	1125	16.3	0.54	868	12.1	0.46	84.2	10.4	0.77	1063	14.4	0.49	766	9.9	0.40	91.1	10.8	0.72
Colon, rectum, anus	C18-21	1718	25.5	0.67	1098	15.1	0.50	83.5	10.7	0.64	2029	29.1	0.71	1196	15.2	0.48	89	8.3	0.59
Liver	C22	115	1.7	0.18	170	2.7	0.26	47.8	32.2	1.48	88	1.3	0.17	132	1.7	0.17	62.5	25	1.50
Pancreas	C25	399	5.7	0.31	364	5.3	0.30	56.9	18.8	0.91	496	6.9	0.34	434	5.8	0.31	63.1	13.3	0.88
Larynx	C32	18	0.4	0.1	8	0.1	0.05	83.3	5.6	0.44	26	0.5	0.1	11	0.2	0.05	100	0	0.42
Trachea and lung	C33-34	427	6.6	0.34	343	5.0	0.29	60.9	14.5	0.80	548	8.4	0.38	410	5.9	0.32	75.4	14.8	0.75
Bone and cartilages	C40-41	32	0.6	0.13	23	0.5	0.12	68.8	6.2	0.72	30	0.7	0.15	14	0.3	0.08	86.7	3.3	0.47
Melanoma of skin	C43	298	5.9	0.37	98	1.7	0.19	99	0	0.33	375	7.4	0.41	99	1.6	0.18	99.5	0.8	0.26
Skin	C44	1437	22	0.64	32	0.5	0.09	98.5	0.4	0.02	1921	27.5	0.69	27	0.3	0.07	99.3	0.6	0.01
Soft tissues	C45-49	152	3	0.29	65	1.4	0.22	80.9	3.9	0.43	121	2.5	0.28	71	1.4	0.22	90.9	**6.6** >	0.59
Breast	C50	2124	39	0.9	723	12.3	0.49	94.1	1.6	0.34	2469	44.8	0.97	740	11.7	0.47	97	1.8	0.30
Cervix uteri	C53	681	15.5	0.62	232	4.7	0.33	97.1	2.3	0.34	760	18.2	0.69	262	5.5	0.36	97.8	1.1	0.34
Corpus uteri	C54-55	766	13.6	0.52	245	3.7	0.25	96.3	5.5	0.32	952	16.4	0.56	288	4.3	0.27	96.2	4.2	0.30
Ovary	C56	489	9.2	0.44	298	5.4	0.34	81.6	6.3	0.61	556	10.6	0.49	334	5.5	0.33	89.9	5.2	0.60
Kidney	C64	454	7.9	0.41	154	2.2	0.19	67	7	0.34	612	9.9	0.44	178	2.3	0.18	78.4	8.5	0.29
Bladder	C67	164	2.5	0.22	65	0.8	0.11	89	7.9	0.40	186	2.7	0.22	58	0.7	0.10	93.5	6.5	0.31
Brain and CNS	C70-72	265	5.6	0.4	172	3.3	0.29	66.4	16.2	0.65	285	5.8	0.41	203	3.8	0.30	63.9	17.2	0.71
Hodgkins lymphoma	C81	57	1.7	0.24	23	0.5	0.12	**78.9** <	3.5	0.40	59	1.6	0.25	18	0.3	0.08	**79.7** <	**5.1** >	0.31
Nonhodgkins lymphoma	C82-85	182	3.2	0.26	93	1.5	0.17	**64.8** <	6	0.51	235	4.3	0.31	96	1.5	0.17	**76.6** <	6.4	0.41
Leukaemia	C91-95	244	5.3	0.42	154	2.8	0.27	82.4	12.7	0.63	240	5	0.4	149	2.6	0.25	83.8	13.3	0.62
Other	a)	420	6.5	0.35	314	4.5	0.28	86.7	10.7	0.75	483	7.2	0.37	307	4.1	0.26	85.9	12.4	0.64
Other and ill-defined	b)	891	18.7	0.68	312	5.2	0.35	81.1	5.6	0.35	1281	27.9	0.86	301	4.1	0.26	88.6	6.8	0.23
All sites	C00-C96	12858	222.3	2.16	6089	94.3	1.36	85.6	6.7	0.47	15225	259.4	2.34	6353	92.1	1.29	90.3	6.2	0.42
All sites but non-melanoma skin	C00-C96 (without C44)	11421	200.3	2.06	6057	93.9	1.35	83.9	7.5	0.53	13304	231.9	2.24	6326	91.8	1.29	89	7	0.48

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.
All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).
[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96
[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S3. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Kaliningrad oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	113	2.6	0.26	64	1.3	0.19	87.6	0	0.57	156	3.5	0.3	78	1.7	0.20	**90.4** >	0.6	0.50
Oesophagus	C15	42	0.9	0.15	36	0.7	0.12	71.4	0	0.86	39	0.7	0.13	42	0.8	0.14	71.8	2.6	1.08
Stomach	C16	543	10.4	0.49	469	8.7	0.44	73.8	1.8	0.86	526	9.6	0.46	433	7.7	0.41	78.1	2.5	0.82
Colon, rectum, anus	C18-21	1074	21.8	0.72	645	12.0	0.52	70.5	1.3	0.60	1212	22.6	0.7	702	11.7	0.48	79.9	1.8	0.58
Liver	C22	80	1.6	0.21	124	2.5	0.24	16.2	6.2	1.55	94	1.6	0.18	152	2.7	0.25	25.5	22.3	1.62
Pancreas	C25	220	4.3	0.32	219	4.3	0.32	17.7	3.2	1.00	279	4.9	0.33	269	4.5	0.30	34.1	3.6	0.96
Larynx	C32	19	0.5	0.12	7	0.2	0.07	94.7	0	0.37	19	0.5	0.11	12	0.2	0.08	84.2	5.3	0.63
Trachea and lung	C33-34	294	6.2	0.39	295	5.6	0.36	45.2	3.4	1.00	359	7	0.4	281	5.2	0.33	64.1	5.3	0.78
Bone and cartilages	C40-41	38	1.5	0.29	25	0.7	0.17	73.7	0	0.66	38	1.2	0.25	23	0.8	0.20	81.6	5.3	0.61
Melanoma of skin	C43	223	5.1	0.37	74	1.5	0.19	91.9	0	0.33	314	7.1	0.44	78	1.6	0.20	**76.1** <	0.3	0.25
Skin	C44	1264	24.7	0.76	45	0.8	0.14	98.7	0	0.04	1578	27.7	0.77	31	0.5	0.09	98.2	0.1	0.02
Soft tissues	C45-49	103	2.4	0.3	40	1.0	0.18	70.9	1.9	0.39	92	2.5	0.32	67	1.7	0.27	71.7	1.1	0.73
Breast	C50	2009	47.9	1.13	923	19.7	0.69	**77.1** <	0.2	0.46	2478	55.3	1.18	850	16.7	0.62	94.5	0.5	0.34
Cervix uteri	C53	618	17.4	0.73	244	6.1	0.41	91.3	0.6	0.39	618	16.3	0.69	274	6.7	0.43	93.9	0.8	0.44
Corpus uteri	C54-55	649	15.2	0.63	228	5.0	0.35	95.2	0.5	0.35	816	17.1	0.63	196	3.6	0.28	96.2	0.7	0.24
Ovary	C56	459	12.1	0.59	277	6.4	0.41	**66.7** <	0.4	0.60	469	10.9	0.54	254	5.5	0.37	76.5	1.3	0.54
Kidney	C64	292	7.2	0.48	106	2.2	0.25	72.3	0	0.36	294	6.3	0.41	110	2.0	0.20	60.9	2	0.37
Bladder	C67	125	2.4	0.23	56	1.0	0.14	68	2.4	0.45	117	2.1	0.21	36	0.6	0.11	70.9	2.6	0.31
Brain and CNS	C70-72	124	3.9	0.4	89	2.6	0.30	64.5	3.2	0.72	117	3.3	0.35	120	3.2	0.34	74.4	8.5	1.03
Hodgkins lymphoma	C81	81	3	0.35	19	0.5	0.13	**43.2** <	2.5	0.23	68	3	0.4	18	0.5	0.12	**69.1** <	0	0.26
Nonhodgkins lymphoma	C82-85	153	4	0.36	50	1.3	0.19	**69.3** <	0	0.33	137	3.2	0.32	54	1.1	0.16	80.3	0.7	0.39
Leukaemia	C91-95	173	4.7	0.44	111	2.9	0.33	26	2.9	0.64	109	3.2	0.38	145	3.0	0.29	87.2	7.3	1.33
Other	a)	255	5.4	0.38	185	3.3	0.27	61.6	0.8	0.73	275	5.6	0.38	229	4.1	0.29	80.7	2.5	0.83
Other and ill-defined	b)	416	9.9	0.53	239	5.0	0.37	56.2	1.2	0.57	615	14.4	0.65	380	6.9	0.39	74.3	2.1	0.62
All sites	C00-C96	9367	215.3	2.43	4569	95.4	1.56	75.1	0.9	0.49	10819	229.9	2.43	4834	93.1	1.48	84.5	1.6	0.45
All sites but non-melanoma skin	C00-C96 (without C44)	8103	190.6	2.31	4524	94.6	1.55	71.4	1	0.56	9241	202.1	2.31	4803	92.6	1.48	82.2	1.8	0.52

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S4. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Republic of Karelia, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	104	3	0.32	39	1.2	0.20	86.5	1	0.38	153	4.7	0.41	71	2.2	0.28	**94.1** >	1.3	0.46
Oesophagus	C15	108	**2.6** >	**0.27**	99	2.3	0.25	71.3	0.9	0.92	107	**2.5** >	**0.26**	87	2.1	0.24	78.5	2.8	0.81
Stomach	C16	562	15.4	0.71	422	11.3	0.60	72.4	2	0.75	505	13.2	0.67	388	9.4	0.55	82.8	5.7	0.77
Colon, rectum, anus	C18-21	956	26.2	0.93	553	13.6	0.64	71	2.5	0.58	1020	26.3	0.9	559	12.8	0.60	83.1	4.7	0.55
Liver	C22	51	1.5	0.22	60	1.6	0.23	43.1	9.8	1.18	67	1.7	0.24	86	2.3	0.27	34.3	37.3	1.28
Pancreas	C25	228	6.2	0.45	210	5.7	0.44	25.4	3.5	0.92	222	5.7	0.42	202	5.1	0.39	56.8	10.8	0.91
Larynx	C32	12	0.4	0.11	8	0.2	0.07	75	0	0.67	14	0.5	0.13	12	0.4	0.13	100	0	0.86
Trachea and lung	C33-34	227	6.6	0.48	185	5.0	0.41	48.5	4.8	0.81	257	7.2	0.49	214	5.8	0.43	67.3	10.9	0.83
Bone and cartilages	C40-41	10	0.4	0.16	12	0.4	0.12	60	0	1.20	15	0.7	0.2	11	0.4	0.12	93.3	6.7	0.73
Melanoma of skin	C43	159	5.4	0.46	50	1.6	0.25	96.2	0	0.31	174	5.6	0.48	68	2.1	0.28	96	0	0.39
Skin	C44	520	13.6	0.67	32	0.8	0.16	94.4	0.4	0.06	956	24	0.86	21	0.4	0.10	98.8	0	0.02
Soft tissues	C45-49	89	3.3	0.42	36	1.3	0.29	86.5	3.4	0.40	93	2.8	0.35	48	1.9	0.35	86	6.5	0.52
Breast	C50	1349	45.5	1.31	519	15.6	0.74	91.3	0.5	0.38	1690	54.9	1.43	537	14.8	0.69	94.7	0.4	0.32
Cervix uteri	C53	659	30.1	1.22	124	4.6	0.44	94.8	0.2	0.19	517	23.7	1.11	135	5.0	0.46	97.5	0.8	0.26
Corpus uteri	C54-55	469	16	0.78	137	4.1	0.37	94.7	0.9	0.29	597	18.9	0.82	156	4.2	0.37	96.1	2	0.26
Ovary	C56	383	13.1	0.73	217	6.6	0.49	77.3	0.8	0.57	334	11	0.66	210	6.1	0.45	85.3	3.6	0.63
Kidney	C64	272	9	0.64	91	2.2	0.26	69.5	0.7	0.33	297	9.1	0.59	79	2.0	0.25	80.5	1.7	0.27
Bladder	C67	75	2	0.26	27	0.6	0.13	64	0	0.36	93	2.3	0.26	46	1.0	0.16	83.9	4.3	0.49
Brain and CNS	C70-72	115	5.2	0.56	87	3.5	0.44	53.9	2.6	0.76	91	3.1	0.39	95	3.0	0.33	61.5	12.1	1.04
Hodgkins lymphoma	C81	28	1.6	0.33	10	0.4	0.14	**46.4** <	3.6	0.36	25	1.6	0.34	3	0.1	0.08	**24** <	0	0.12
Nonhodgkins lymphoma	C82-85	87	3.1	0.39	41	1.2	0.20	**48.3** <	0	0.47	101	3.4	0.4	55	1.4	0.23	**42.6** <	1	0.54
Leukaemia	C91-95	137	4.8	0.56	104	2.8	0.33	51.1	2.2	0.76	130	5.3	0.62	76	2.1	0.30	51.5	5.4	0.58
Other	a)	218	6.1	0.46	188	4.9	0.41	72.5	4.1	0.86	256	6.8	0.46	179	4.4	0.36	79.3	8.6	0.70
Other and ill-defined	b)	804	35.3	1.34	212	5.8	0.45	82.7	1.4	0.26	792	36.7	1.43	215	5.5	0.43	89.9	1.3	0.27
All sites	C00-C96	7622	256.4	3.26	3463	97.2	1.85	79	1.4	0.45	8506	271.6	3.32	3554	94.3	1.77	87	3.1	0.42
All sites but non-melanoma skin	C00-C96 (without C44)	7102	242.9	3.19	3431	96.4	1.84	77.9	1.5	0.48	7550	247.6	3.2	3533	93.9	1.77	85.5	3.5	0.47

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S5. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Republic of Komi, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	109	3	0.29	52	1.4	0.21	87.2	0	0.48	203	5.3	0.39	61	1.7	0.22	**86.2** >	3.4	0.30
Oesophagus	C15	88	2	0.23	77	1.7	0.20	76.1	2.3	0.88	103	**2.5** >	**0.26**	85	2.0	0.23	75.7	13.6	0.83
Stomach	C16	495	12.7	0.61	411	10.3	0.54	72.3	2	0.83	522	12.1	0.57	377	8.4	0.46	78.2	10	0.72
Colon, rectum, anus	C18-21	972	24.7	0.84	634	15.4	0.65	76.9	2.2	0.65	1233	29.6	0.9	692	15.3	0.62	80.3	8.3	0.56
Liver	C22	73	1.9	0.23	115	2.9	0.29	16.4	11	1.58	106	2.4	0.26	106	2.4	0.25	33	29.2	1.00
Pancreas	C25	186	4.7	0.36	185	4.7	0.37	34.9	3.8	0.99	256	5.9	0.39	220	4.9	0.35	51.2	21.5	0.86
Larynx	C32	15	0.4	0.11	10	0.2	0.07	93.3	0	0.67	14	0.4	0.12	10	0.3	0.08	85.7	7.1	0.71
Trachea and lung	C33-34	356	9.2	0.51	253	6.4	0.43	47.5	2.8	0.71	442	10.6	0.53	294	7.1	0.43	57.5	12.4	0.67
Bone and cartilages	C40-41	12	0.5	0.16	6	0.2	0.07	83.3	0	0.50	25	1	0.22	16	0.5	0.12	68	20	0.64
Melanoma of skin	C43	160	4.6	0.38	41	1.1	0.18	96.3	0	0.26	206	5.8	0.43	55	1.3	0.19	93.2	1	0.27
Skin	C44	613	15	0.64	29	0.7	0.15	89.2	0.3	0.05	883	20.6	0.75	25	0.5	0.11	93.7	0.3	0.03
Soft tissues	C45-49	85	2.6	0.31	41	1.3	0.23	74.1	0	0.48	116	3.6	0.38	46	1.2	0.19	78.4	**6.9** >	0.40
Breast	C50	1595	44.1	1.14	554	14.7	0.65	89.7	0.2	0.35	2071	56.5	1.29	537	13.7	0.62	94.5	1.3	0.26
Cervix uteri	C53	525	16.3	0.73	209	5.8	0.42	85.7	0.2	0.40	625	19.4	0.81	197	5.6	0.42	93	3.5	0.32
Corpus uteri	C54-55	492	13.8	0.64	124	3.1	0.29	92.7	1.4	0.25	630	16.4	0.68	167	4.1	0.33	92.4	4.1	0.27
Ovary	C56	407	11.7	0.62	214	5.5	0.40	77.6	1.5	0.53	500	14.2	0.68	257	6.5	0.43	82	6.8	0.51
Kidney	C64	335	8.8	0.51	116	3.0	0.29	71.6	1.2	0.35	429	10.8	0.55	105	2.3	0.24	74.6	4.7	0.24
Bladder	C67	102	2.6	0.27	37	0.9	0.15	85.3	2	0.36	138	3.3	0.3	40	0.8	0.14	71.7	4.3	0.29
Brain and CNS	C70-72	138	4.7	0.44	95	3.0	0.34	68.8	4.3	0.69	119	4.3	0.45	101	2.9	0.31	58.8	23.5	0.85
Hodgkins lymphoma	C81	63	2.5	0.34	15	0.5	0.16	**81** <	1.6	0.24	60	2.3	0.34	18	0.6	0.17	**71.7** <	0	0.30
Nonhodgkins lymphoma	C82-85	112	3.2	0.32	34	0.9	0.17	**14.3** <	0.9	0.30	140	3.9	0.37	62	1.6	0.21	**58.6** <	5.7	0.44
Leukaemia	C91-95	184	5.6	0.47	99	3.1	0.36	17.9	3.3	0.54	208	5.9	0.47	112	3.0	0.32	38	13	0.54
Other	a)	207	5.5	0.42	186	4.5	0.35	66.2	3.9	0.90	309	7.8	0.48	183	4.1	0.32	72.8	8.4	0.59
Other and ill-defined	b)	999	31.2	1.02	195	5.1	0.40	85.1	1.3	0.20	1226	39.1	1.2	215	5.1	0.38	86	2.3	0.18
All sites	C00-C96	8323	231.2	2.68	3733	96.2	1.69	77.6	1.4	0.45	10564	284.1	2.96	3981	95.9	1.62	82.5	5.6	0.38
All sites but non-melanoma skin	C00-C96 (without C44)	7710	216.2	2.6	3704	95.5	1.68	76.7	1.5	0.48	9681	263.4	2.87	3956	95.4	1.62	81.4	6	0.41

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S6. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Leningrad oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	206	2.5	0.19	127	1.4	0.14	68.4	1.5	0.62	281	3.3	0.22	153	1.5	0.13	**81.9** >	**5** >	0.54
Oesophagus	C15	116	1.2	0.13	153	1.4	0.12	62.9	6	1.32	121	1.1	0.11	159	1.2	0.11	62.8	17.4	1.31
Stomach	C16	964	9.1	0.34	1062	9.0	0.31	61.8	8.3	1.10	696	6.5	0.28	1126	8.7	0.30	67	11.5	1.62
Colon, rectum, anus	C18-21	1813	18.6	0.49	1515	13.2	0.38	68.6	6.7	0.84	1596	14.6	0.4	1573	11.6	0.33	76.1	9.8	0.99
Liver	C22	107	1.2	0.16	290	2.4	0.16	10.3	26.2	2.71	93	0.8	0.09	321	2.6	0.16	14	36.6	3.45
Pancreas	C25	347	3.3	0.2	572	4.9	0.23	31.1	12.1	1.65	330	2.9	0.18	674	5.3	0.23	42.1	19.1	2.04
Larynx	C32	18	0.2	0.05	16	0.2	0.05	83.3	5.6	0.89	33	0.4	0.07	17	0.2	0.05	84.8	0	0.52
Trachea and lung	C33-34	420	4.5	0.24	597	5.9	0.27	35.2	9	1.42	410	4.2	0.23	720	6.5	0.27	40.2	17.3	1.76
Bone and cartilages	C40-41	54	0.9	0.17	47	0.7	0.13	59.3	7.4	0.87	37	0.8	0.16	35	0.4	0.09	73	10.8	0.95
Melanoma of skin	C43	359	4.7	0.27	131	1.5	0.14	**81.9** <	1.1	0.36	377	4.1	0.23	122	1.3	0.14	**89.1** <	**3.7** >	0.32
Skin	C44	1586	14.7	0.43	62	0.5	0.07	86.2	0.2	0.04	1401	11.8	0.36	80	0.5	0.07	93.9	0.7	0.06
Soft tissues	C45-49	155	2.2	0.23	96	1.3	0.19	60.6	3.9	0.62	103	1.8	0.24	110	1.1	0.13	68	4.9	1.07
Breast	C50	3268	41.6	0.79	1375	14.8	0.44	**78.3** <	1	0.42	3385	40.4	0.75	1405	13.4	0.40	87.6	2.7	0.42
Cervix uteri	C53	875	13.5	0.48	471	6.2	0.31	**78.4** <	1.1	0.54	758	11.3	0.44	451	5.7	0.29	89.6	2.5	0.59
Corpus uteri	C54-55	991	11.8	0.4	483	4.9	0.25	80.2	3	0.49	1217	13.3	0.4	546	4.9	0.24	89.7	3.1	0.45
Ovary	C56	674	9.6	0.4	507	5.7	0.29	**67.7** <	2.5	0.75	736	9.5	0.38	494	5.0	0.25	79.5	4.9	0.67
Kidney	C64	388	4.9	0.3	225	2.1	0.16	55.2	3.1	0.58	499	5.2	0.26	281	2.3	0.15	77	6.8	0.56
Bladder	C67	187	2	0.17	120	1.0	0.10	61	2.7	0.64	233	2.1	0.15	121	0.8	0.09	83.7	6	0.52
Brain and CNS	C70-72	142	2.3	0.24	226	3.0	0.23	33.8	18.3	1.59	150	2.3	0.24	277	3.1	0.23	24	24.7	1.85
Hodgkins lymphoma	C81	65	1.5	0.21	24	0.4	0.10	**24.6** <	3.1	0.37	63	1.4	0.2	27	0.3	0.06	**71.4** <	1.6	0.43
Nonhodgkins lymphoma	C82-85	158	1.9	0.17	137	1.3	0.13	**15.8** <	5.1	0.87	197	2.5	0.2	164	1.5	0.14	**49.2** <	9.6	0.83
Leukaemia	C91-95	158	2.5	0.27	220	2.7	0.26	22.2	13.3	1.39	126	1.8	0.21	232	2.2	0.19	19.8	13.5	1.84
Other	a)	419	4.7	0.27	414	3.6	0.20	58.7	5.5	0.99	454	4.6	0.25	481	3.8	0.20	65.4	11.2	1.06
Other and ill-defined	b)	1063	15.2	0.51	295	3.0	0.20	63.6	1.2	0.28	980	13.4	0.47	553	5.0	0.25	82.7	3	0.56
All sites	C00-C96	14533	174.5	1.64	9165	91.1	1.10	**68.8** <	3.7	0.63	14276	160.1	1.51	10124	88.7	1.02	79.1	6	0.71
All sites but non-melanoma skin	C00-C96 (without C44)	12947	159.7	1.59	9103	90.6	1.09	**66.6** <	4.1	0.70	12875	148.3	1.47	10044	88.2	1.02	77.5	6.6	0.78

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S7. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Murmansk oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	114	3.3	0.32	43	1.3	0.21	97.4	0	0.38	148	4.2	0.36	75	2.2	0.27	**95.9 >**	2	0.51
Oesophagus	C15	61	1.6	0.21	44	1.2	0.18	95.1	1.6	0.72	78	2	0.24	63	1.5	0.21	93.6	5.1	0.81
Stomach	C16	505	13.7	0.64	340	9.1	0.52	91.9	2.4	0.67	510	13.1	0.61	323	8.1	0.48	91.8	6.3	0.63
Colon, rectum, anus	C18-21	1056	28.8	0.93	596	16.0	0.69	90.8	1.8	0.56	1130	29.3	0.91	599	15.1	0.65	93.2	5.1	0.53
Liver	C22	56	1.6	0.22	57	1.6	0.22	83.9	17.9	1.02	68	1.9	0.27	67	1.7	0.22	72.1	29.4	0.99
Pancreas	C25	193	5.4	0.41	168	4.7	0.38	65.8	4.7	0.87	267	6.9	0.45	223	5.5	0.39	83.5	18.7	0.84
Larynx	C32	11	0.3	0.1	5	0.1	0.06	100	9.1	0.45	17	0.5	0.13	5	0.2	0.07	100	0	0.29
Trachea and lung	C33-34	302	8.9	0.53	178	5.3	0.41	68.9	2.6	0.59	369	10.2	0.56	221	5.9	0.41	79.9	8.4	0.60
Bone and cartilages	C40-41	19	0.8	0.23	8	0.3	0.13	89.5	0	0.42	17	0.8	0.24	12	0.4	0.16	76.5	0	0.71
Melanoma of skin	C43	181	5.7	0.45	54	1.7	0.24	93.4	0	0.30	211	6.7	0.5	50	1.5	0.22	95.3	0	0.24
Skin	C44	669	18	0.73	7	0.2	0.09	98.8	0	0.01	897	22.6	0.8	12	0.3	0.08	98.9	0.1	0.01
Soft tissues	C45-49	81	2.5	0.31	35	1.1	0.22	90.1	1.2	0.43	76	2.7	0.37	35	1.0	0.19	90.8	5.3	0.46
Breast	C50	1795	54.1	1.32	540	15.5	0.69	96.1	0.2	0.30	1915	56.9	1.35	569	15.6	0.68	96	0.9	0.30
Cervix uteri	C53	394	12.7	0.66	184	5.9	0.46	95.7	0	0.47	490	17.2	0.81	170	5.5	0.44	97.1	2	0.35
Corpus uteri	C54-55	572	16.6	0.72	125	3.5	0.32	97.2	0.7	0.22	678	19.6	0.78	149	4.0	0.34	95.1	2.1	0.22
Ovary	C56	377	11.8	0.65	213	6.1	0.44	94.4	1.3	0.56	378	12	0.65	218	6.1	0.43	96.3	4	0.58
Kidney	C64	295	9.1	0.58	71	1.9	0.24	74.6	3.1	0.24	400	11.6	0.63	92	2.5	0.27	85	6.8	0.23
Bladder	C67	58	1.5	0.21	27	0.7	0.14	87.9	3.4	0.47	102	2.7	0.29	30	0.7	0.14	94.1	3.9	0.29
Brain and CNS	C70-72	107	3.9	0.42	76	2.7	0.34	80.4	2.8	0.71	95	3.5	0.4	77	2.6	0.32	92.6	8.4	0.81
Hodgkins lymphoma	C81	57	2.7	0.38	12	0.4	0.13	91.2	0	0.21	45	2.1	0.37	15	0.5	0.13	86.7	4.4	0.33
Nonhodgkins lymphoma	C82-85	102	3	0.31	57	1.7	0.24	89.2	0	0.56	158	4.5	0.39	53	1.2	0.18	81.6	3.8	0.34
Leukaemia	C91-95	233	7.9	0.61	108	3.3	0.35	91.4	2.1	0.46	260	8.1	0.57	112	2.9	0.31	90.8	6.9	0.43
Other	a)	260	7.1	0.46	159	4.1	0.34	93.5	2.7	0.61	250	6.7	0.47	158	3.9	0.33	91.6	9.6	0.63
Other and ill-defined	b)	658	21	0.88	220	6.1	0.44	81.6	2.1	0.33	700	22.5	0.92	143	3.9	0.34	88.1	2.6	0.20
All sites	C00-C96	8156	242.1	2.84	3327	94.6	1.73	90.9	1.4	0.41	9259	268.3	2.99	3471	92.8	1.67	92.8	4	0.37
All sites but non-melanoma skin	C00-C96 (without C44)	7487	224.1	2.75	3320	94.4	1.73	90.2	1.5	0.44	8362	245.7	2.88	3459	92.5	1.66	92.1	4.4	0.41

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S8. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Novgorod oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	71	2.3	0.29	43	1.4	0.24	97.2	0	0.61	111	3.2	0.36	41	1.2	0.21	66.7	2.7	0.37
Oesophagus	C15	87	2.1	0.26	61	1.4	0.21	71.3	10.3	0.70	71	1.7	0.23	42	1.0	0.17	60.6	8.5	0.59
Stomach	C16	620	15	0.72	462	10.6	0.58	79.4	7.9	0.75	529	11.7	0.61	354	7.5	0.47	55.4	9.6	0.67
Colon, rectum, anus	C18-21	947	23.1	0.86	526	11.5	0.58	83.6	7.4	0.56	969	24	0.87	476	10.4	0.54	62.3	8.2	0.49
Liver	C22	54	1.4	0.22	65	1.6	0.23	38.9	40.7	1.20	79	1.8	0.23	106	2.3	0.26	22.8	43	1.34
Pancreas	C25	199	5	0.4	184	4.4	0.36	46.2	14.6	0.92	255	5.7	0.41	254	5.5	0.40	25.1	24.3	1.00
Larynx	C32	16	0.6	0.15	4	0.1	0.07	87.5	6.2	0.25	18	0.5	0.14	11	0.3	0.09	66.7	5.6	0.61
Trachea and lung	C33-34	241	6.6	0.47	173	4.7	0.40	65.6	12.4	0.72	310	8.3	0.51	209	5.4	0.41	48.1	11.9	0.67
Bone and cartilages	C40-41	14	0.7	0.22	14	0.5	0.13	78.6	7.1	1.00	24	1.1	0.31	14	0.6	0.22	**33.3** <	4.2	0.58
Melanoma of skin	C43	165	5.1	0.45	62	1.8	0.26	90.9	0.6	0.38	178	5.3	0.46	46	1.3	0.22	**61.8** <	**3.4** >	0.26
Skin	C44	1093	25.6	0.91	22	0.4	0.10	95.5	0.4	0.02	1121	25.3	0.87	21	0.3	0.08	**70.1** <	0.6	0.02
Soft tissues	C45-49	62	2	0.31	28	0.9	0.20	75.8	0	0.45	79	2.4	0.33	52	1.5	0.24	62	**7.6** >	0.66
Breast	C50	1496	48.4	1.37	527	15.6	0.74	94.4	0.7	0.35	1577	52.1	1.44	398	11.5	0.65	**71** <	1.3	0.25
Cervix uteri	C53	446	19.4	0.98	147	5.3	0.48	91.9	1.6	0.33	430	19.2	1	100	3.8	0.42	**67** <	0.7	0.23
Corpus uteri	C54-55	537	16.2	0.76	156	4.2	0.37	93.9	1.9	0.29	647	18.7	0.79	141	3.8	0.36	66.8	2.6	0.22
Ovary	C56	373	12.6	0.73	185	5.5	0.44	90.1	2.9	0.50	363	12.3	0.73	176	5.0	0.42	**65.3** <	3.9	0.48
Kidney	C64	246	7.4	0.54	80	1.9	0.24	72.4	5.3	0.33	243	7	0.5	71	1.8	0.26	51	6.2	0.29
Bladder	C67	88	2.2	0.27	32	0.7	0.14	86.4	2.3	0.36	129	2.9	0.29	28	0.6	0.12	51.2	4.7	0.22
Brain and CNS	C70-72	109	4.6	0.53	80	3.8	0.52	63.3	21.1	0.73	105	4.2	0.51	83	2.5	0.30	48.6	18.1	0.79
Hodgkins lymphoma	C81	53	3.1	0.49	8	0.4	0.15	**71.7** <	3.8	0.15	38	2.5	0.47	4	0.1	0.08	**44.7** <	5.3	0.11
Nonhodgkins lymphoma	C82-85	103	3.3	0.39	38	1.1	0.19	**70.9** <	5.8	0.37	130	3.9	0.39	47	1.3	0.22	**55.4** <	1.5	0.36
Leukaemia	C91-95	147	5.4	0.59	97	3.0	0.36	80.3	8.2	0.66	169	6	0.63	97	2.9	0.38	45.6	5.3	0.57
Other	a)	225	6.2	0.47	148	3.5	0.33	85.8	6.2	0.66	276	7	0.48	173	4.2	0.36	58.7	10.5	0.63
Other and ill-defined	b)	735	30.4	1.21	139	3.7	0.35	88.7	2.3	0.19	694	28.2	1.2	141	3.4	0.36	73.8	2.6	0.20
All sites	C00-C96	8127	248.6	3.17	3281	87.8	1.77	86.3	4.2	0.40	8545	255.1	3.2	3084	78.3	1.64	**62.8** <	5.2	0.36
All sites but non-melanoma skin	C00-C96 (without C44)	7034	223	3.04	3259	87.4	1.77	84.8	4.8	0.46	7424	229.8	3.08	3063	77.9	1.64	**61.7** <	5.9	0.41

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S9. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Saint-Petersburg, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	786	3	0.12	423	1.5	0.09	**80 >**	**12.6 >**	0.54	1029	3.8	0.13	485	1.5	0.08	**80 >**	**10 >**	0.47
Oesophagus	C15	458	1.3	0.07	396	1.1	0.06	59	**28.4 >**	0.86	496	1.4	0.07	399	1.0	0.06	65.3	**23.4 >**	0.80
Stomach	C16	4236	12.4	0.22	3506	9.9	0.19	**61.6 <**	**28.4 >**	0.83	4147	11.4	0.2	3099	7.9	0.16	66.5	**22.9 >**	0.75
Colon, rectum, anus	C18-21	9639	29.1	0.33	6032	16.0	0.23	67.4	**23 >**	0.63	10640	30.4	0.33	5930	14.7	0.22	73.6	**17.2 >**	0.56
Liver	C22	740	2.2	0.11	802	2.3	0.10	**12.4 <**	**58 >**	1.08	941	2.6	0.1	998	2.7	0.10	**21.5 <**	**45.3 >**	1.06
Pancreas	C25	2351	6.9	0.16	2295	6.6	0.16	**23.1 <**	**40 >**	0.98	2830	7.4	0.16	2583	6.6	0.15	**31.6 <**	**30 >**	0.91
Larynx	C32	132	0.5	0.04	79	0.3	0.03	**68.2 <**	**26.5 >**	0.60	131	0.5	0.04	63	0.2	0.03	74.8	**13.7 >**	0.48
Trachea and lung	C33-34	2766	9	0.19	2225	6.8	0.16	**39.5 <**	**35.6 >**	0.80	3446	10.8	0.2	2502	7.2	0.16	**51.6 <**	**24 >**	0.73
Bone and cartilages	C40-41	150	0.8	0.09	121	0.5	0.06	**54 <**	**26 >**	0.81	154	0.9	0.1	114	0.5	0.06	71.4	11.7	0.74
Melanoma of skin	C43	1532	6.1	0.17	572	2.0	0.09	**86.9 <**	**8.6 >**	0.37	1952	7.3	0.19	584	1.9	0.09	**88.6 <**	**4.9 >**	0.30
Skin	C44	4907	15	0.24	212	0.5	0.04	89.5	1.9	0.04	7288	20.6	0.27	166	0.3	0.03	95.1	0.9	0.02
Soft tissues	C45-49	610	2.6	0.14	401	1.5	0.10	54.8	**26.7 >**	0.66	737	3.1	0.15	443	1.7	0.11	62	**19.3 >**	0.60
Breast	C50	13020	53	0.5	5790	20.6	0.30	**76.9 <**	**11.5 >**	0.44	15429	59.4	0.52	5719	18.6	0.27	**84.7 <**	**7 >**	0.37
Cervix uteri	C53	2434	11.5	0.25	1232	5.1	0.16	**80 <**	**14.9 >**	0.51	2791	12.7	0.26	1294	5.3	0.16	**85.3 <**	**9.2 >**	0.46
Corpus uteri	C54-55	4266	16.4	0.27	1543	5.0	0.14	82	**13.1 >**	0.36	5227	18.9	0.28	1769	5.3	0.14	83.5	**9.9 >**	0.34
Ovary	C56	3068	12.5	0.25	1917	6.8	0.17	**61.4 <**	**20.5 >**	0.62	3384	13.1	0.25	1957	6.5	0.16	**69 <**	**15.4 >**	0.58
Kidney	C64	2060	7.4	0.2	852	2.4	0.10	**55.7 <**	**18.8 >**	0.41	2322	7.7	0.19	853	2.1	0.09	**62.7 <**	**16.2 >**	0.37
Bladder	C67	844	2.5	0.1	429	1.0	0.06	**60 <**	**20.1 >**	0.51	1041	2.9	0.1	369	0.8	0.05	**68.6 <**	**13.4 >**	0.35
Brain and CNS	C70-72	1070	4.8	0.18	861	3.6	0.16	**40.1 <**	**34.5 >**	0.80	1418	6	0.2	1108	4.3	0.16	49.2	**26.2 >**	0.78
Hodgkins lymphoma	C81	381	2.5	0.14	120	0.6	0.06	**59.3 <**	**9.2 >**	0.31	383	2.4	0.15	80	0.4	0.05	**55.4 <**	**5.7 >**	0.21
Nonhodgkins lymphoma	C82-85	1125	4.4	0.15	563	1.8	0.09	**44.8 <**	**21.4 >**	0.50	1531	5.6	0.17	677	1.9	0.09	**47.1 <**	**12.9 >**	0.44
Leukaemia	C91-95	1690	7.6	0.26	842	3.5	0.17	79.3	**22.5 >**	0.50	1737	7.3	0.24	911	3.4	0.16	76.1	**17 >**	0.52
Other	a)	2214	7.1	0.18	1698	4.8	0.13	58.9	**31.4 >**	0.77	2669	7.9	0.18	2026	5.4	0.14	**59.3 >**	**25.4 >**	0.76
Other and ill-defined	b)	3510	15.9	0.31	1448	4.6	0.15	**75.4 >**	12.5	0.41	5438	23.8	0.37	1852	5.5	0.16	**80.2 >**	7.9	0.34
All sites	C00-C96	63989	234.5	1.06	34358	109.0	0.68	**67.8 <**	**19.1 >**	0.54	77161	267.8	1.11	35981	105.8	0.66	**74.1 <**	**13.4 >**	0.47
All sites but non-melanoma skin	C00-C96 (without C44)	59082	219.5	1.03	34146	108.5	0.68	**66 <**	**20.5 >**	0.58	69873	247.1	1.08	35816	105.5	0.66	**71.9 <**	**14.7 >**	0.51

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S10. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Pskov oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	89	2.3	0.3	52	1.4	0.22	93.3	0	0.58	108	2.6	0.3	49	1.2	0.20	88.9	0.9	0.45
Oesophagus	C15	40	0.9	0.17	33	0.7	0.14	80	7.5	0.82	48	1	0.17	41	0.8	0.14	85.4	6.2	0.85
Stomach	C16	557	12.5	0.6	545	11.6	0.58	74.5	3.8	0.98	480	10.7	0.57	390	8.2	0.49	86.9	9.4	0.81
Colon, rectum, anus	C18-21	838	19.5	0.76	606	12.5	0.59	73.7	2.9	0.72	1029	23.5	0.83	562	11.7	0.57	87.9	6.4	0.55
Liver	C22	68	1.8	0.27	95	2.1	0.25	22.1	10.3	1.40	96	1.9	0.22	124	2.5	0.26	44.8	37.5	1.29
Pancreas	C25	213	4.8	0.38	221	4.6	0.36	25.8	8.9	1.04	235	5.3	0.39	208	4.4	0.35	51.5	18.3	0.89
Larynx	C32	9	0.3	0.11	6	0.2	0.07	100	0	0.67	15	0.5	0.15	9	0.3	0.11	100	6.7	0.60
Trachea and lung	C33-34	197	5.2	0.41	188	4.6	0.38	56.3	8.6	0.95	321	7.8	0.48	240	5.8	0.41	66.4	13.7	0.75
Bone and cartilages	C40-41	27	0.8	0.18	24	0.7	0.16	55.6	0	0.89	28	1.1	0.24	16	0.4	0.12	92.9	3.6	0.57
Melanoma of skin	C43	163	4.9	0.42	51	1.4	0.23	96.3	0.6	0.31	156	4.4	0.4	46	1.2	0.21	96.8	0.6	0.29
Skin	C44	1417	33	1	21	0.3	0.09	99.5	0	0.01	1770	41	1.12	18	0.3	0.08	99.5	0.1	0.01
Soft tissues	C45-49	77	2.7	0.38	45	1.2	0.21	83.1	2.6	0.58	93	3	0.41	43	1.0	0.21	75.3	3.2	0.46
Breast	C50	1395	42.3	1.24	630	16.3	0.72	89.3	0.5	0.45	1573	47.6	1.32	613	15.3	0.69	96.2	1.2	0.39
Cervix uteri	C53	538	23.8	1.09	159	5.1	0.44	96.7	0.2	0.30	435	18.5	0.96	149	5.5	0.49	97.7	0.5	0.34
Corpus uteri	C54-55	604	17.3	0.76	204	4.8	0.38	97	1.7	0.34	688	19	0.78	179	3.9	0.33	98.1	2.5	0.26
Ovary	C56	367	12.7	0.71	213	6.5	0.48	86.6	1.1	0.58	393	12.5	0.72	245	6.9	0.49	88.8	3.6	0.62
Kidney	C64	202	5.8	0.49	84	2.1	0.29	64.9	1	0.42	259	7.2	0.54	91	1.8	0.21	77.6	5.8	0.35
Bladder	C67	93	2	0.23	61	1.2	0.18	60.2	0	0.66	101	2.1	0.24	53	0.9	0.14	76.2	5	0.52
Brain and CNS	C70-72	89	3.7	0.49	92	3.0	0.37	57.3	15.7	1.03	121	4.1	0.46	109	3.5	0.40	79.3	25.6	0.90
Hodgkins lymphoma	C81	55	3.1	0.48	16	0.6	0.16	**47.3** <	3.6	0.29	63	3.3	0.48	17	0.6	0.17	**61.9** <	3.2	0.27
Nonhodgkins lymphoma	C82-85	88	2.7	0.32	42	1.0	0.18	**42** <	4.5	0.48	112	3.3	0.41	38	1.0	0.18	**37.5** <	6.2	0.34
Leukaemia	C91-95	109	4.3	0.61	106	2.5	0.31	31.2	11.9	0.97	152	5.4	0.57	92	2.7	0.37	35.5	13.8	0.61
Other	a)	205	5.2	0.42	159	3.6	0.34	74.6	3.9	0.78	261	6.6	0.47	192	4.5	0.37	87.7	9.2	0.74
Other and ill-defined	b)	686	31.9	1.33	162	4.0	0.35	86.6	0.9	0.24	648	25.8	1.16	165	4.1	0.39	80.2	3.1	0.25
All sites	C00-C96	8126	243.4	3.13	3815	92.1	1.72	82.9	2	0.47	9185	258.6	3.14	3689	88.4	1.70	88	4.6	0.40
All sites but non-melanoma skin	C00-C96 (without C44)	6709	210.4	2.97	3794	91.8	1.72	79.4	2.5	0.57	7415	217.5	2.93	3671	88.1	1.69	85.2	5.7	0.50

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S11. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Vologda oblast, 2008-2012 and 2013-2017, Females.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	159	2.4	0.21	68	1.1	0.15	78	3.1	0.43	170	2.8	0.24	88	1.4	0.17	**91.8** >	3.5	0.52
Oesophagus	C15	122	1.7	0.17	128	1.7	0.17	73	7.4	1.05	120	1.6	0.16	112	1.4	0.15	75	15.8	0.93
Stomach	C16	904	13.3	0.5	846	11.2	0.44	74.8	7.3	0.94	791	11	0.44	699	9.0	0.39	72.4	20.9	0.88
Colon, rectum, anus	C18-21	1479	22.8	0.66	1000	13.4	0.48	84.1	5.5	0.68	1570	23.6	0.65	919	12.2	0.45	84.3	11	0.59
Liver	C22	97	1.6	0.18	170	2.3	0.20	22.7	14.4	1.75	136	2.2	0.22	177	2.7	0.23	39	32.4	1.30
Pancreas	C25	292	4.4	0.29	352	4.8	0.29	40.1	12.3	1.21	301	4.4	0.28	341	4.8	0.29	37.5	33.6	1.13
Larynx	C32	16	0.3	0.08	9	0.1	0.05	62.5	6.2	0.56	12	0.2	0.06	8	0.1	0.05	83.3	16.7	0.67
Trachea and lung	C33-34	312	5.5	0.34	293	4.6	0.32	57.1	7.7	0.94	384	6.1	0.34	329	4.7	0.29	59.4	20.3	0.86
Bone and cartilages	C40-41	34	0.9	0.2	42	0.7	0.12	79.4	8.8	1.24	45	1.1	0.2	27	0.5	0.13	80	4.4	0.60
Melanoma of skin	C43	290	5.5	0.35	85	1.4	0.17	**69.3** <	0.7	0.29	316	5.9	0.36	75	1.3	0.16	93.7	1.3	0.24
Skin	C44	1850	26.9	0.71	53	0.7	0.11	**14.6** <	0.1	0.03	1943	27.2	0.68	24	0.3	0.08	98.4	0.2	0.01
Soft tissues	C45-49	119	2.6	0.29	57	0.8	0.12	80.7	3.4	0.48	135	2.7	0.28	61	1.1	0.16	78.5	5.2	0.45
Breast	C50	2010	38.6	0.92	782	13.2	0.51	87.7	2	0.39	2490	46.5	1	788	12.9	0.50	93.2	3.3	0.32
Cervix uteri	C53	774	18.7	0.7	177	3.4	0.28	**61** <	0.6	0.23	914	22.9	0.8	186	3.8	0.30	93.5	1.9	0.20
Corpus uteri	C54-55	686	12.8	0.51	222	3.7	0.27	93	1.2	0.32	970	17	0.58	189	3.0	0.23	92.9	3.4	0.19
Ovary	C56	540	10.9	0.5	266	4.5	0.30	83.9	2.4	0.49	630	12.5	0.54	272	4.7	0.31	90.8	4.4	0.43
Kidney	C64	365	6.6	0.4	138	2.1	0.19	76.2	1.9	0.38	424	7.6	0.42	140	2.0	0.19	85.4	5.2	0.33
Bladder	C67	117	1.7	0.18	48	0.5	0.08	75.2	9.4	0.41	156	2.2	0.2	76	0.8	0.11	78.8	12.8	0.49
Brain and CNS	C70-72	153	3.9	0.38	158	3.3	0.32	36.6	19	1.03	200	4.5	0.37	194	3.6	0.29	33	17.5	0.97
Hodgkins lymphoma	C81	14	**0.4** <	**0.12**	18	0.4	0.09	**7.1** <	0	1.29	86	3	0.36	11	0.3	0.09	**65.1** <	1.2	0.13
Nonhodgkins lymphoma	C82-85	41	**0.6** <	**0.11**	66	1.0	0.14	**36.6** <	12.2	1.61	194	3.6	0.29	79	1.3	0.16	**58.2** <	4.6	0.41
Leukaemia	C91-95	157	3	0.3	149	2.3	0.25	49	10.2	0.95	308	6.4	0.46	142	2.4	0.25	53.2	10.1	0.46
Other	a)	269	4.4	0.31	357	5.0	0.30	77.7	4.5	1.33	365	5.9	0.35	319	4.4	0.27	65.5	14.5	0.87
Other and ill-defined	b)	562	10.7	0.5	347	5.0	0.31	64.1	7.8	0.62	719	14.2	0.6	427	6.2	0.34	67.5	14.9	0.59
All sites	C00-C96	11362	200.3	2.1	5831	87.2	1.31	**65.7** <	3.8	0.51	13379	235.1	2.28	5683	84.9	1.27	83.4	7.8	0.42
All sites but non-melanoma skin	C00-C96 (without C44)	9512	173.4	1.97	5778	86.5	1.30	75.6	4.6	0.61	11436	207.9	2.17	5659	84.6	1.27	80.8	9.1	0.49

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S12. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Arkhangelsk oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	575	15.3	0.67	311	8.2	0.48	**95.8 >**	2.8	0.54	558	14.5	0.63	329	8.5	0.48	**97.3 >**	3.2	0.59
Oesophagus	C15	466	12.9	0.63	398	11.1	0.59	86.3	8.4	0.85	511	13	0.59	439	11.3	0.55	93	7.4	0.86
Stomach	C16	1325	36.4	1.05	1080	29.6	0.95	87.6	7.2	0.82	1293	34	0.98	991	26.1	0.86	91.7	8	0.77
Colon, rectum, anus	C18-21	1298	36.2	1.06	765	21.4	0.82	88.4	7.3	0.59	1482	39.5	1.06	912	24.4	0.83	92.4	6.8	0.62
Liver	C22	135	4	0.36	186	5.6	0.44	60	28.9	1.38	126	3.5	0.33	173	4.8	0.38	54	19.8	1.37
Pancreas	C25	361	10.1	0.56	340	9.5	0.54	54.8	16.9	0.94	446	11.7	0.57	380	9.9	0.52	66.8	15	0.85
Larynx	C32	246	6.7	0.45	161	4.5	0.37	92.7	7.3	0.65	261	6.7	0.42	143	3.7	0.31	97.3	2.7	0.55
Trachea and lung	C33-34	2370	65.5	1.41	2021	56.7	1.32	68.1	10.9	0.85	2451	63.3	1.32	2095	54.5	1.22	80	12.4	0.85
Bone and cartilages	C40-41	31	0.9	0.19	25	0.7	0.14	80.6	3.2	0.81	25	0.8	0.18	21	0.6	0.15	92	8	0.84
Melanoma of skin	C43	154	4.2	0.35	75	2.0	0.23	96.1	3.9	0.49	159	4.3	0.35	72	1.9	0.23	99.4	1.9	0.45
Skin	C44	802	23	0.87	19	0.5	0.13	99.3	0	0.02	931	24.8	0.84	18	0.5	0.11	99.4	0.2	0.02
Soft tissues	C45-49	114	3.6	0.37	56	1.8	0.26	78.1	**7.9 >**	0.49	101	3	0.32	41	1.0	0.16	87.1	6.9	0.41
Breast	C50	11	0.4	0.12	2	0.1	0.04	90.9	9.1	0.18	19	0.5	0.12	5	0.1	0.05	89.5	0	0.26
Prostate	C61	1163	33.7	1.05	331	9.5	0.57	94.2	6.9	0.28	1749	46.7	1.15	434	11.6	0.58	97.3	4.3	0.25
Kidney	C64	501	14.3	0.68	223	6.6	0.48	71.9	7.6	0.45	630	16.6	0.68	248	6.5	0.42	77.5	7.1	0.39
Bladder	C67	502	14.1	0.66	166	4.6	0.38	88	4.4	0.33	515	13.5	0.61	175	4.7	0.37	92.4	3.3	0.34
Brain and CNS	C70-72	205	6	0.44	158	4.4	0.36	77.6	16.1	0.77	230	7	0.49	173	4.8	0.39	71.3	14.3	0.75
Hodgkins lymphoma	C81	55	1.7	0.24	23	0.6	0.12	80	7.3	0.42	71	2.3	0.3	25	0.7	0.15	88.7	1.4	0.35
Nonhodgkins lymphoma	C82-85	188	5.3	0.41	112	3.0	0.29	**63.8 <**	6.4	0.60	178	4.9	0.38	108	2.8	0.28	**67.4 <**	7.9	0.61
Leukaemia	C91-95	230	7.2	0.51	137	4.3	0.39	83.5	11.3	0.60	238	7.4	0.52	138	3.7	0.33	86.6	11.8	0.58
Other	a)	341	9.6	0.54	211	6.0	0.44	85.6	7	0.62	355	9.5	0.52	220	5.9	0.41	87.9	8.5	0.62
Other and ill-defined	b)	413	11.8	0.62	279	8.2	0.52	63.9	14.5	0.68	441	12	0.6	268	7.3	0.46	70.1	16.1	0.61
All sites	C00-C96	11486	322.8	3.18	7078	198.8	2.49	82	8.2	0.62	12770	339.5	3.11	7407	195.3	2.34	87.8	7.8	0.58
All sites but non-melanoma skin	C00-C96 (without C44)	10684	299.7	3.06	7059	198.3	2.49	80.7	8.8	0.66	11839	314.7	3	7389	194.9	2.34	86.8	8.4	0.62

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

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[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S13. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Kaliningrad oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	290	10.1	0.61	199	6.8	0.50	90.7	0.3	0.69	450	14.2	0.68	241	7.8	0.51	92	1.8	0.54
Oesophagus	C15	152	5.2	0.44	140	4.6	0.40	69.1	2	0.92	175	5.6	0.43	161	5.2	0.42	77.1	4.6	0.92
Stomach	C16	716	25.6	0.99	630	22.3	0.92	76.8	1.7	0.88	659	21.1	0.84	524	17.0	0.76	85.3	2.3	0.80
Colon, rectum, anus	C18-21	784	28	1.04	488	17.8	0.84	72.7	0.6	0.62	989	31.9	1.04	576	18.4	0.79	81.8	1.5	0.58
Liver	C22	78	2.9	0.34	145	5.1	0.45	16.7	10.3	1.86	114	3.6	0.35	176	6.0	0.47	26.3	14	1.54
Pancreas	C25	244	8.6	0.57	254	9.0	0.59	20.1	4.9	1.04	217	6.8	0.47	232	7.3	0.49	30.9	4.1	1.07
Larynx	C32	229	8	0.55	155	5.4	0.45	86.9	1.7	0.68	247	7.8	0.5	173	5.4	0.42	90.7	2	0.70
Trachea and lung	C33-34	1220	43.4	1.29	1188	41.9	1.27	55.8	3	0.97	1288	40.9	1.16	1257	39.9	1.15	70	4.3	0.98
Bone and cartilages	C40-41	37	1.6	0.28	32	1.2	0.22	62.2	2.7	0.86	47	1.6	0.26	30	1.1	0.22	80.9	0	0.64
Melanoma of skin	C43	123	4.3	0.4	72	2.4	0.30	86.2	0	0.59	175	5.5	0.43	63	2.0	0.26	**81.7** <	0	0.36
Skin	C44	834	30	1.09	20	0.7	0.16	98.3	0.1	0.02	971	30.9	1.02	28	0.9	0.18	97.5	0	0.03
Soft tissues	C45-49	85	3.2	0.37	45	1.8	0.28	77.6	4.7	0.53	119	4.2	0.41	51	1.7	0.26	75.6	2.5	0.43
Breast	C50	17	0.6	0.14	10	0.4	0.14	94.1	0	0.59	19	0.6	0.14	14	0.4	0.12	84.2	0	0.74
Prostate	C61	751	27.7	1.06	315	11.3	0.68	85.9	0.7	0.42	1067	34.9	1.09	389	12.2	0.64	87.4	1	0.36
Kidney	C64	375	13.1	0.7	166	6.2	0.50	67.7	1.6	0.44	396	12.7	0.66	184	6.1	0.46	62.9	0.8	0.46
Bladder	C67	409	14.7	0.76	184	6.9	0.54	74.8	1	0.45	432	13.6	0.67	189	5.7	0.43	82.2	0.7	0.44
Brain and CNS	C70-72	118	4.5	0.44	118	4.4	0.43	57.6	5.1	1.00	108	3.9	0.4	106	3.7	0.38	79.6	5.6	0.98
Hodgkins lymphoma	C81	59	2.2	0.3	23	0.8	0.16	**32.2** <	0	0.39	48	1.9	0.28	20	0.7	0.15	**60.4** <	2.1	0.42
Nonhodgkins lymphoma	C82-85	148	5.9	0.52	52	2.0	0.29	**66.9** <	3.4	0.35	140	4.8	0.42	61	2.1	0.29	78.6	0.7	0.44
Leukaemia	C91-95	175	7.2	0.59	107	4.1	0.42	30.9	1.1	0.61	127	5.3	0.52	144	5.4	0.47	87.4	5.5	1.13
Other	a)	217	8	0.56	191	6.8	0.51	61.3	1.8	0.88	223	7.4	0.51	170	5.5	0.43	83	2.2	0.76
Other and ill-defined	b)	343	12.4	0.7	264	9.6	0.62	38.2	1.2	0.77	317	10.7	0.63	365	11.7	0.63	59.3	2.2	1.15
All sites	C00-C96	7404	267.1	3.25	4798	171.6	2.59	69.8	1.7	0.65	8328	270.1	3.05	5154	166.4	2.38	79.5	2.1	0.62
All sites but non-melanoma skin	C00-C96 (without C44)	6570	237.1	3.06	4778	171.0	2.58	66.2	1.9	0.73	7357	239.2	2.87	5126	165.5	2.37	77.1	2.4	0.70

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.
All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).
[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96
[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S14. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Republic of Karelia, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	261	13.2	0.85	141	7.1	0.63	88.5	0.8	0.54	320	15.6	0.89	194	9.5	0.70	94.1	1.3	0.61
Oesophagus	C15	215	11.1	0.8	206	10.3	0.75	65.1	2.8	0.96	231	11	0.74	197	9.5	0.70	78.8	5.2	0.85
Stomach	C16	724	37.4	1.47	570	29.3	1.30	73.8	2.8	0.79	672	33.5	1.34	517	25.8	1.18	85.7	4.6	0.77
Colon, rectum, anus	C18-21	699	37.4	1.5	416	22.1	1.16	76.3	2.3	0.60	842	41.4	1.47	492	24.1	1.13	84.4	3.2	0.58
Liver	C22	74	3.9	0.47	101	5.9	0.62	24.3	9.5	1.36	97	4.9	0.51	119	5.9	0.56	49.5	36.1	1.23
Pancreas	C25	215	11.4	0.82	200	10.7	0.80	35.8	6	0.93	189	9.6	0.72	182	9.1	0.70	51.9	10.6	0.96
Larynx	C32	120	6.2	0.59	101	5.2	0.54	90	1.7	0.84	161	7.9	0.64	105	5.4	0.54	90.1	3.7	0.65
Trachea and lung	C33-34	1266	66.1	1.95	1200	62.5	1.90	47.9	4.3	0.95	1278	61.9	1.78	1109	53.4	1.65	69.4	9.1	0.87
Bone and cartilages	C40-41	21	1.3	0.31	28	1.7	0.35	85.7	4.8	1.33	20	1.2	0.29	19	0.9	0.21	75	5	0.95
Melanoma of skin	C43	92	4.7	0.52	32	1.5	0.26	92.4	2.2	0.35	112	5.7	0.56	50	2.5	0.37	96.4	0.9	0.45
Skin	C44	322	17.2	1.03	23	1.2	0.29	97.5	0	0.07	517	25.9	1.19	27	1.5	0.31	96.3	0.2	0.05
Soft tissues	C45-49	64	3.6	0.48	30	1.7	0.32	87.5	0	0.47	48	2.5	0.38	21	1.1	0.24	85.4	4.2	0.44
Breast	C50	7	0.4	0.14	5	0.3	0.12	85.7	0	0.71	12	0.6	0.18	6	0.3	0.12	100	0	0.50
Prostate	C61	627	34	1.43	222	12.4	0.90	84.4	1	0.35	739	37.5	1.43	283	14.4	0.90	90.8	1.6	0.38
Kidney	C64	262	13.4	0.87	118	6.5	0.64	67.6	1.9	0.45	322	15.8	0.91	116	5.6	0.53	78.6	3.1	0.36
Bladder	C67	246	13.2	0.89	150	8.3	0.73	74.8	1.2	0.61	293	14.9	0.91	124	6.4	0.59	86	1	0.42
Brain and CNS	C70-72	92	5.4	0.6	79	4.1	0.49	60.9	3.3	0.86	113	6.5	0.67	87	4.6	0.52	77.9	5.3	0.77
Hodgkins lymphoma	C81	40	2.6	0.43	9	0.4	0.15	**22.5** <	0	0.22	21	1.2	0.29	9	0.5	0.16	**28.6** <	4.8	0.43
Nonhodgkins lymphoma	C82-85	68	3.7	0.48	39	2.1	0.37	**47.1** <	0	0.57	76	4.3	0.52	42	2.2	0.36	**38.2** <	2.6	0.55
Leukaemia	C91-95	128	7.6	0.73	81	4.7	0.57	43.8	0.8	0.63	119	6.7	0.67	76	4.7	0.57	53.8	5	0.64
Other	a)	162	8.7	0.72	133	7.2	0.67	70.4	3.7	0.82	192	10.5	0.79	123	6.5	0.61	80.7	4.7	0.64
Other and ill-defined	b)	281	15.6	1	193	10.3	0.80	41.3	6	0.69	230	11.6	0.8	194	9.8	0.73	56.1	4.3	0.84
All sites	C00-C96	5986	317.8	4.35	4077	215.5	3.58	66.8	2.7	0.68	6604	330.7	4.23	4092	203.5	3.30	79.8	4.8	0.62
All sites but non-melanoma skin	C00-C96 (without C44)	5664	300.6	4.22	4054	214.3	3.57	65.1	2.9	0.72	6087	304.8	4.06	4065	202.0	3.29	78.4	5.2	0.67

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S15. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Republic of Komi, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	346	14.6	0.86	211	9.3	0.72	91.6	1.7	0.61	449	17.5	0.87	235	9.1	0.63	88.2	**5.1** >	0.52
Oesophagus	C15	255	11	0.76	246	10.9	0.76	78.8	1.6	0.96	348	13.6	0.77	277	11.0	0.70	85.1	8.6	0.80
Stomach	C16	679	29.2	1.21	573	25.6	1.18	77.9	1.8	0.84	784	32.9	1.25	541	23.2	1.06	81	9.1	0.69
Colon, rectum, anus	C18-21	794	37.2	1.44	514	25.2	1.22	81.1	2.3	0.65	1003	44.2	1.49	580	26.8	1.19	80.9	8	0.58
Liver	C22	104	4.7	0.51	158	7.0	0.61	16.3	8.7	1.52	136	6	0.55	151	6.8	0.58	32.4	28.7	1.11
Pancreas	C25	231	9.8	0.7	208	9.2	0.70	32.5	4.8	0.90	283	11.8	0.75	253	10.8	0.72	46.6	20.8	0.89
Larynx	C32	162	6.6	0.55	122	5.2	0.50	92	1.2	0.75	209	8.2	0.59	129	5.3	0.49	87.1	6.2	0.62
Trachea and lung	C33-34	1499	65.5	1.83	1251	55.5	1.70	61.6	2.9	0.83	1680	69.4	1.79	1326	55.8	1.63	65.1	12.1	0.79
Bone and cartilages	C40-41	25	1.1	0.23	30	1.3	0.26	68	4	1.20	24	1.2	0.27	14	0.7	0.21	66.7	4.2	0.58
Melanoma of skin	C43	80	3.3	0.41	41	1.7	0.28	92.5	0	0.51	150	6	0.52	55	2.2	0.31	91.3	2.7	0.37
Skin	C44	354	16.7	1.01	26	1.3	0.29	88.7	0.3	0.07	442	19.9	1.02	23	1.1	0.26	94.3	0.5	0.05
Soft tissues	C45-49	83	3.6	0.42	45	2.2	0.37	75.9	0	0.54	91	3.9	0.44	56	2.8	0.40	78	**8.8** >	0.62
Breast	C50	37	1.7	0.3	4	0.2	0.11	97.3	0	0.11	16	0.7	0.18	4	0.2	0.09	100	0	0.25
Prostate	C61	448	22.7	1.18	204	11.0	0.87	82.1	1.3	0.46	937	43.1	1.49	292	14.4	0.90	88.9	3.3	0.31
Kidney	C64	420	17.6	0.94	164	7.2	0.61	69	1.4	0.39	528	21.2	0.97	172	7.2	0.58	71.2	5.1	0.33
Bladder	C67	286	13.2	0.87	130	6.9	0.70	84.6	2.4	0.45	381	16.8	0.92	135	6.4	0.59	81.4	2.6	0.35
Brain and CNS	C70-72	116	4.9	0.49	88	3.7	0.41	61.2	2.6	0.76	153	6.2	0.54	115	4.7	0.47	58.2	21.6	0.75
Hodgkins lymphoma	C81	66	2.8	0.36	19	0.6	0.15	**77.3** <	0	0.29	63	2.8	0.38	21	0.9	0.21	**66.7** <	**9.5** >	0.33
Nonhodgkins lymphoma	C82-85	114	5.1	0.51	53	2.7	0.41	**14.9** <	0	0.46	128	5.2	0.49	53	2.2	0.31	**54.7** <	5.5	0.41
Leukaemia	C91-95	207	9.6	0.73	117	5.9	0.59	13	2.9	0.57	210	9.5	0.7	112	5.1	0.51	37.6	10.5	0.53
Other	a)	179	8.2	0.68	138	6.2	0.59	65.4	1.1	0.77	252	10.7	0.71	158	6.9	0.58	73	11.5	0.63
Other and ill-defined	b)	295	13.3	0.86	205	10.0	0.78	56.6	0.3	0.69	329	14.4	0.85	217	10.0	0.72	62	7.6	0.66
All sites	C00-C96	6780	302.4	4.02	4547	208.9	3.41	69.5	2.1	0.67	8596	365.6	4.19	4919	213.6	3.25	74.8	8.4	0.57
All sites but non-melanoma skin	C00-C96 (without C44)	6426	285.7	3.89	4522	207.6	3.40	68.4	2.1	0.70	8154	345.7	4.07	4896	212.5	3.24	73.8	8.8	0.60

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.
All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S16. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Leningrad oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	544	9.5	0.42	526	9.3	0.42	73.9	3.1	0.97	619	9.9	0.4	511	7.9	0.36	**86.1** >	**4.8** >	0.83
Oesophagus	C15	361	6.2	0.34	451	7.8	0.38	64.8	5.3	1.25	274	4.3	0.27	459	7.3	0.35	62.8	12.8	1.68
Stomach	C16	1154	20.6	0.63	1268	22.3	0.66	65.9	7.3	1.10	884	13.9	0.48	1235	19.3	0.57	70.4	10.3	1.40
Colon, rectum, anus	C18-21	1367	24.5	0.7	1077	18.8	0.61	71.7	4	0.79	1331	21.1	0.6	1232	19.1	0.56	79.1	7.4	0.93
Liver	C22	128	2.3	0.21	350	6.1	0.34	7.8	33.6	2.73	121	1.8	0.18	369	5.8	0.31	18.2	36.4	3.05
Pancreas	C25	336	5.9	0.34	611	10.8	0.46	33	13.7	1.82	266	4.2	0.26	611	9.6	0.40	40.6	21.8	2.30
Larynx	C32	290	5	0.31	300	5.2	0.31	76.9	4.1	1.03	336	5.4	0.3	240	3.8	0.26	86.6	3.3	0.71
Trachea and lung	C33-34	1742	30.9	0.77	2747	48.6	0.97	42	11.1	1.58	1428	22.6	0.61	2955	46.8	0.88	42.6	18.3	2.07
Bone and cartilages	C40-41	47	1	0.16	36	0.8	0.15	70.2	4.3	0.77	23	0.6	0.14	40	0.7	0.13	73.9	13	1.74
Melanoma of skin	C43	171	3	0.23	87	1.5	0.17	**73.7** <	1.2	0.51	191	3.2	0.24	105	1.6	0.16	90.1	1.6	0.55
Skin	C44	763	13.9	0.54	41	0.7	0.12	85.7	0.3	0.05	691	10.9	0.43	64	1.0	0.13	94.1	0.4	0.09
Soft tissues	C45-49	100	2	0.22	80	1.5	0.18	60	3	0.80	97	2	0.23	75	1.3	0.15	84.5	5.2	0.77
Breast	C50	31	0.5	0.09	10	0.2	0.08	67.7	0	0.32	37	0.6	0.1	4	0.1	0.03	86.5	0	0.11
Prostate	C61	1334	23.9	0.69	666	11.7	0.49	66.5	2.4	0.50	1140	18.1	0.55	820	12.6	0.46	80.8	5.6	0.72
Kidney	C64	457	8.1	0.39	340	6.1	0.34	56.2	3.3	0.74	487	8	0.37	381	6.1	0.32	78	7	0.78
Bladder	C67	570	10.4	0.46	326	5.6	0.34	**60.2** <	3.5	0.57	598	9.5	0.4	305	4.8	0.28	86.1	2	0.51
Brain and CNS	C70-72	138	2.9	0.27	212	4.5	0.34	17.4	13.8	1.54	113	**2.2** <	**0.23**	237	4.0	0.28	28.3	24.8	2.10
Hodgkins lymphoma	C81	54	1.2	0.17	27	0.5	0.11	**27.8** <	1.9	0.50	61	1.3	0.18	21	0.4	0.09	**70.5** <	0	0.34
Nonhodgkins lymphoma	C82-85	126	2.4	0.23	148	2.7	0.23	**12.7** <	7.1	1.17	154	2.8	0.25	172	2.7	0.22	**40.3** <	9.1	1.12
Leukaemia	C91-95	166	3.8	0.35	186	3.5	0.28	19.3	12.7	1.12	132	**2.4** <	**0.22**	207	3.4	0.26	28	12.1	1.57
Other	a)	289	5.4	0.33	267	4.6	0.30	51.9	7.6	0.92	290	5	0.31	302	4.7	0.28	68.6	8.3	1.04
Other and ill-defined	b)	458	8.4	0.41	254	5.0	0.34	50	4.6	0.55	231	4.2	0.31	427	7.3	0.38	63.2	6.9	1.85
All sites	C00-C96	10626	191.6	1.96	10011	177.9	1.88	59.3	6	0.94	9504	153.9	1.64	10772	170.4	1.70	70.5	9	1.13
All sites but non-melanoma skin	C00-C96 (without C44)	9863	177.7	1.88	9970	177.2	1.87	57.2	6.5	1.01	8813	143	1.59	10708	169.5	1.70	68.6	9.6	1.22

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S17. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Murmansk oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	309	14.4	0.87	177	8.4	0.67	97.1	0.3	0.57	367	16.3	0.89	224	10.2	0.73	96.5	3.5	0.61
Oesophagus	C15	182	8.8	0.69	141	6.9	0.61	94.5	1.1	0.77	224	10.2	0.72	177	7.9	0.63	95.1	5.4	0.79
Stomach	C16	598	32.7	1.59	421	22.4	1.22	91.3	2.2	0.70	585	29.2	1.28	397	19.4	1.03	92.1	6.5	0.68
Colon, rectum, anus	C18-21	715	39	1.58	404	22.7	1.24	92.2	2.2	0.57	848	43.9	1.61	444	24.1	1.22	92.9	7	0.52
Liver	C22	90	4.8	0.58	94	4.7	0.57	77.8	10	1.04	99	4.8	0.52	96	4.6	0.50	85.9	36.4	0.97
Pancreas	C25	201	9.8	0.73	163	8.1	0.71	71.1	8	0.81	230	10.9	0.76	197	9.3	0.71	85.2	17	0.86
Larynx	C32	168	8.1	0.71	92	4.6	0.50	97	1.8	0.55	127	5.7	0.53	58	2.6	0.36	96.1	4.7	0.46
Trachea and lung	C33-34	1257	64.5	2.01	928	47.6	1.70	77.7	2.9	0.74	1296	63.1	1.85	934	46.0	1.60	82.7	9.2	0.72
Bone and cartilages	C40-41	25	1.2	0.25	13	0.5	0.14	80	4	0.52	25	1.4	0.31	18	0.9	0.23	88	8	0.72
Melanoma of skin	C43	99	4.5	0.47	48	2.2	0.34	98	1	0.48	134	6.4	0.59	49	2.3	0.36	94	4.5	0.37
Skin	C44	399	22.2	1.27	8	0.3	0.12	98.5	0.3	0.02	415	21.7	1.15	6	0.3	0.12	97.8	0.5	0.01
Soft tissues	C45-49	58	2.9	0.47	38	1.7	0.30	86.2	**12.1** >	0.66	79	3.8	0.47	38	1.9	0.34	89.9	6.3	0.48
Breast	C50	11	0.5	0.15	5	0.3	0.13	90.9	9.1	0.45	18	0.9	0.21	4	0.2	0.09	100	0	0.22
Prostate	C61	758	45.5	1.83	188	12.3	1.02	96.6	0.9	0.25	1148	62.4	1.95	245	14.1	0.96	96.9	3.7	0.21
Kidney	C64	343	17.1	1.01	126	6.3	0.59	77.8	1.5	0.37	525	24.1	1.1	149	7.4	0.67	88.6	8.6	0.28
Bladder	C67	200	11.4	0.96	98	7.0	0.93	91	1.5	0.49	348	17.2	0.97	111	5.8	0.58	95.4	2.9	0.32
Brain and CNS	C70-72	119	5.7	0.57	92	3.9	0.42	71.4	0.8	0.77	117	5.9	0.59	77	3.8	0.45	81.2	9.4	0.66
Hodgkins lymphoma	C81	81	3.7	0.43	30	1.2	0.23	92.6	2.5	0.37	61	3.2	0.44	19	0.8	0.20	91.8	3.3	0.31
Nonhodgkins lymphoma	C82-85	94	4.4	0.53	46	2.2	0.34	84	2.1	0.49	125	5.8	0.55	50	2.2	0.32	85.6	8.8	0.40
Leukaemia	C91-95	206	11	0.82	86	4.5	0.52	90.3	1.5	0.42	180	9.3	0.74	85	4.3	0.50	90	4.4	0.47
Other	a)	187	8.9	0.69	102	5.0	0.52	91.4	2.1	0.55	214	10.5	0.76	118	5.4	0.52	89.3	7	0.55
Other and ill-defined	b)	322	16.7	1.05	189	9.8	0.76	71.1	2.8	0.59	295	14.6	0.91	148	7.4	0.65	77.3	4.7	0.50
All sites	C00-C96	6422	337.8	4.7	3489	182.6	3.43	87.3	2.2	0.54	7460	371.2	4.57	3644	180.9	3.20	90.6	6.6	0.49
All sites but non-melanoma skin	C00-C96 (without C44)	6023	315.5	4.53	3481	182.3	3.43	86.6	2.4	0.58	7045	349.5	4.42	3638	180.6	3.20	90.2	7	0.52

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S18. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Novgorod oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	**ICD-10**	**Cases**	**ASR (W)**	**SE**	**Deaths**	**ASR (W)**	**SE**	**MV(%)**	**DCO(%)**	**M:I ratio**	**Cases**	**ASR (W)**	**SE**	**Deaths**	**ASR (W)**	**SE**	**MV(%)**	**DCO(%)**	**M:I ratio**
Lip, oral, pharynx	C00-14	325	15.6	0.89	184	8.8	0.67	93.2	1.5	0.57	354	16.3	0.89	170	8.0	0.62	70.9	2.3	0.48
Oesophagus	C15	208	9.8	0.7	183	8.8	0.68	83.2	7.2	0.88	211	10	0.7	168	7.7	0.61	64.9	6.6	0.80
Stomach	C16	713	34	1.33	571	27.4	1.20	81.6	7.6	0.80	714	32.8	1.27	474	21.7	1.03	60.8	8.1	0.66
Colon, rectum, anus	C18-21	713	32.9	1.29	413	19.3	1.00	85.7	4.8	0.58	784	35.9	1.33	355	16.2	0.89	64	6.4	0.45
Liver	C22	54	2.7	0.38	65	3.6	0.45	35.2	42.6	1.20	108	4.7	0.47	152	7.6	0.65	29.6	33.3	1.41
Pancreas	C25	183	8.7	0.67	165	7.8	0.63	44.8	21.9	0.90	251	11.9	0.78	235	10.9	0.73	31.5	19.9	0.94
Larynx	C32	171	8.4	0.66	132	6.7	0.60	89.5	4.7	0.77	158	7.3	0.59	74	3.5	0.41	72.2	5.1	0.47
Trachea and lung	C33-34	1347	64.9	1.84	1143	54.2	1.66	69.6	9.8	0.85	1349	62.5	1.74	982	45.6	1.49	48.5	11.6	0.73
Bone and cartilages	C40-41	15	0.9	0.24	23	1.2	0.26	80	13.3	1.53	20	1.2	0.29	16	0.9	0.23	55	10	0.80
Melanoma of skin	C43	64	3.2	0.41	28	1.4	0.27	92.2	0	0.44	91	4.4	0.47	37	1.7	0.29	**59.3** <	2.2	0.41
Skin	C44	536	26.4	1.22	18	0.8	0.20	95.3	0	0.03	604	27.9	1.17	10	0.4	0.15	75.2	0	0.02
Soft tissues	C45-49	42	2	0.34	31	1.5	0.28	88.1	2.4	0.74	62	3.2	0.43	26	1.5	0.31	75.8	4.8	0.42
Breast	C50	4	0.2	0.08	2	0.1	0.09	100	0	0.50	16	0.8	0.21	7	0.2	0.10	68.8	0	0.44
Prostate	C61	648	30.8	1.29	215	10.0	0.73	90.3	3.2	0.33	692	31.5	1.24	208	9.5	0.68	65.9	4.8	0.30
Kidney	C64	267	13	0.84	133	6.4	0.58	59.9	6.7	0.50	308	14.7	0.86	113	5.4	0.52	48.7	5.8	0.37
Bladder	C67	324	15.7	0.92	126	6.0	0.57	87.3	4.6	0.39	357	16.7	0.92	90	4.0	0.44	58.8	4.2	0.25
Brain and CNS	C70-72	87	5.4	0.65	74	4.2	0.54	69	12.6	0.85	116	7.3	0.74	80	4.4	0.54	43.1	19.8	0.69
Hodgkins lymphoma	C81	34	2.2	0.39	11	0.7	0.20	85.3	2.9	0.32	36	2.7	0.49	8	0.4	0.14	**38.9** <	2.8	0.22
Nonhodgkins lymphoma	C82-85	119	6.3	0.62	56	2.9	0.41	**70.6** <	5	0.47	96	4.8	0.51	49	2.3	0.37	**52.1** <	3.1	0.51
Leukaemia	C91-95	145	8.1	0.76	86	4.4	0.53	80.7	9.7	0.59	140	8.4	0.79	60	2.9	0.39	37.1	3.6	0.43
Other	a)	177	9.4	0.75	115	5.7	0.56	84.2	6.8	0.65	205	10.3	0.76	133	6.3	0.56	60.5	3.9	0.65
Other and ill-defined	b)	193	10.1	0.78	155	7.5	0.64	61.1	6.2	0.80	208	10.1	0.73	152	7.1	0.60	52.9	10.1	0.73
All sites	C00-C96	6369	310.4	4.11	3929	189.5	3.17	79.6	6.7	0.62	6880	325.3	4.08	3599	168.2	2.90	58.1	7.5	0.52
All sites but non-melanoma skin	C00-C96 (without C44)	5833	283.9	3.93	3911	188.7	3.16	78.1	7.3	0.67	6276	297.3	3.91	3589	167.8	2.90	56.4	8.2	0.57

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S19. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Saint-Petersburg, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	1998	13	0.3	1349	8.7	0.24	**78** >	**14.5** >	0.68	2284	13.6	0.29	1387	8.2	0.22	**81.6** >	**10.7** >	0.61
Oesophagus	C15	1134	7.1	0.22	1032	6.5	0.21	**64** <	**25.9** >	0.91	1133	6.5	0.2	940	5.4	0.18	67.8	**20.7** >	0.83
Stomach	C16	4372	26.9	0.42	3563	21.7	0.38	**66.1** <	**26.2** >	0.81	4420	24.3	0.38	3403	18.4	0.33	68.8	**21.6** >	0.77
Colon, rectum, anus	C18-21	6538	39.4	0.51	4052	23.9	0.39	70.9	**20.8** >	0.62	7311	40.1	0.48	4002	21.1	0.35	77.1	**15.1** >	0.55
Liver	C22	825	5.2	0.19	895	5.6	0.20	**15.4** <	**54.3** >	1.08	1017	5.7	0.19	1093	6.2	0.20	**22.4** <	**44.2** >	1.07
Pancreas	C25	1854	11.5	0.28	1789	11.2	0.27	**25.6** <	**37.7** >	0.96	2236	12.4	0.27	2053	11.4	0.26	**33** <	**29.8** >	0.92
Larynx	C32	958	6.2	0.2	587	3.7	0.16	**74.8** <	**17.5** >	0.61	1074	6.3	0.2	583	3.4	0.14	**76.4** <	**13.4** >	0.54
Trachea and lung	C33-34	7479	46.6	0.56	6594	40.7	0.52	**46.7** <	**30.3** >	0.88	7792	44.1	0.51	6547	36.7	0.47	**52.2** <	**24.5** >	0.84
Bone and cartilages	C40-41	154	1.3	0.12	127	1.0	0.10	**58.4** <	**27.3** >	0.82	182	1.4	0.12	113	0.8	0.09	69.8	18.1	0.62
Melanoma of skin	C43	864	5.5	0.19	412	2.6	0.13	**83** <	**11.6** >	0.48	1036	6	0.19	468	2.6	0.13	**85.6** <	**7.2** >	0.45
Skin	C44	2452	14.8	0.31	130	0.8	0.07	89.3	2.2	0.05	3570	19	0.33	150	0.8	0.07	94.7	1.3	0.04
Soft tissues	C45-49	460	3.2	0.17	298	2.0	0.13	57.8	**25.7** >	0.65	525	3.3	0.16	311	1.9	0.12	62.7	**19.2** >	0.59
Breast	C50	74	0.4	0.05	26	0.2	0.03	**73** <	**13.5** >	0.35	86	0.5	0.05	33	0.2	0.03	**74.4** <	**12.8** >	0.38
Prostate	C61	5748	35.2	0.48	2203	12.9	0.29	77.7	**13.6** >	0.38	7876	43.1	0.5	2611	12.9	0.26	82.8	**8.7** >	0.33
Kidney	C64	2199	14.2	0.32	1058	6.6	0.21	**57.5** <	**18.1** >	0.48	2577	15	0.31	1095	6.1	0.19	**66.1** <	**14.4** >	0.42
Bladder	C67	2080	12.7	0.29	952	5.6	0.19	**69.6** <	**16.2** >	0.46	2553	13.9	0.29	907	4.6	0.16	**73.1** <	**11** >	0.36
Brain and CNS	C70-72	902	6.5	0.24	727	5.2	0.22	47.8	**29.5** >	0.81	1077	7	0.23	845	5.4	0.20	54	22.1	0.78
Hodgkins lymphoma	C81	304	2.4	0.14	116	0.8	0.08	**57.6** <	**11.2** >	0.38	322	2.5	0.16	85	0.5	0.06	**48.1** <	**5.6** >	0.26
Nonhodgkins lymphoma	C82-85	875	5.8	0.21	473	3.0	0.15	**45** <	**21.7** >	0.54	1273	7.7	0.23	570	3.2	0.14	**48.6** <	**13.5** >	0.45
Leukaemia	C91-95	1381	10	0.31	698	4.8	0.20	80.7	**21.5** >	0.51	1466	9.8	0.29	772	5.1	0.21	76.1	**13.8** >	0.53
Other	a)	1409	9.1	0.25	947	6.0	0.21	64	**24.7** >	0.67	1872	11.3	0.27	1088	6.1	0.19	66.6	**18.1** >	0.58
Other and ill-defined	b)	1240	8.5	0.26	1014	6.9	0.24	47.6	23.5	0.82	1720	10.8	0.28	1264	7.3	0.22	62.2	18.2	0.73
All sites	C00-C96	45300	285.4	1.41	29043	180.6	1.11	**63.4** <	**22** >	0.64	53402	304.4	1.38	30320	168.4	1.01	**69** <	**16.1** >	0.57
All sites but non-melanoma skin	C00-C96 (without C44)	42848	270.6	1.37	28913	179.8	1.11	**61.9** <	**23.1** >	0.67	49832	285.4	1.34	30170	167.6	1.01	**67.1** <	**17.2** >	0.61

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

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[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S20. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Pskov oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	310	13.3	0.78	237	10.2	0.68	92.9	0.3	0.76	354	15.2	0.83	242	10.5	0.69	96.9	1.4	0.68
Oesophagus	C15	190	8.2	0.61	168	7.2	0.57	78.9	2.6	0.88	203	8.7	0.63	165	7.0	0.56	91.1	7.9	0.81
Stomach	C16	736	31.4	1.2	685	29.3	1.16	75.7	4.1	0.93	667	28.5	1.14	557	23.6	1.03	87.4	9.7	0.84
Colon, rectum, anus	C18-21	711	31.1	1.22	478	20.3	0.98	79.2	3	0.67	762	32.4	1.21	490	21.0	1.00	87.5	7.2	0.64
Liver	C22	93	4.1	0.45	130	5.6	0.51	18.3	15.1	1.40	101	4.4	0.46	119	5.1	0.48	49.5	30.7	1.18
Pancreas	C25	210	8.7	0.62	228	9.7	0.66	27.6	10.5	1.09	229	9.5	0.65	219	9.0	0.63	55.9	20.5	0.96
Larynx	C32	256	11	0.71	191	8.3	0.62	92.2	1.2	0.75	305	13.3	0.78	220	9.5	0.66	97	4.9	0.72
Trachea and lung	C33-34	1335	58.5	1.66	1281	55.3	1.61	58.5	4.6	0.96	1361	58.1	1.61	1131	48.2	1.47	71	11.8	0.83
Bone and cartilages	C40-41	19	1	0.24	23	1.1	0.23	57.9	0	1.21	20	1	0.26	21	1.0	0.23	75	0	1.05
Melanoma of skin	C43	77	3.6	0.43	38	1.8	0.31	97.4	0	0.49	81	3.7	0.43	37	1.6	0.27	97.5	1.2	0.46
Skin	C44	603	26.3	1.12	19	0.9	0.22	99.2	0.2	0.03	703	29.7	1.16	21	0.9	0.21	99.7	0.3	0.03
Soft tissues	C45-49	55	2.7	0.4	36	1.6	0.28	56.4	3.6	0.65	71	3.5	0.46	50	2.3	0.36	74.6	7	0.70
Breast	C50	12	0.6	0.17	7	0.3	0.13	91.7	8.3	0.58	10	0.4	0.14	3	0.1	0.07	90	0	0.30
Prostate	C61	559	23.2	1.04	268	10.9	0.70	75.5	1.8	0.48	836	34.9	1.25	316	12.8	0.75	91.1	3.1	0.38
Kidney	C64	280	12.2	0.76	166	7.2	0.58	60	2.9	0.59	313	14.1	0.84	151	6.3	0.53	76.7	5.8	0.48
Bladder	C67	256	10.9	0.71	179	7.4	0.58	67.2	2.7	0.70	299	12.8	0.76	159	6.6	0.54	82.6	5	0.53
Brain and CNS	C70-72	101	5.4	0.59	103	5.5	0.59	42.6	8.9	1.02	117	5.8	0.58	101	4.5	0.48	72.6	14.5	0.86
Hodgkins lymphoma	C81	56	3	0.42	22	1.0	0.21	**50 <**	3.6	0.39	53	2.8	0.41	23	1.2	0.25	**64.2 <**	5.7	0.43
Nonhodgkins lymphoma	C82-85	91	4.8	0.57	36	1.6	0.28	**39.6 <**	3.3	0.40	96	4.4	0.47	38	1.6	0.27	**43.8 <**	4.2	0.40
Leukaemia	C91-95	89	4.5	0.55	76	3.5	0.44	24.7	19.1	0.85	131	6.6	0.65	93	4.2	0.48	46.6	18.3	0.71
Other	a)	139	6.6	0.59	128	5.3	0.48	69.8	6.5	0.92	186	8.6	0.66	134	5.8	0.51	87.6	9.7	0.72
Other and ill-defined	b)	168	7.5	0.62	166	7.4	0.61	36.9	1.8	0.99	228	10.5	0.75	142	6.3	0.56	50.4	6.1	0.62
All sites	C00-C96	6346	278.5	3.67	4665	201.4	3.08	69.7	3.6	0.74	7126	308.9	3.8	4432	189.2	2.94	81.7	7.6	0.62
All sites but non-melanoma skin	C00-C96 (without C44)	5743	252.2	3.49	4646	200.5	3.08	66.7	4	0.81	6423	279.2	3.62	4411	188.3	2.94	79.8	8.4	0.69

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

[a] 'Other' group includes following ICD-10 codes: C17, C23-24, C26, C30-31, C37-39, C51-52, C57-58, C60, C62-63, C65-66, C68, C90. [b] 'Other and ill-defined' group includes following ICD-10 codes: C69, C73-80, C88, C96

[*] ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) [†] MV% - proportion of morphologically verified cases. [‡] DCO% - proportion of cases reported only by death certificate. [§] M:I ratio - mortality to incidence ratio.

Table S21. Comparison of incidence and mortality rates (ASRs), MV%, DCO% and M:I ratios, Vologda oblast, 2008-2012 and 2013-2017, Males.

		2008-2012									2013-2017								
		Incidence			Mortality						Incidence			Mortality					
Site	ICD-10	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio	Cases	ASR (W)	SE	Deaths	ASR (W)	SE	MV(%)	DCO(%)	M:I ratio
Lip, oral, pharynx	C00-14	405	10.5	0.55	250	6.5	0.43	87.2	1.5	0.62	516	13.2	0.6	298	7.6	0.46	**89.1** >	**4.8** >	0.58
Oesophagus	C15	298	7.9	0.48	303	8.1	0.49	82.2	4.4	1.02	307	8	0.47	312	8.1	0.47	77.5	14.3	1.02
Stomach	C16	1218	33	0.99	1113	29.7	0.94	80	7.6	0.91	1124	28.8	0.89	1004	25.4	0.83	73.1	**24.3** >	0.89
Colon, rectum, anus	C18-21	1124	29.8	0.94	757	20.6	0.80	86.4	4.9	0.67	1288	33.3	0.96	766	19.4	0.73	84.5	10.2	0.59
Liver	C22	88	2.5	0.29	193	5.7	0.44	29.5	26.1	2.19	143	3.7	0.32	227	6.2	0.43	43.4	28	1.59
Pancreas	C25	279	7.4	0.46	348	9.3	0.52	47	12.2	1.25	307	8	0.47	347	8.9	0.49	40.7	33.6	1.13
Larynx	C32	250	6.6	0.44	159	4.2	0.35	93.2	1.6	0.64	271	7	0.44	144	3.8	0.32	93.7	2.6	0.53
Trachea and lung	C33-34	1893	50.6	1.22	1961	52.0	1.24	55.8	7.8	1.04	1982	50.7	1.18	1806	46.2	1.13	63.4	19.4	0.91
Bone and cartilages	C40-41	42	1.3	0.21	43	1.2	0.20	47.6	11.9	1.02	46	1.4	0.22	40	1.1	0.19	63	13	0.87
Melanoma of skin	C43	153	4.1	0.35	69	1.9	0.23	**68** <	2.6	0.45	159	4.3	0.35	55	1.4	0.20	94.3	3.1	0.35
Skin	C44	839	22.5	0.83	36	0.9	0.17	**20.3** <	0	0.04	909	23.9	0.83	21	0.5	0.11	99	0.2	0.02
Soft tissues	C45-49	96	3.1	0.33	62	1.8	0.24	75	3.1	0.65	73	2	0.25	44	1.3	0.20	78.1	8.2	0.60
Breast	C50	7	0.2	0.08	6	0.1	0.05	100	0	0.86	32	0.8	0.15	1	0.0	0.02	90.6	3.1	0.03
Prostate	C61	743	20.3	0.79	434	11.7	0.61	91.1	3	0.58	1108	29	0.91	461	12.3	0.60	89.7	5.1	0.42
Kidney	C64	457	12.5	0.62	230	6.4	0.45	74	4.2	0.50	499	13	0.6	246	6.5	0.43	77.4	6	0.49
Bladder	C67	488	13.5	0.65	254	6.5	0.43	85.5	2.9	0.52	498	12.9	0.6	252	6.5	0.43	85.9	6.6	0.51
Brain and CNS	C70-72	142	4.6	0.42	176	5.6	0.45	35.2	16.9	1.24	186	5.8	0.46	166	4.9	0.40	38.7	21	0.89
Hodgkins lymphoma	C81	9	**0.3** <	**0.09**	13	0.4	0.10	**22.2** <	0	1.44	83	2.8	0.33	18	0.5	0.13	**57.8** <	4.8	0.22
Nonhodgkins lymphoma	C82-85	24	**0.7** <	**0.15**	85	2.2	0.25	**33.3** <	20.8	3.54	187	5.4	0.42	80	2.1	0.25	**58.3** <	2.1	0.43
Leukaemia	C91-95	154	4.8	0.42	133	4.0	0.38	51.9	9.7	0.86	282	8.5	0.55	138	4.0	0.36	50.7	7.8	0.49
Other	a)	202	5.8	0.43	232	6.4	0.44	79.2	4	1.15	292	8	0.49	234	6.2	0.42	75.7	9.6	0.80
Other and ill-defined	b)	304	8.2	0.5	359	9.8	0.55	43.4	10.2	1.18	427	11.5	0.59	436	11.3	0.56	48.9	25.1	1.02
All sites	C00-C96	9215	250.3	2.76	7216	194.9	2.44	67.6	5.7	0.78	10719	282.1	2.84	7097	184.2	2.27	75.4	12.6	0.66
All sites but non-melanoma skin	C00-C96 (without C44)	8376	227.7	2.63	7180	193.9	2.43	72.3	6.3	0.86	9810	258.2	2.72	7076	183.7	2.27	73.2	13.8	0.72

Cancer sites groups are based on ICD-10 death coding classfication to match national mortality statistics coding system. Lower (<) or higher (>) results are marked in bold and color when compared with that from 12 cancer registries in CI5X 2003-2007: Bulgaria, Croatia, Czech Republic, Latvia, Lithuania, Poland (Cracow), Poland (Lower Silesia), Poland (Kielce), Poland (Podkarpackie), Slovakia, Slovenia, Serbia.

All statistical tests are described in Cancer Incidence in Five Continents Volume VIII (IARC Scientific Publications No. 155, 2002, Chapter 5. Comparability and quality of data, D.M. Parkin and M. Plummer). Tests are performed for incidence ASRs, MV(%) and DCO(%).

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* ASR (W) - age-standardised rate (world standard population by Segi and Doll, 1966) † MV% - proportion of morphologically verified cases. ‡ DCO% - proportion of cases reported only by death certificate. § M:I ratio - mortality to incidence ratio.

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Completeness of cancer registry data in northwest Russia 2008-2017

Barchuk, Anton, Rustam Tursun-zade, Ekaterina Nazarova, Yuri Komarov, Ekaterina Tyurina, Yulia Tumanova, Alexey Belyaev, and Znaor Ariana

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Breast and cervical cancer incidence and mortality trends in Russia 1980–2013

Barchuk, Anton, Aleksandr Bespalov, Heini Huhtala, Tuvshinjargal Chimed, Irina Laricheva, Alexey Belyaev, Freddie Bray, Ahti Anttila, and Anssi Auvinen

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Breast and cervical cancer incidence and mortality trends in Russia 1980–2013

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ABSTRACT

Background: Breast and cervical cancer are among the leading causes of preventable cancer deaths in women in Russia. The aim of this study is to analyze changes in breast and cervical cancer incidence and mortality trends using data from the Russian State Cancer Registry.

Methods: The age-standardized rates of cervical cancer incidence (1993–2013) and mortality (1980–2013) were analyzed using piecewise linear regression. Age-period-cohort models were used to estimate the temporal effects and provide future predictions.

Results: Breast and cervical cancer incidence rates uniformly increased over two decades from 33.0 to 47.0 per 100,000 and from 10.6 to 14.2 per 100,000, respectively. Breast cancer mortality rates however declined from 17.6 to 15.7 in 2013, while cervical cancer mortality increased steadily from 5.6 to 6.7. Breakpoints in the risk occurred in cohorts born 1937–1953, indicating a recent generational decrease in breast cancer mortality, but a concomitant increase in cervical cancer. Cervical cancer has already surpassed breast cancer in terms of years of life lost (YLL) (23.4 per death vs 18.5 in 2009–2013), while future projections suggest that the annual YLL could reach 1.2 million for cervical cancer and (decline to) 1.8 million for breast cancer by the year 2030.

Conclusion: The temporal patterns of breast cancer incidence and mortality in Russia are in line with other countries in Europe, although cervical cancer rates and the risk of occurrence in recent generations is rapidly increasing; these trends underscore the need to place immediate priority in national cervical vaccination and screening programs.

1. Introduction

Breast cancer is the most common cancer type of women globally while cervical cancer is among most common cancer types in less developed regions [1]. Both breast and cervical cancer are among the leading causes of preventable cancer deaths in women in Russia [2]. Despite their high frequency, systematic large-scale efforts aimed at primary and secondary prevention to control breast and cervical tumours, while available [3–5], are not systematically implemented in the country [6].

A thorough quantification of the healthcare problem and its eligibility is the first of the WHO criteria for screening described by Wilson and Jungner [7]. Cost-effectiveness of interventions also depends on the cancer scale and profile, an assessment of trends, and projections evaluating possible impacts in the presence and absence of cancer control programmes [8,9]. Assessing cancer patterns and trends is essential for setting the health care priorities, identifying targets for intervention as well as guiding further research. Appropriate quantification requires valid, consistent and comparable data over time to reflect real trends and interpretation of the underlying changes [10].

Epidemiological data from Russia has not been extensively reported for several reasons: the language barrier, still limited formal education in epidemiology, scarce resources for cancer epidemiologic research and a lack of formal quality evaluation of registry data [11,12]. This is

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unfortunate given the vast proportion of the European population that Russia constitutes and the long history of the population-based cancer registration system in the country, established in the USSR in 1953 [12]. All medical facilities are obliged to notify the regional population-based cancer registries of all newly-diagnosed cancer cases and any new hospitalization of patients with cancer. The State Cancer Registry (SCR) based at the Herzen Research Institute of Oncology in Moscow aggregates the data from the regional registries and produces an annual report with crude data that is freely available [13]. Several changes in lifestyle, behavioral and reproductive factors in the last few decades in Russia, together with socioeconomic changes, likely influence the changing cancer profiles now observed [14].

The analysis of cancer trends and their changes in Russia are thus essential to understand the impact of cancer on the health care system in Russia. The aim of this study is to describe breast and cervical cancer incidence and mortality trends in Russia, quantifying changes using several indicators of the cancer burden including years of life lost (YLL), and a prediction of the future burden circa 2030, via an extrapolation of recent trends and demographic changes, as a baseline for cancer control action.

2. Materials and methods

2.1. Incidence, mortality, and population data

This study followed the data analysis protocol developed for the Russian cancer registries (details are described in *Supplementary Material 1*). Female breast and cervical cancer incidence (1993–2013) and mortality (1993–2013) data were acquired from the SCR based at the *P. Herzen Moscow Oncological Research Center* in Moscow. Obligatory cancer registration covers the entire population of the Russian Federation (143.5 million people in 2013) since 1953, but the SCR was officially established only in 1996 [15]. Registry operations are described in detail in the official order of the Ministry of Healthcare of Russian Federation (MOH) and involve the sending out of standardized paper-based notifications to the regional population-based cancer registries in Russia (at the moment more than 80 regional registries are operating in Russia), from which paper-based and electronic reports are then forwarded to the SCR [16]. The incidence data are collected under the supervision of the MOH, while the mortality data (based on death certificates) is collected independently as a part of the demographic data capture by the regional civil registries. At present, no comprehensive report is available about quality of the data in Russia. For cancers identified from death certificates only an overall number for all age groups and sexes for each regional cancer registry is provided [15].

All registered incident cancer cases and deaths were tabulated by age, sex and calendar period. Age-specific data was available for age-groups 20–24 and above for breast cancer incidence, breast and cervical cancer mortality, and for age-groups 15–19 and above for cervical cancer incidence. Overall number of cases and deaths registered for the study period was reported according to SCR. The number of cases and deaths registered before age of 20 was at most 0.08% (29 cases of breast cancer were registered in 1993 before age of 20). Population data were retrieved from the Federal State Statistics Service (FSSS) [17].

For comparative and validation purposes, additional sources of mortality data (1980–2011) were obtained from the World Health Organization (the WHO) Mortality Database and the Human Mortality Database [18,19]. Both databases use data reported by the MOH based on civil registration system. The mortality data before 1991 refer to the Russian Soviet Federative Socialist Republic (the RSFSR). The comparison of overlapping data from WHO and SCR (1993–2011) revealed only minor disparities. Most of them were for the years 2004 and 2005, for which the differences in the number of deaths were at most 0.4% and distributed equally by age group (e.g. for year 2004 overall 22,757 vs. 22,797 for breast cancer and 6003 vs. 6022 for cervical cancer as reported in the SRC and WHO data systems, respectively). For all years in this period, the disparities were less than 0.05% and the absolute difference was less than 10 cases. SCR data were thus used in the analysis.

In order to correct for possible inaccuracies in the reported deaths from uterine cancers (endometrial, cervical, and other and unspecified cancers), we applied the reallocation rules developed and applied in an earlier analysis of cervical cancer mortality trends [20]. Cervical cancer mortality in Russia was corrected using WHO mortality data for similar periods using the "gold standard" of Hungary (Fig. 1 and Table 1 in *Supplementary Material 2*). The incidence data reported by SCR did not include *uterus not otherwise specified* (NOS) cases (ICD-10 C55), hence the previously-used correction was not feasible, and in any case, the equivalent NOS proportions were minor, relative to mortality. The mortality trends from Uterus and Uterus NOS (C54, 55) and Uterus (C54) incidence are presented as Figs. 4 and 5 in *Supplementary Material 2*.

2.2. Statistical analysis

Age-standardized rates (ASR) of cancer incidence and mortality per 100,000 person-years were calculated using the Segi-Doll world standard population [21]. In order to find breakpoints (joinpoints) in trends, we fitted simple linear regression models with the ASR as response, calendar period the explanatory variable, using an iterative procedure proposed for estimation of regression models with piecewise linear relationships[22]. Estimates from the final model were plotted against the original trend with breakpoints and the annual percentage changes (EAPC) between linear segments were reported. Incidence and mortality ASRs per 100,000 person-years in 2008 and 2013 were obtained for 82 regional cancer registries in order to compare with national trends.

Age (A), calendar period (P), and birth cohort (C = P-A) effects on incidence and mortality were estimated using age-period-cohort models, that have been described elsewhere[23]. Briefly, the rates are described as a function of age, period, and cohort using a log-linear model, with Poisson errors and a logarithmic link function: $\log[I(A, P)] = a(A) + p(P) + c(C)$, where a, p, and c are the functions each parameterized with a limited number of parameters. We restricted our analyses to age intervals of 20–84 years and both maximum likelihood and sequential procedures for modelling were applied. A unique solution was provided by imposing constraints on the cohort and period effects (C_o = 1945 or P_o = 2000) with the first-order (linear) trend set to birth cohort, and the longitudinal age curve based on the reference cohort reported. The drift parameter was estimated as EAPC = $(\exp(\text{drift}) - 1) \times 100$). Natural splines were used to model the functions with seven knots applied to each effect category. In Table 2–5 of *Supplementary Material 2*, we present comparison based on the differences of residual deviances and degrees of freedom using χ^2 tests; the goodness-of-fit measures of the models are not reported as some have suggested they do not convey meaningful information about the actual model fit [23].

After comparing the likelihood ratio statistics, the final reported results were derived from the age-cohort model, with the age effects as rates for the reference cohort and cohort effects as rates relative to the reference cohort. Period effects were obtained from the model with the period term alone, using log (fitted values) from the age-cohort model as offset [24]. In order to simultaneously assess and present changes in incidence and mortality, we also show hodographs for cohort effect functions.

To predict future rates, we applied a validated approach that also utilizes age-period-cohort models (Nordpred) based on three plausible scenarios (Scenario 1: without reduction of drift; Scenario2: with 100% reduction for all periods; Scenario 3: 0–25%-50%-75% reduction in each following projection period) alongside official predicted population retrieved from FSSS [25](for details see *Supplementary Material 1*). The projection was done for four 5-year periods till (2014–2033) based

on four most recent 5-year periods (1994–2013). Years of life lost were calculated as the sum of age-specific YLL for each period year, derived as a composition of cancer deaths and life-expectancy. Cause-deleted period life-tables from 1980 till 2033 were generated based on data from Human Mortality Database and forecasts with functional demographic model [26]. All analyses were performed in R (version 3.2.3, 2015-12-10)), using packages "Epi" (version 2.0) [27], "segmented"(-version 0.5–1.4) [28], "popEpi" (version 0.3.1) [29], "Nordpred" (assessed on 15.05.2016) [30] and "demography" (version 1.18) [31]. We used 95% confidence intervals.

2.3. Ethical considerations

This study analyzed publically available secondary aggregate data, and thus did not require, according to the current legislature, additional ethical approval.

3. Results

3.1. Incidence and mortality: overall patterns and trends

During the study period 1993–2013, an average 47,700 cases of breast cancer were registered in Russia annually, with 18,830 deaths from the disease for the period 1980–2013. Correspondingly, an average of 12,990 cervical cancer cases were registered in Russia in the period 1993–2013, with 7430 cervical cancer deaths (corrected estimates) registered in 1980–2013 (number of cases and deaths for 4 and 5-year periods are presented in Table 1). A constant increase in incidence rates for breast cancer was observed, with no significant breakpoints. Incidence rates increased from 33.0 per 100,000 in 1993 to 47.0 per 100,000 in 2013 (Fig. 1A), with an APC of 1.3% (95%CI: 1.0; 1.6) over this period. Breast cancer mortality exhibited an opposite trend after 2000, however, reaching a peak of 17.6 per 100,000 circa 2000 and declining thereafter (APC −0.5% (95%CI: −0.7; −0.3), to 15.7 per 100,000 in 2013 (Fig. 1C). A pattern somewhat similar to breast cancer incidence was observed also for cervical cancer incidence, with trends increasing from 10.6 per 100,000 in 1993 to 14.2 per 100,000 in 2013, and a single breakpoint detected in 2002, with a stronger increase in the more recent period (APC 0.7% (95%CI: 0.5; 1.0) before and 2.3% (95%CI: 2.1; 2.6) after 2002 (Fig. 1B). The corrected cervical cancer mortality rates exhibited a trend opposite to breast cancer mortality, rising after 1997 with an APC of 1% (95%CI: 0.6; 1.4) (Fig. 1D). Regional trends were consistent with national in most of the regions between 2008 and 2013 (Table 12 in *Supplementary material 2*).

3.2. Age-period-cohort analyses

An increasing risk was observed with age for both breast cancer incidence and mortality (Fig. 2A, C). For cervical cancer incidence and mortality, age effects plateaued at ages 45–49 to 60–64 years (Fig. 2B, D). The comparison of models in the age-period-cohort analysis revealed strong non-linear cohort effects across all four datasets (Tables 2–5 *Supplementary material 2*). The breakpoints of cervical and breast cancer risks were observed for the cohorts born between the late-1930 s and early-1950 s (Fig. 2). In assessing the interrelationship of cohort effects for incidence and mortality, the hodograph for breast cancer revealed an increase in both incidence and mortality for cohorts of women born before 1950, followed by rather stable cohort-specific incidence trends but decreasing cohort-specific death trends (Fig. 6A in *Supplementary material 2*). A similar graphical comparison of cohort effects for cervical cancer showed decreasing risks up to the 1937 birth cohort followed by markedly increasing risks thereafter (Fig. 6B *Supplementary material 2*). The mortality trends for breast and cervical cancer were opposite: for breast cancer, successive cohorts were at increasing risk up to those born around 1949, but the risks declined thereafter (the relative risk for breast cancer death was 0.71 (95%CI: 0.70; 0.72) for women born in 1970 compared to 1945 reference cohort). For cervical cancer mortality, the decreasing risk for birth cohorts from 1915 to 1937 was followed by an increasing risk among the more recent birth cohorts (the relative risk for cervical cancer death was 1.55 (95%CI: 1.56; 1.63) for women born in 1970 compared to the 1945 reference cohort). The ratio of the cohort effects for cervical and breast cancer mortality and incidence showed a constant increase in risk of cervical cancer death for cohorts born after 1940 (Figs. 2 and 3 in *Supplementary material 2*).

3.3. Predictions

Different assumptions regarding the cut of the drift were used to illustrate the uncertainty of the predictions (Tables 6–9 in *Supplementary material 2*). The scenario with a sequential drift cut provided intermediate estimates and was arbitrarily selected for reporting. The predictions showed future declines in breast cancer mortality rates beyond 2030, but they were offset by equivalent increases in cervical cancer (Fig. 3). The absolute number of breast cancer cases and deaths was predicted to increase to circa 2030, with 72,000 cases and 22,000 deaths annually projected for the period 2029–2033, a similar number of deaths as observed in 1999–2003. The increasing cervical cancer incidence and mortality trends are predicted to result in around 22,100 cases and 10,500 deaths yearly over the period 2029–2033 – more than 2700 additional annual cervical cancer deaths compared with 2004–2008, assuming current trends continue in the next decades.

Table 1
Total number of breast and cervical cancer cases and deaths, average annual age-standardized incidence (ASIRs) and mortality (ASMRs) rates per 100,000 women in Russia 1980–2013 (for periods 1980–1983 and 1984–1988 incidence data are not available, for period 1980–1983 number of deaths is report for 4-year period, for all other periods absolute number of cases and deaths is reported for 5-year periods.).

Year	Breast cancer				Cervical cancer					
	Total number of cases	ASIRs (W) per 100,000	Total number of deaths	ASMRs (W) per 100,000	Total number of cases	ASIRs (W) per 100,000	Total number of deaths		ASMRs (W) per 100,000	
							Reported	Corrected	Reported	Corrected
1980–1983	–	–	47,754	11.3	–	–	27,705	29,891	6.2	6.8
1984–1988	–	–	70,285	12.8	–	–	32,035	35,579	5.4	6.2
1989–1993	36,041*	33.0*	84,812	14.6	11,714*	10.6*	31,040	35,644	5.0	6.0
1994–1998	196,600	35.1	99,143	16.5	59,326	10.7	30,727	36,137	4.9	6.0
1999–2003	226,764	38.6	108,808	17.2	61,243	11.2	31,239	35,825	5.1	6.0
2004–2008	253,404	41.8	113,407	17.2	66,147	12.3	30,244	39,006	5.0	6.4
2009–2013	288,844	45.6	115,945	16.4	74,382	13.8	31,618	40,544	5.2	6.6

* - incidence estimates for 1989–1993 are reported from 1993 only.

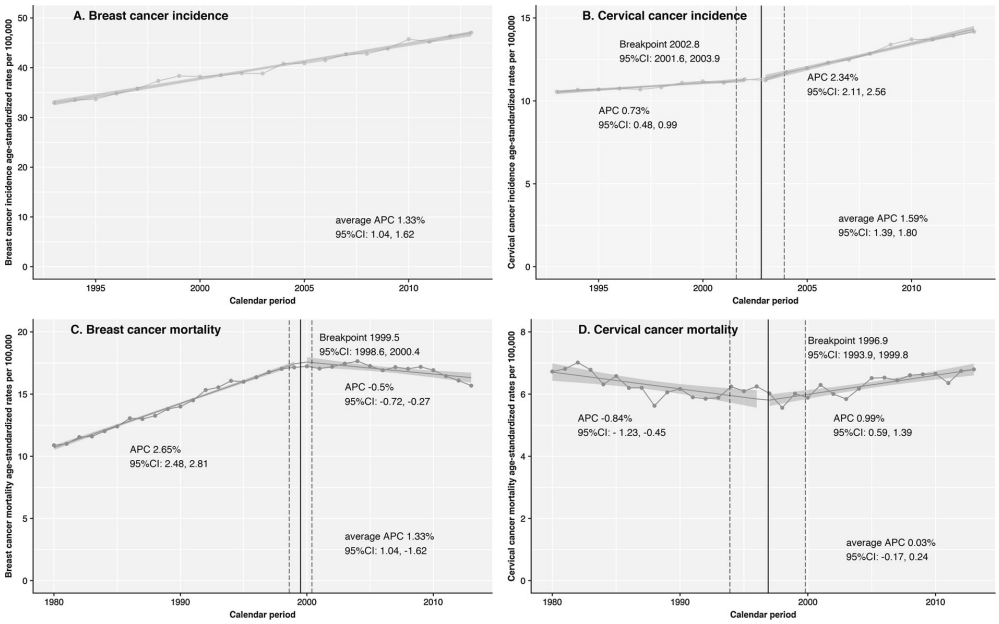

Fig. 1. Cancer incidence (1993–2013) and mortality (1980–2013) age-standardized rates per 100,000 women in Russia with fitted lines from piecewise linear regression and corresponding broken points and EAPCs (if available) and average EAPCs.

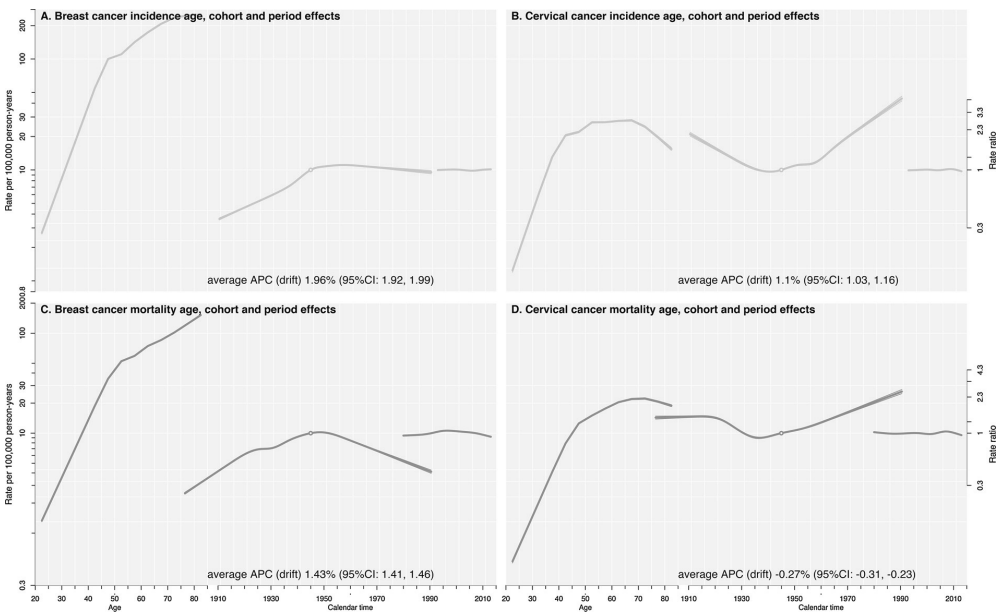

Fig. 2. Age, cohort, and period effects for breast and cervical cancer incidence (1993–2013) and mortality (1980–2013) among women in Russia (the age effects are rates for the reference cohort born in 1945 from the age-cohort model, cohort effects are rates relative to the reference cohort the age-cohort model, period effects are from the separate model with log (fitted values) from the age-cohort model as offset).

3.4. Years of life lost

The number of YLL per death for cervical cancer surpassed that of breast cancer in the early 1990 s, with the gap widening in projection to 23.8 YL L per cervical cancer death, compared with 17.1 YL L per breast cancer death by 2019–2023 (Fig. 4 A; Table 10 in *Supplementary*

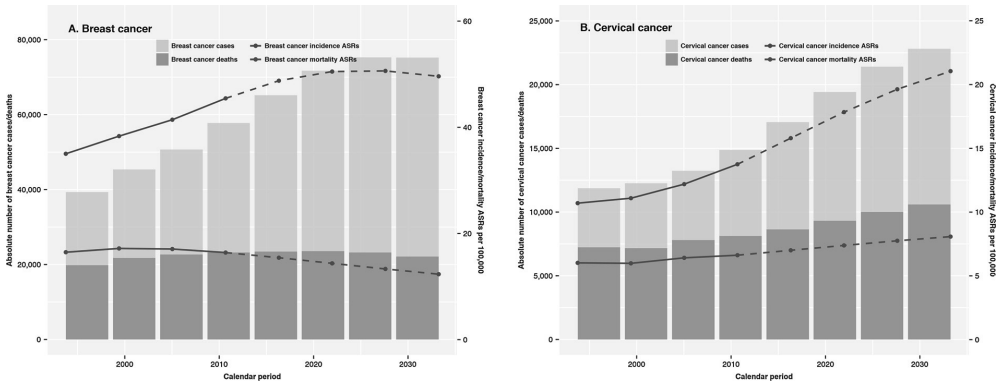

Fig. 3. Observed and predicted breast (A) and cervical (B) cancer mortality and incidence among women in Russia 2014–2032 (age-standardized rates per 100,000 women and absolute number of cases, "nordpred" predictions with sequential drift cut based on 4 most recent 5-year period 1994–2013).

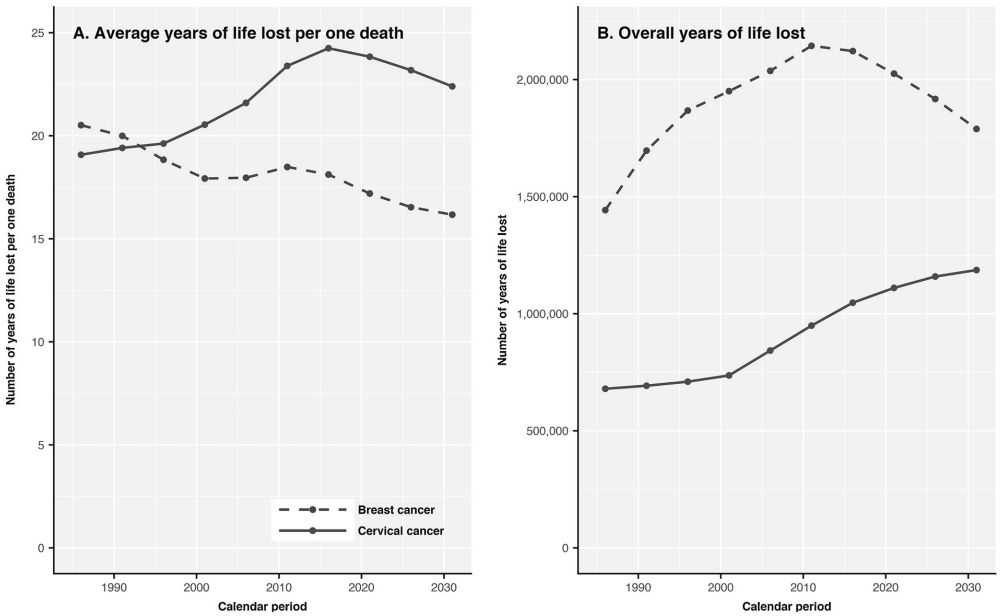

Fig. 4. Years of life lost to breast and cervical cancer among women in Russia (1984–2032): average per one death (A), and overall (B).

material 2). An increase in YLL was observed each year for both cervical and breast cancer, exceeding 900,000 and 2,000,000, respectively (Fig. 4B; Table 11 in *Supplementary material 2*). The YLL from breast cancer peaked and declined from 2009 to 2013, whereas the YLL for cervical cancer is predicted to constantly increase over the next decades.

4. Discussion

This study is the first broad assessment of cancer incidence and mortality patterns and trends from the State Cancer Registry of Russia. The results revealed substantial and somewhat contrasting changes in trends of breast and cervical cancer in Russian women during the past decades. For cervical cancer, an alarming increase in incidence and mortality rates is clearly observed, while the pattern for breast cancer was not dissimilar to many European countries, with an increasing incidence trend and a downward mortality trend following an extended period of increasing trends [32].

Our results are consistent with previous reports on breast cancer mortality trends in Russia based on both available and reconstructed data, as well as the assessment of cervical cancer incidence trends and projections [14,33,34]. Our report is however the first to include combined analysis of both incidence and mortality trends for the most recent periods in Russia, and incorporate years of life lost and future predictions of the burden.

The increasing risk of both breast and cervical cancer among birth cohorts of women born 1937–1953 can partly be explained by changing fertility patterns in Russia, with a strong decline in fertility at the beginning of the 20th century, reaching its lowest point in the 1950 s. The completed fertility rate declined until the 1945-50 birth cohort and was stable and low at around 2 for all subsequent cohorts [35]. Decreasing birth rates may partially explain the initial increase in cohort-specific

risk in breast cancer incidence and mortality, and the equivalent declines in cervical cancer incidence and mortality. Breast cancer incidence in the post-war generations was stable, probably attributable to several balancing factors, including declining fertility rates, increasing obesity prevalence and changing dietary habits, alongside improved diagnostics and opportunistic efforts at early detection. The rise of breast cancer incidence attributable to cancer screening observed in several European countries probably plays a lesser role in explaining the mortality decline in Russia [36], with the decrease in breast cancer mortality suggesting an improvement in diagnosis and treatment in Russia in recent years. Adjuvant therapy was introduced in the 1990 s in Russia and the first clinical trials were focused on early detection and the multimodality treatment of breast cancer; their indirect effect could have resulted in implementation of adjuvant protocols across oncology centers [37]. It is also worthy to note the observed cohort-led decrease in mortality at younger ages (< 55 years of age) is more likely to be effect of treatment. This finding is consistent with reports from other European countries [38].

Increasing trends in cervical cancer cohort-specific incidence and mortality risk likely reflect changes in sexual behavior among young generations leading to increased persistence of high-risk HPV (hr-HPV) infection against a background of a continued absence of effective national screening programs. Detailed analysis of trends of HPV burden in Russia are not available. Based on cross-sectional data, the hr-HPV prevalence among women with normal cytology ranged from 0 to 48%, but was higher in women with intraepithelial lesions [39,40]. Although direct data on sexual behavior is not available, indirect measures such as the rise in the number of abortions in the USSR in the 1960 s could explain the observed cohort risk changes. While this may well reflect many other societal factors, in the absence of barrier and hormonal contraception methods, abortion was reported to be the most common measure of birth control in the USSR until the 1980s [41]. Smoking prevalence was traditionally low in women in the USSR, but recent studies report a doubling of prevalence between 1992 and 2003 [42].

The parallel increases in cervical cancer incidence and mortality is indicative of a lack of population-based screening and subsequent improvements in treatment. Additional information provided by the cohort analysis are comparable to results of studies from a number of other countries indicating the post-war increase of HPV prevalence [43]. Despite the major impact of HPV-related disease burden in post-war cohorts in most countries, the magnitude of increase is considerably lower in countries with effective cervical cancer control programs [5]. The rising number of cervical cancer cases and deaths predicted in Russia in the near future underscores the urgency of the implementation of control policies – population-based, quality-assured screening and vaccination programs [6].

The possible impact of both cytology-based and HPV detection methods as well as the effect of primary prevention - HPV vaccination - has been evaluated in models that incorporate cost-effectiveness. The results of these studies have indicated that both HPV and cytology screening can be a highly effective intervention in high-risk populations, with vaccination combined with screening the potential to reduce incidence from 7.0 to 0.2 cases per 100,000 women [44]. On the other hand, field studies are equally essential in implementing population-based programs to ensure quality assurance. The awareness among public and health care providers is reported to be limited in Russia [39]; integrating health promotion activities into cervical cancer prevention is essential as part of national cancer control policy.

Despite the recently declining rates, breast cancer remains one the major causes of death in Russian women. Further development of evidence-based early detection policies and the optimization of current treatment strategies is essential for reducing the death toll. Current trends could be an indicator of diagnostic and treatment successes, but individual-level studies are also needed to assess the impact. The transition from opportunistic to population-based quality-assured mammography screening could further decrease breast cancer deaths [45]. Meanwhile, quantification of the magnitude of breast cancer incidence increases and mortality decreases that are due to screening and the level of over-diagnosis still remains [46].

Currently, opportunistic breast and cervical cancer screening in Russia is embedded in the “dispensarization” programme, which was introduced with a MOH order fin 2012. The latest guidelines on intervals, target age groups and tests were issued in 2017, and are mostly in line with international recommendations (Pap-test every 3 years from age 30 to 60 years, mammography every 3 years ate ages 39–48 years, followed by biennial mammography for women aged 50 to 70 years) [47]. Although detailed information on quality, actual intervals and coverage is not currently available, implementation of population-based screening is possible based on resources allocated by the MOH to “dispensarization”. HPV vaccination is not in the national vaccination calendar, while local vaccination campaigns with limited coverage were reported in several regional starting from 2009 [39].

Predicted incidence and mortality trends were consistent with the results of age-period-cohort analysis. At the same time, absolute numbers of breast and cervical cancer cases were predicted to increase, as the demographic projections conveyed continuing trends of population ageing and growth. Increasing numbers of breast and cervical cancer incident cases should be taken into account in planning healthcare resources at the national level. Despite increasing number of cervical cancer cases colorectal cancer remains second most common among cancer types amenable to screening in Russian women. Decisions on implementation of cancer control activities should be not be limited to breast and cervical cancer only.

The analysis of YLL underlined the fact that cervical cancer is now leading to a greater number of deaths among younger generations of Russian women. It can be speculated that it could reach the level of breast cancer YLL, creating a unique pattern for Russia with breast and cervical cancers among the leading sites of cancer mortality, given the currently stable lung cancer mortality trend.

The lack of a formal assessment of the quality of the data is an important limitation of the study. The DCO proportions for cervical cancer are reported between 1 and 2% in 2007–2013, while the proportion of morphological verification was 97% for the same period [48]. Even though these estimates are published, a comprehensive assessment of cancer registry data quality has not been performed, neither at national or subnational level. The reasons behind the observed trends may include true changes in risk factor distribution and cancer control activities, but can be also biased by changes in coding or registration practices [49]. However, the regional cancer registries did not report any changes that might influence breast, cervical, uterus NOS and female genital organs NOS cancer registration during the study period. In addition, we did not observe any sudden deviations in trends of age-specific or overall rates. On the other hand, the mortality from Uterus and Uterus NOS cancer (C54, C55) showed a decline in the last few years, which could suggest increased specificity of cervical cancer deaths. A few studies have explored cancer registry data quality in Russia, one assessing the heterogeneity in the registration of causes of death between the regions of Russia, and showing that the proportion of cancers and motor vehicle accidents deaths in the mortality structure are reported consistently across the country, in contrast to cardiovascular and infectious diseases [50]. The fact that cancer management demands morphological verification and in some instances expensive chemotherapy agents, often provided and financed by the state, makes high quality registration an aspect that is more likely to be established within oncology than in other fields of health care. However, further formal quality assessments are needed. Only few cancer registers are members of the International Association of Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR). Therefore, the cancer statistics reported by international organizations are based on the limited data. Further initiatives should be focused on making Russian cancer registries data transparent and comparable. Without formal assessment of the quality of cancer registration, the interpretation of

any future cancer registry-based research would be problematic in Russia.

In our study, we did not correct for possible biases in the estimates of country population. The official population figures are lower than the figures reported during the censuses. However it is not clear whether it is the result of the underestimation between the censuses or the double registration during the censuses [51].

In an effort to avoid underestimation of the true burden, we applied a correction to cervical cancer mortality. However, this re-allocation is not an optimal method for correcting rates. Systematic and continuous linkage between the cancer incidence and mortality records is the only reliable way to build up reliable estimates. Cancer registries in several regions in Russia systematically link their data with regional civil registries. However, this process needs to be adequately implemented. Finally, we did not report hysterectomy-corrected cervical cancer rates, as no estimate of the number of hysterectomies was available. This may also have resulted in an underestimation of the cervical cancer burden [52]. The study, as its major strength, does however provide, using observed data on both incidence and mortality from the National Cancer Registry, a detailed assessment of the breast and cervical cancer burden in Russia, correcting for known misclassification of uterine cancer mortality.

In conclusion, changes in breast cancer incidence and mortality in Russia are similar to other European countries, with incidence increasing overall, while mortality rates have begun to decline. Of utmost concern however, are the uniformly increasing trends in cervical cancer incidence and mortality rates. These results should be used as an aid to setting cancer control priorities in Russia, including the need for the implementation of effective and cost-effect screening and prevention programs, as well the planning of future cancer services based on an allocation of finite resources to ensure their operationalization.

Conflict ofinterest statement

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions

Anton Barchuk: study design, literature search and review, data identification and extraction, data analysis, data interpretation, writing, reviewing and revising the manuscript, final approval of the version to be submitted.

Anssi Auvinen: study design, data interpretation, reviewing manuscript, writing, reviewing and revising the manuscript, final approval of the version to be submitted.

Ahti Anttila: study design, data interpretation, reviewing manuscript, final approval of the version to be submitted.

Irina Laricheva on behalf of the Russian State Cancer Registry research group (Andrey Kaprin, Olga Gretsova, Galina Petrov, Mikhail Prostov, Irina Laricheva and Valery Starinsky): data identification and extraction, reviewing manuscript, final approval of the version to be submitted.

Alexander Bespalov and Heini Huhtala: study design, data analysis, reviewing manuscript, final approval of the version to be submitted.

Tuvshinjargal Chimed and Alexey Belyaev: data interpretation, reviewing manuscript, final approval of the version to be submitted.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2018.05.008.

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Supplementary material 1: Breast and cervical cancer incidence and mortality trends in Russia 1980-2013

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Russian State Cancer Registry Data Analysis Protocol

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Introduction

This protocol is a part of the research project to evaluate the quality of data and recent cancer trends in cancer mortality and incidence in Russia. The data discussed here are derived from the State Cancer Registry (SCR). All the data discussed here is publicly available.

1. Cancer data

1.1 Data description

Incidence and mortality data are taken from the Federal Cancer Registry based at Hertzen Research Institute of Oncology, Moscow. The Federal Cancer Registry covers the entire population of the Russian Federation (143.5 million people in 2013) [1].

A system of obligatory registration and lifetime follow-up of cancer patients was established in the USSR in 1953 [2]. All medical institutions are obliged to notify regional population-based Cancer Registries of all both newly diagnosed cancer cases and any new hospitalization of patients with cancer. Current cancer registration procedures and cancer registry status are stipulated by Order 135 of the Ministry of Healthcare issued in 1999 [3]. Briefly, standardized written notifications are forwarded for analysis to regional population-based cancer registries which deliver both written and electronic reports to the State Cancer Registry. Incidence data are collected under supervision of the Ministry of Healthcare, independently while mortality data are collected as part of demographic data. Both regional and national cancer registries have access to an independent mortality database, although the timelessness varies.

The notification carries information on the date of diagnosis, morphological verification, stage, treatment details and personal data transferred and kept in the electronic databases of regional registries. Only one regional cancer registry (Saint-Petersburg Population Based Cancer registry) reported data to the International Agency for Research on Cancer (IARC), which were presented in its quinquennial publications: Cancer Incidence in Five Continents, volumes IV–X [4]. However, data collection and work-up comply with the same legislation and are uniform across the country. The quality of data needs further formal assessment. Nevertheless, a recent analysis of differences in cause-of-death coding practices across Russian regions showed that only cancer and transport accidents have roughly comparable cause-specific shares across regional mortality structures. [17]

Over the study period of 1993-2013, more than 9.5 million cases were registered. More than 6.1 million deaths were registered as cancer deaths. All cancer cases in this report are classified according to the 3-digit rubrics of ICD-9 (1993-1997) and ICD-10 (1998-2013). Order N 135 mentioned above introduced mixed classification which takes a topography part from ICD-10 and a morphology part from ICD-O-2.

1.2 Incidence and mortality data

Data from 1993 till 2013 were available for the following cancer types and groups: breast, women only (C50), cervix uteri (C53), corpus uteri, uterus NOS (C54-55).

All registered incident cancer cases were tabulated by age, sex, and calendar period. Most of the original data included 14 age classes (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and 85+) and 21 1-year periods (1993-2013). Cervical cancer incidence data also included 15-19 age group.

Mortality data were available from 1993 till 2013 for the following cancer types: breast (C50), cervix uteri (C53), corpus uteri, uterus NOS (C54-55).

An additional source of mortality data was the WHO (World Health Organisation) Mortality Database available at http://www.who.int/healthinfo/mortality_data/en/. This database contains aggregated data on the number of deaths by country, sex, age group and cause of death. Both the number of deaths and population data are available from 1980 to 2011 for the Russian Federation (as of August 3, 2016).

1.3 Cervical cancer mortality adjustment

In order to adjust for possible inaccuracies in the reported deaths from uterine cancers (endometrial, cervical, other and unspecified), we applied reallocation rules developed and used earlier for analysis of cervical cancer mortality trends [22,23,24]. The adjustment algorithms depend on the availability of data and the proportion of NOS cases. Cancer mortality data for Russia were reported using the so called "shortlist" mortality nomenclature. In 1980-1998, it was reported with ICD-9 and in 1999-2013 with ICD-10. In both periods, cervical cancer deaths (C53) were reported separately and corpus uteri and uterus, NOS (C55,C54) were reported combined (table 1).

Table 1. Nomenclature used in the WHO mortality database to report uterine cancers.

Period and nomenclature	Codes for cervical and uterus cancer
1980-1998, 09N – ICD-9th revision, Special List of causes as reported by some countries of the newly independent states of the former USSR	B120 - Malignant neoplasm of cervix uteri (C53) B122 - Malignant neoplasm of uterus, other and unspecified (C54,55)
1999-2013, 101 - ICD-10 Mortality Tabulation List 1	1037 - Malignant neoplasm of cervix uteri (C53) 1038 - Malignant neoplasm of other and unspecified parts of uterus (C54,55)

In this case, two possible reallocation algorithms can be applied, but for both options reference population is needed. Although in reports of cervical cancer mortality trends Hungarian population is used as reference for Russia, we applied consecutively Hungarian and Lithuanian population as part of a sensitivity analysis. All the data were downloaded from the WHO mortality database.

In order to obtain adjusted estimates, cases from the NOS category (C55) should be reallocated to cervical cancer (C53) and uterus cancer (C54). In countries with low proportion of NOS cases (less then 25%) it can be done by simply applying C53/C54 proportion to divide C55 in each age and period category cell. Then those C55 cases were added to either C53 or C54 number in the corresponding age-period cell. We applied this procedure to derive an adjusted estimate of cervical cancer mortality in Hungary and Lithuania.

Then we used two options to re-allocate cases in Russia. Fo the first option, we assumed that C54, C55 combined estimate in each age-period cell in Russia can be divided based on the corresponding proportion in Hungary or Lithuania. After getting C54 estimates, the re-allocation procedure similar to the one described for Hungary and Lithuania was applied. However, this option has weak assumptions of having very low proportion of NOS cases in Russia, that may not be true. In that case the corrected cervical cancer mortality is still underestimated.

Fo the second option, we assume that the proportion of C53 deaths out of all uterine cancer deaths (C53+C54+C55) in Russia is the same as the proportion in Hungary and Lithuania (with already adjusted C53 estimates). Based on this assumption, adjusted C53 estimates were derived by applying the reference proportion (C53/(C53+C54+C55) in Hungary or Lithuania) to the total sum of uterine deaths in each corresponding age-period cell.

Both adjustments (Lithuania, Hungary) produced similar results, so the adjustment by Hungary (similar to the one in other papers) as a template country was applied in the final report. A similar correction can be applied to incidence data if NOS categories estimates are available. Additionally, if available, C57.9 category (Malignant neoplasm of female genital organs, unspecified) can be used to re-allocate deaths and cases.

1.4 Population data

Population data in the form of sex-specific age (1 year age-class, 0-85+) distributions was retrieved from the Federal State Statistics Service (FSSS) [5]. The data were based on population surveys of 1989, 2002, 2010, adjusted for annual mortality and birth statistics.

For each period, FSSS reports population estimates as of the 1st of January, from 1993 to 2014 the average population from two subsequent years was taken to estimate the annual rates (for example, in order to calculate population of 1993 for the analysis - 1993 and 1994 population from FSSS was averaged). Population estimates were used to approximate person-years at risk [6]. Population data from 1980 were downloaded alongside with the mortality data from the WHO website.

1.5 Ethical considerations

This study analyzed publicly available secondary aggregate data, and thus requires no additional ethical approval.

2. Statistical analysis

2.1 Data transformation

For this analysis, we used two types of data resolution for practical reasons. Original data, with 5-year age-class and 1-year periods (5x1), and aggregated data with 5-year age-class and 1-year periods (5x5) were used to create Lexis diagrams with the number of events and person-years (D, Y). The mean age, period and cohort in each cell of the table we used as continuous covariates.

2.2 Crude and age-standardized rates (ASRs)

Rates per 100,000 person-years for the 21 1-year period from 1993 to 2013 were calculated for 17 5-year age-classes (0-85+).

Crude rates per 100,000 person-years were calculated as a simple sum of age-specific rates for each period year.

Incidence and mortality age-standartized rates (ASRs) per 100,000 person-years were calculated using the Segi/Doll 1960 world standard population with the direct method [18].

2.3 Breakpoints in ASRs trends

In order to find breakpoints in trends occurred, we built simple linear regression with ASRs and period years and used iterative procedure proposed for estimation of regression models with piecewise linear relationships having a fixed number of breakpoints [7]. In order to apply this algorithm, either starting breakpoints should be selected (in that case starting breakpoints were selected by visual inspection of plots as recommended, and the bootstrap restarting was applied to make the algorithm less sensitive to starting values [8]), or an "automatic" breakpoint selection procedure that deals with an unknown number of breakpoints can be used [9]. In both methods, breakpoint estimates were reported with a 95% confidence interval as well as slopes representing the annual percent changes (APCs).

Both "manual" and "automatic" methods were used to produce the maximum number breakpoints for each trend. Then slopes (APCs) with 95% confidence interval were compared and in case of an overlap between two neighboring slopes the procedure was repeated with a reduced number of starting breakpoints. The choice of wide confidence intervals for comparison is based on the intention to produce the minimal number of meaningful breakpoints.

The final fitted broken-line was designed against the original trend. Average APC, break-points and APCs between them are reported with 95% confidence intervals.

2.4 Ecological age-period-cohort analysis

We restricted our analyses to age intervals of 20–84 to avoid statistical instability.

The results are effects reported for defined number 5-year age intervals (for example 13 for age interval 20-84), available number of periods (for example 21 for period interval 1993-2013) and calculated number of synthetic birth cohorts (see Table 2 for the exact number in each case).

For preliminary visualization, we applied 4 rate plots: a) rates according to age of diagnosis for different periods; b) rates according to the age of diagnosis for different cohorts; c) rate according to the date of diagnosis for different age-classes; d) rate according to the date of birth for different age-classes). For better visualization, plots were built using 5-year age-classes merged to 10-year age classes (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79) and 3 or 4 merged periods.

Table 2. Number of age-classes, periods and cohorts in the age-period-cohort analyses

Data resolution	**5x1**		**5x5**	
	1980-2013 (34 periods)	1993-2013 (21 periods)	1984-2013 (6 periods)	1994-2013 (4 periods)
20-84 (13 age-classes)	94 cohorts	81 cohorts	18 cohorts	16 cohorts

2.4.1 Model

Age (A), calendar period (P), and birth cohort (C=P-A) effects on incidence and mortality were estimated with age-period-cohort Poisson regression models described elsewhere [10, 11]. Briefly, the rates are described as a function of age, period, and cohort using a log-linear model, with Poisson errors and a logarithmic link function: $\log[\lambda(A, P)] = a(A) + p(P) + c(C)$, where a, p, and c are the functions each parameterized with a limited number of parameters.

2.4.2 Choice of parameterization

In our analyses, we followed the recommendations by Bendix Carstensen [12].

In order to derive the estimates of effects, both classical maximum likelihood and sequential procedures were applied. Sub-models were derived from both methods (representing classical age-drift, age-period, age-cohort, age-period-cohort and very similar models from the sequential procedures). In the analysis to solve the identifiability problem constrains were put on cohort and period effects (depending on the type of model, C_0=1945 or P_o=2000 were used).

The drift parameter was extracted by a weighted approach in maximum likelihood models. Natural splines constrained to be linear beyond the outermost knots were used to model the functions (a, p and c) with 7 knots applied to each effect category (age, period, cohort).

2.4.3 Models fit and comparison

The models fit the data well, however, overall goodness-of-fit of models was not reported, mainly because it doesn't reflect the adequacy of the model in describing the rates, rather the type of tabulation. In the tables of supplementary material we presented comparison based on residual deviances and degrees of freedom, their differences and Akaike's information criterion (AIC). Significance of the pairwise comparisons was examined by comparing the difference in residual deviance using $\chi 2$ tests. In this case, a sub-models comparison helped to evaluate the following effect: the linear effect of period/cohort (drift), non-linear effect of period, non-linear effect of cohort, non-linear effect of cohort (in the presence of period), non-linear effect of period (in the presence of cohort).

2.4.4 Reported model

As we were particularly interested in the cohort effect (the non-linear component which also showed to be stronger than the period after comparing the likelihood ratio statistics) the final reported results were derived from the model where age effects are rates for the reference cohort in the age-cohort model, cohort effects are RR relative to the reference cohort. Period effects are from the model with period alone, using log (fitted values) from the age-cohort model as offset (13).

2.4.5 Drift

The drift parameter representing the (average) annual relative change in rates was extracted from the age–drift model. It was reported as the APC with 95% confidence interval and calculated with formula $APC=(\exp(drift) - 1) \times 100$).

2.5 Predictions

To make the prediction of rates, we applied the method also utilizing age-period-cohort models (14). With 5x5 data resolution the recent slope method, with the power link and reduction of drift applied. Building the prediction, we used the slope for the last 10 years instead of whole 20 or 15 years period average trend. The projection is done for 4 periods till 2033 (2014-2018, 2019-2023, 2024-2028, 2029-2033) based on four or three most recent periods (1994-1999, 1999-2003, 2004-2008, 2009-2013). The p value for goodness of fit of the prediction model was reported. Three scenarios were projected: 1) without reduction of drift, 2) with 100% reduction for all projection periods and 3) 0-25%-50%-75% cut in each following projection period.

The projected age-standardized rates and the absolute number of cases were then calculated using official predicted population retrieved from FSSS (for period 2015-2031, 2032 and 2033 additionally projected using autoregressive integrated moving average (ARIMA) model). Both predicted age-standardized and absolute number of cases were plotted.

2.6 Hodograph

In order to simultaneously assess and present changes in incidence and mortality, we build hodographs. The hodograph plot captures secular information about both incidence and mortality. Hodographs were built for age-standardized rates and risk in cohorts from age-period-cohort models. The x-axis represents the incidence, the y-axis represents the mortality and each point refers to period year (for ASRs) or cohort (for cohort effects). Each point is plotted with ellipse representing 95%CIs both for incidence and mortality trend, points are then connected with lines.

2.7 Year of life lost (YLL)

The quantification of YLL is another important measure of cancer burden [19]. YLL were reported as the sum of age-specific YLL for each period year. Age-specific YLL were calculated as a composition of cancer deaths and life-expectancy in each age-period cell. Period life-tables were generated based on the data downloaded from the Human mortality database [20], with included age-specific death-rates and population at risk from 1980 till 2013. The cause-deleted period life-table was obtained via subtraction of death rate from cancer of interest from the overall death-rate. A functional demographic model was built in order to forecast life-tables up to year 2033 [21]. Deaths from specific cancer up to year 2033 were obtained from the prediction model described above. The final result included YLL trend from 1980 till 2033 and YLL per 1 cancer death trend for the same period.

2.8 Data quality assessment

This research is a first part of the larger project for continuous quality assessment of cancer data in Russia. Quality assessment usually requires individual level data. The discussion of assessment of data from the federal cancer registry started in 2015 and the plan for this project is being prepared. However, even with aggregated data it is possible to assess some of the quality markers (15).

As part of semi-quantitative assessment of completeness of data, we inspected the stability of rates over time. We also assessed the shape of age-specific curves to test the completeness by age, age-specific rates from other countries were used as a comparator.

2.9 Significance level and confidence intervals

If not otherwise mentioned, we used two-sided probability with a significance level of 0.05, consistent with a type I error of 5%, and 95% confidence intervals.

2.10 Software

All analyses were performed in R (version 3.2.3, 2015-12-10)), using packages “Epi” (version 2.0), “segmented”(version 0.5-1.4), “popEpi” (version 0.3.1), “nordpred” (assessed on 15.05.2016 www.kreftregisteret.no/en/Research/Projects/Nordpred/Nordpred-software), and “demography” (version 1.18).

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Supplementary material 2: Breast and cervical cancer incidence and mortality trends in Russia 1980-2013

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Figures:

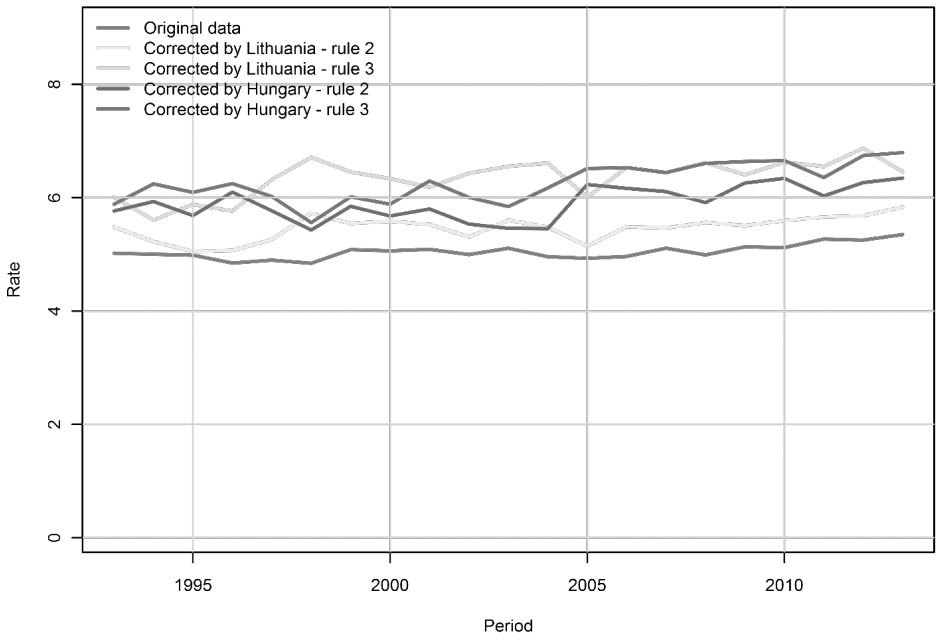

Figure 1. Original and corrected cervical cancer mortality ASRs per 100,000 (1993-2013) in women in Russia. Rule 2 assumes that only the proportion of C54 (Uterine cancer) and C55 (Uterus NOS) equals same proportion in template countries. then C53 (Cervical cancer) is quantified according reallocation rule 1 (applies. only if NOS is less then 25% - assumption that cannot be verified for Russian data). Rule 3 assumes that the proportion of C53 out of sum of all uterine cancers (C53. C54 and C55) equals same proportion in template countries (For more information about reallocation rules see Arbyn et al., 2011). Data corrected by Hungary as a template country applying rule 3 is reported and analyzed in the paper.

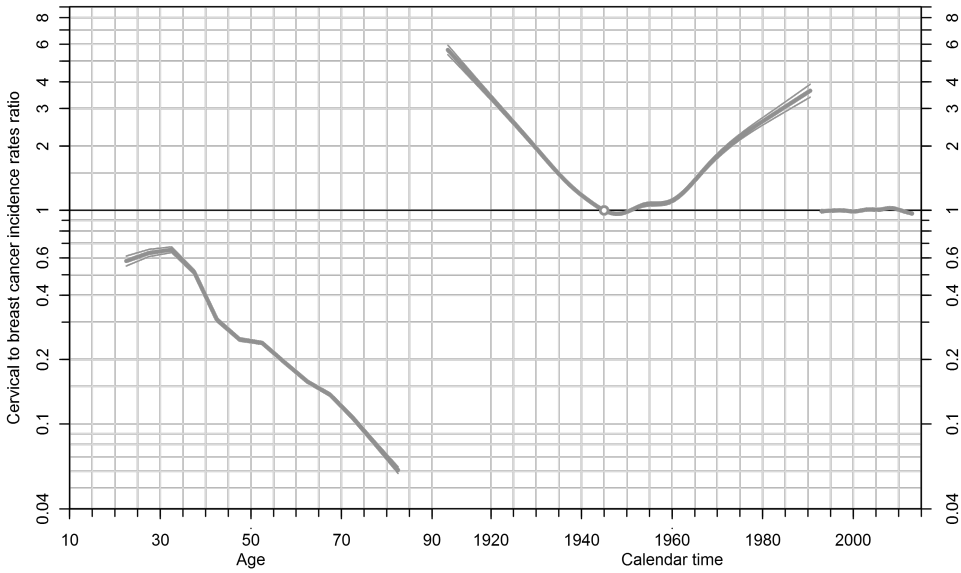

Figure 2. Ratio of cervical to breast cancer incidence age, cohort and period effect.

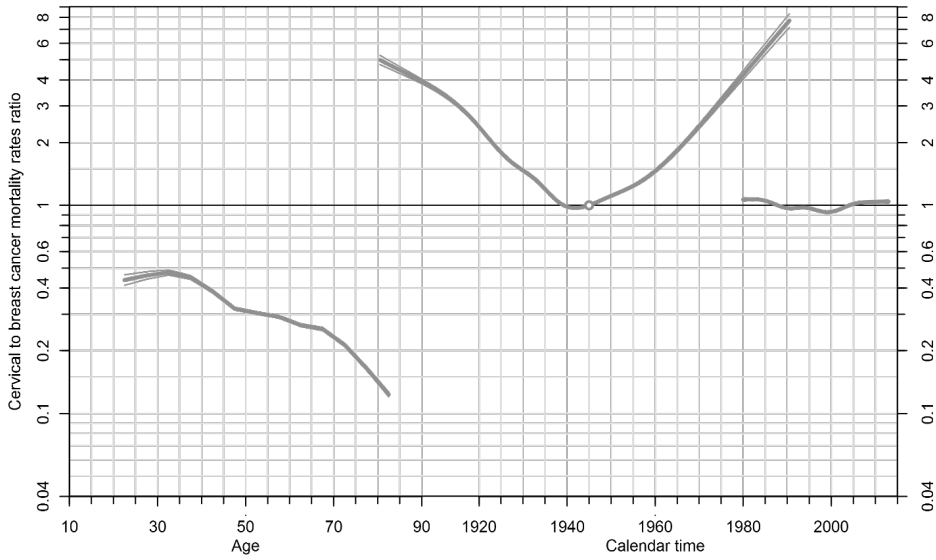

Figure 3. Ratio of cervical to breast cancer mortality age, cohort and period effect.

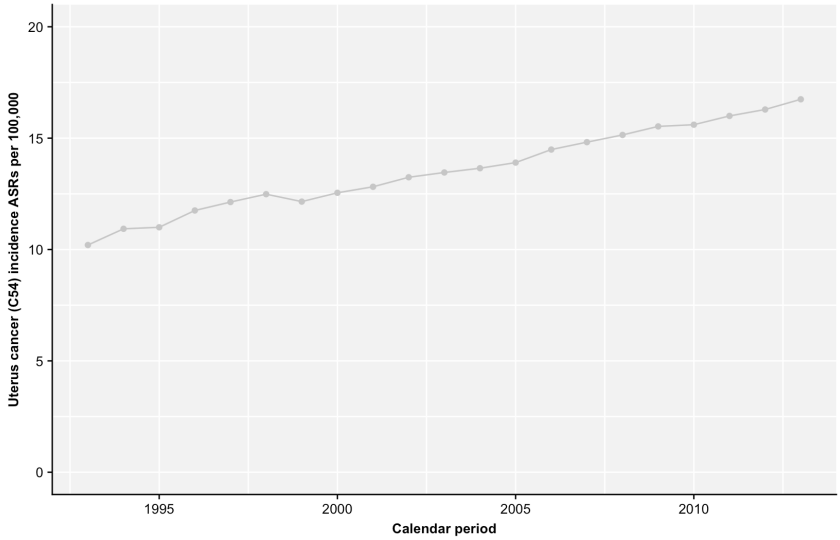

Figure 4. Corpus uteri (C54) cancer incidence age-standardized rates per 100,000 in Russia 1993-2013.

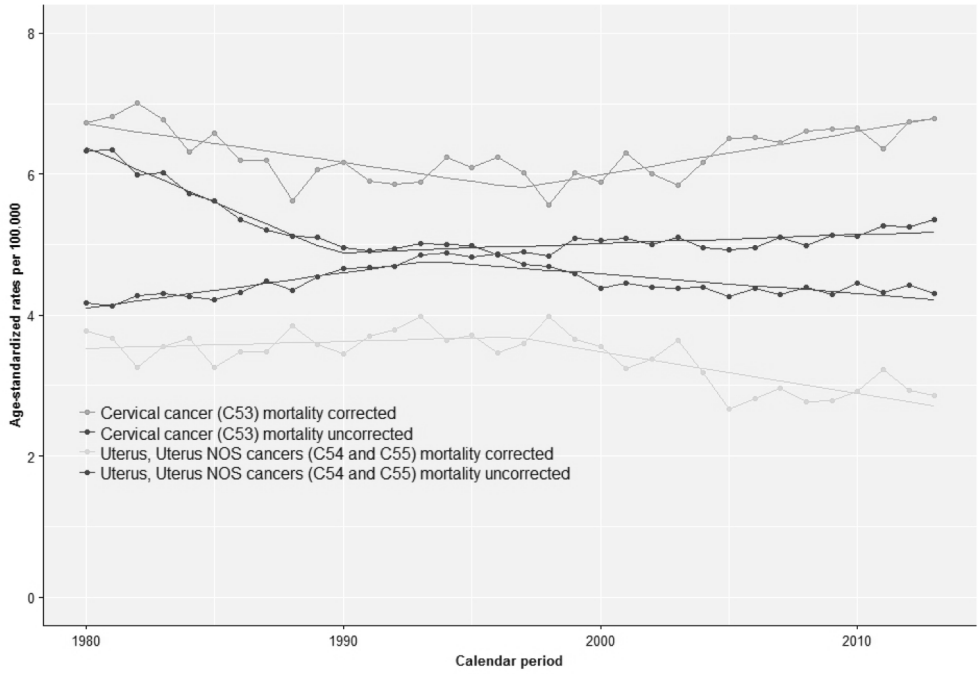

Figure 5. Cervical (C53) and Uterus, Uterus NOS (C54, 55) cancer mortality age-standardized rates per 100 000 in Russia 1980-2013 before and after reallocation.

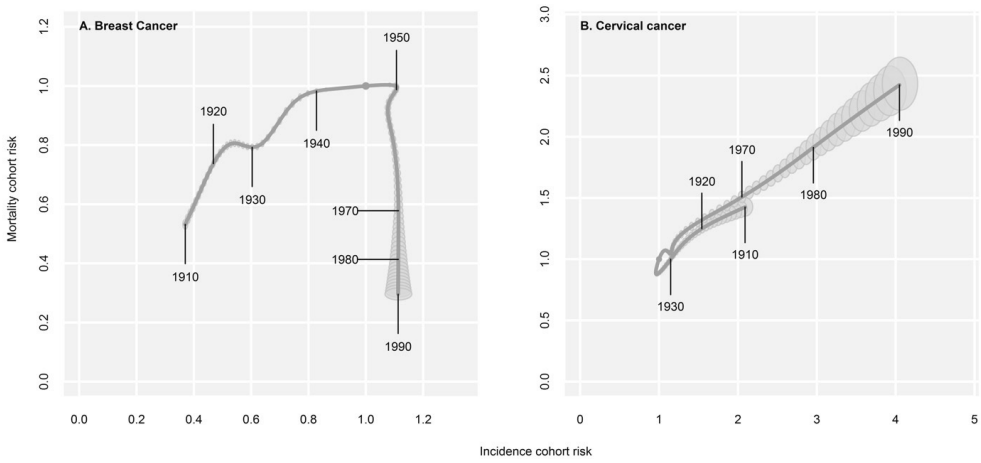

Figure 6. Hodographs with cohort effects for breast (A) and cervical (B) cancer mortality and incidence for each cohort among women in Russia born in the period 1910-1990.

Tables:

Table 1. Original and corrected cervical cancer mortality ASRs per 100 000 (1993-2013) in women in Russia.

Year	Original data	Corrected by Hungary rule 2	Corrected by Hungary rule 3	Corrected by Lithuania rule 2	Corrected by Lithuania rule 3
1993	5	5.8	5.9	5.5	6
1994	5	5.9	6.2	5.2	5.6
1995	5	5.7	6.1	5.1	5.9
1996	4.8	6.1	6.2	5.1	5.8
1997	4.9	5.8	6	5.3	6.3
1998	4.8	5.4	5.6	5.7	6.7
1999	5.1	5.8	6	5.5	6.5
2000	5.1	5.7	5.9	5.6	6.3
2001	5.1	5.8	6.3	5.5	6.2
2002	5	5.5	6	5.3	6.4
2003	5.1	5.5	5.8	5.6	6.6
2004	5	5.5	6.2	5.5	6.6
2005	4.9	6.2	6.5	5.1	6
2006	5	6.2	6.5	5.5	6.5
2007	5.1	6.1	6.4	5.5	6.4
2008	5	5.9	6.6	5.6	6.6
2009	5.1	6.3	6.6	5.5	6.4
2010	5.1	6.3	6.7	5.6	6.6
2011	5.3	6	6.4	5.7	6.5
2012	5.3	6.3	6.7	5.7	6.9
2013	5.3	6.3	6.8	5.8	6.5

Table 2. Age. period and cohort analysis submodels comparison and interpretation for breast cancer incidence in women in Russia (1993-2013).

Models compared	Difference of degrees of freedom	Difference in Deviances	P value (χ2 test)	Test interpretation
Age-Drift vs Age	1	13,281	<0.001	Linear effect of period/cohort
Age-Cohort vs Age-Drift	6	6,459	<0.001	Non-linear effect of cohort
Age-Period-Cohort vs Age-Cohort	6	90	<0.001	Non-linear effect of period (in the presence of cohort)
Age-Period vs Age-Period-Cohort	6	6,432	<0.001	Non-linear effect of cohort (in the presence of period)
Age-Drift vs Age-Period	6	116	<0.001	Non-linear effect of period

Table 3. Age. period and cohort analysis submodels comparison and interpretation for breast cancer mortality in women in Russia (1993-2013).

Models compared	Difference of degrees of freedom	Difference in Deviances	P value (χ2 test)	Test interpretation
Age-Drift vs Age	1	11,835	<0.001	Linear effect of period/cohort
Age-Cohort vs Age-Drift	6	10,742	<0.001	Non-linear effect of cohort
Age-Period-Cohort vs Age-Cohort	6	1,106	<0.001	Non-linear effect of period (in the presence of cohort)
Age-Period vs Age-Period-Cohort	6	8,379	<0.001	Non-linear effect of cohort (in the presence of period)
Age-Drift vs Age-Period	6	3,468	<0.001	Non-linear effect of period

Table 4. Age, period and cohort analysis submodels comparison and interpretation for cervical cancer incidence in women in Russia (1980-2013).

Models compared	Difference of degrees of freedom	Difference in Deviances	P value (χ2 test)	Test interpretation
Age-Drift vs Age	1	1,158	<0.001	Linear effect of period/cohort
Age-Cohort vs Age-Drift	6	6,168	<0.001	Non-linear effect of cohort
Age-Period-Cohort vs Age-Cohort	6	28	<0.001	Non-linear effect of period (in the presence of cohort)
Age-Period vs Age-Period-Cohort	6	-6,013	<0.001	Non-linear effect of cohort (in the presence of period)
Age-Drift vs Age-Period	6	-183	<0.001	Non-linear effect of period

Table 5. Age, period and cohort analysis submodels comparison and interpretation for corrected cervical cancer mortality in women in Russia (1980-2013).

Models compared	Difference of degrees of freedom	Difference in Deviances	P value (χ2 test)	Test interpretation
Age-Drift vs Age	1	174	<0.001	Linear effect of period/cohort
Age-Cohort vs Age-Drift	6	6,579	<0.001	Non-linear effect of cohort
Age-Period-Cohort vs	6	119	<0.001	Non-linear effect of period

Age-Cohort				(in the presence of cohort)
Age-Period vs Age-Period-Cohort	-6	-6,254	<0.001	Non-linear effect of cohort (in the presence of period)
Age-Drift vs Age-Period	-6	-444	<0.001	Non-linear effect of period

Table 6. Predicted age-standardized rates per 100,000 women and absolute number of cases per year for breast cancer incidence

Years	Standardized rates per 100,000			Average absolute numbers per year		
	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift
2009-2013	45.6	45.6	45.6	57,770	57,770	57,770
2014-2018	48.0	48.0	43.9	64,331	64,331	58,961
2019-2023	49.9	48.8	41.8	71,198	69,696	59,883
2024-2028	51.6	48.3	39.4	77,044	72,313	59,514
2029-2033	53.6	46.9	37.3	81,296	71,665	57,681

Table 7. Predicted age-standardized rates per 100,000 women and absolute number of cases per year for breast cancer mortality.

Years	Standardized rates per 100 000			Average absolute numbers per year		
	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift
2009-2013	16.5	16.5	16.5	23,197	23,197	23,197
2014-2018	15.4	15.4	15.4	23,527	23,527	23,422
2019-2023	14.4	14.3	14.2	23,632	23,606	23,421
2024-2028	13.3	13.2	13.1	23,274	23,196	22,962
2029-2033	12.3	12.2	12.1	22,223	22,073	21,823

Table 8. Predicted age-standardized rates per 100,000 women and absolute number of cases per year for cervical cancer incidence.

Years	Age-standardized rates per 100,000			Average absolute numbers per year		
	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift	Scenario 1: Drift not cut	Scenario 2: Sequential cut of drift	Scenario 3: Full cut of drift
2009-2013	13.8	13.8	13.8	14,882	14,882	14,882
2014-2018	15.7	15.7	15.2	16,933	16,933	16,394
2019-2023	17.6	17.5	16.6	19,247	19,096	18,068
2024-2028	19.6	19.1	17.8	21,379	20,893	19,488
2029-2033	21.3	20.4	18.9	23,163	22,142	20,522

Table 9. Predicted age-standardized rates per 100,000 women and absolute number of cases per year for cervical cancer mortality.

Years	Age-standardized rates per 100,000			Average absolute numbers per year		
	Drift not cut	Sequential cut of drift	Full cut of drift	Drift not cut	Sequential cut of drift	Full cut of drift
2009-2013	6.6	6.6	6.6	8,115	8,115	8,115
2014-2018	7	7	7.2	8,644	8,644	8,905
2019-2023	7.3	7.4	7.7	9,226	9,294	9,783
2024-2028	7.5	7.7	8.2	9,731	9,946	10,611
2029-2033	7.6	8	8.6	10,075	10,517	11,289

Table 10. Estimated years of life lost to breast and cervical cancer per one death (historical data and predictions based on sequential drift cut).

Period (years)	YLL to Breast Cancer per Death	YLL to Cervical Cancer per Death
1984-1988	20.5	19.1
1989-1993	20.0	19.4
1994-1998	18.8	19.6
1999-2003	17.9	20.5
2004-2008	18.0	21.6
2009-2013	18.5	23.4
2014-2018	18.1	24.2
2019-2023	17.1	23.8
2024-2028	16.5	23.1
2029-2033	16.1	22.3

Table 11. Estimated overall years of life lost to breast and cervical cancer in 1-year and 5-year periods (historical data and predictions based on sequential drift cut).

Period (years)	Average overall YLL to breast cancer per calendar year	Average overall YLL to cervical cancer per calendar year	Overall YLL to breast cancer in 5 years period	Overall YLL to cervical cancer in 5 years period
1984-1988	1,442,419	679,508	7,212,095	3,397,540
1989-1993	1,696,532	692,477	8,482,660	3,462,385
1994-1998	1,867,630	709,777	9,338,150	3,548,885
1999-2003	1,950,463	736,448	9,752,315	3,682,240
2004-2008	2,037,226	842,712	10,186,130	4,213,560
2009-2013	2,144,044	949,120	10,720,220	4,745,600
2014-2018	2,127,327	1,046,132	10,636,635	5,230,660
2019-2023	2,023,579	1,104,646	10,117,895	5,523,230
2024-2028	1,909,143	1,149,155	9,545,715	5,745,775
2029-2033	1,775,866	1,173,614	8,879,330	5,868,070

Table 12. Breast and cervical cancer mortality and incidence ASRs per 100,000 in 2008 and 2013 in Russian regions (red cell – positive change, green cell – negative change, statistical tests were not performed).

	Breast cancer				Cervical cancer			
	Incidence		Mortality		Incidence		Mortality	
	2008	2013	2008	2013	2008	2013	2008	2013
National Data	42.83	47.05	17.05	15.68	12.84	14.17	4.99	5.35
Adygea. Republic of	43.03	44.31	15.7	20.88	15.44	11.02	4.18	4.97
Altai Krai	42.65	44.29	16.69	15.54	16.27	17.19	5.4	5.92
Altai. Republic of	33.59	36.53	20.32	11.35	18.6	22.43	10.28	11.19
Amur Oblast	46.83	52.52	17.9	19.26	14.76	15.47	6.41	8.65
Arkhangelsk Oblast	37.89	44.54	12.3	12.02	11.21	16.15	4.02	5.66
Astrakhan Oblast	46.04	47.27	18.77	15.98	12.48	17.56	5.69	5.01
Bashkortostan. Republic of	38.45	41.87	14.31	12.61	9.54	10.63	4.13	4.38
Belgorod Oblast	45.87	45.45	17.01	17.02	14.69	12.45	4.93	6.42
Bryansk Oblast	40.33	48.23	16.08	13.43	9.54	11.28	3.12	5
Buryatia. Republic of	31.2	39.4	13.1	17.66	22.9	31.27	11.69	12.47
Chechen. Republic of	61.16	52.21	11.58	16.53	37.69	11.21	3.83	5.69
Chelyabinsk Oblast	46.2	46.1	16.4	16.53	11.83	14.33	5.7	6.12
Chukotka Autonomous Okrug	25.19	49.01	18.13	42.98	27.84	24.86	0	3.42
Chuvash. Republic of	32.33	39.38	11.01	9.73	7.83	8.5	3.36	3.46
Dagestan. Republic of	26.93	28.2	10.4	10.72	9.53	10.45	3.61	5.36
hakassia. Republic of	45.1	47.51	11.93	11.6	14.04	20.55	8.39	10.55
Ingushetia. Republic of	36.19	43.71	11.91	12.98	8.59	9.31	2.16	2.45
Irkutsk Oblast	45.8	51.96	17.82	15.72	19	22.21	8.36	8.51
Ivanovo Oblast	38.94	52.03	16.14	17.69	18.32	20.82	7.31	6.23
Jewish Autonomous Oblast	37.03	45.12	25.02	12.34	14.36	17.38	8.47	2.9
Kabardino-Balkar Republic	36.54	45.03	19.05	15.73	11.2	12.59	4.46	5.17
Kaliningrad Oblast	40.72	54.16	19.25	18.25	15.15	13.37	5.68	6.22
Kalmykia. Republic of	40.15	33.8	8.49	14.82	18.55	12.9	7.88	3.78
Kaluga Oblast	42.12	58.21	16.12	15.69	14.99	14.47	5.1	6.83
Kamchatka Krai	43.49	52.68	13.21	20.39	14.47	26.23	5.81	12.35
Karachay-Cherkess Republic	41.38	39.88	13.95	15.47	11.69	12.98	6.27	3.93
Karelia. Republic of	41.87	49.32	16.43	13.31	18.69	22.72	4.59	5.44
Kemerovo Oblast	42.54	44.48	17.32	17.86	10.78	14.29	3.96	7.12
Khabarovsk Krai	47.49	49.78	17.64	16.28	14.09	13.4	5.7	5.01
Khanty–Mansi Autonomous Okrug – Yugra*	-	50.65	-	14.68	-	11.7	-	3.84
Kirov Oblast	33.66	41.17	11.79	12.12	11.83	11.51	4.52	4.35
Komi. Republic of	39.48	46.06	14.75	14.04	18.02	17.41	6.78	5.41
Kostroma Oblast	37.02	42.53	15.31	14.64	12.24	17.64	4.74	5.82
Kransoyarsk край	43.98	51.57	18.94	16.09	14.25	17.29	6.6	6.12
Krasnodar край	43.39	47.7	18.86	15.41	14.78	14.72	5.73	5.39
Kurgan Oblast	37.58	42.21	12.17	13.21	14.73	20.89	6.02	9.8

Kursk Oblast	41.5	53.44	14.66	15.23	12.98	13.69	5.31	4.77
Leningrad Oblast	38.72	33.09	15.99	12.33	15.42	13	8.05	6.04
Lipetsk Oblast	40.99	49.69	16.32	15.59	14.87	15.96	4.62	5.41
Magadan Oblast	44.56	51.88	23.03	18.79	25.58	32.26	5.28	5.3
Mari El Republic	34.19	35.81	11.8	14	8.85	13.78	2.51	5.16
Mordovia. Republic of	40.92	47.96	12.94	12.35	15.87	15.78	2.75	2.57
Moscow	51.53	48.8	21.48	16.18	9.89	8.46	4.27	3.97
Moscow Oblast	46.5	48.95	19.78	18.15	12.01	12.99	4.86	4.11
Murmansk Oblast	46.77	54.39	16.19	14.46	14.44	11.21	6.45	4.96
Nizhny Novgorod Oblast	41.07	47.43	15.51	16.34	10.74	13.85	3.88	5.1
North Ossetia-Alania. Republic of	46.25	61.02	20.04	20.35	7.71	12.32	3.62	3.48
Novgorod Oblast	45.84	43.9	16.82	11.47	16.77	19.69	4.51	4.77
Novosibirsk Oblast	47.84	54.7	18.3	15.69	11.4	15.13	4.99	5.14
Omsk Oblast	46.12	58.8	21.18	17.78	12.84	14.2	5.55	5.91
Orenburg Oblast	45.11	56.84	18.44	18.35	10.13	14.21	2.68	7.47
Oryol Oblast	41.43	46.48	16.07	15.98	12.43	14.45	4.44	4.36
Penza Oblast	38.67	42.58	12.36	14.15	10.45	12.44	3.34	3.27
Perm Krai	37.81	42.39	15.55	14.11	11.05	12.92	5.48	4.81
Primorsky Krai	40.31	49.07	16.93	17.47	15.06	14.15	5.83	7.37
Pskov Oblast	36.3	37.24	15.95	16.44	19.91	23.74	4.68	4.7
Rostov Oblast	42.3	44.71	18.95	17.01	14.87	17.78	6.55	7.19
Ryazan Oblast	45.94	48.68	16.8	13.99	13.16	13.99	5.1	4.83
Saint-Petersburg	44.58	47.14	20.63	19.26	10.22	10.39	4.95	5.49
Sakha (Yakutia) Republic	26.72	38.91	11.24	9.6	17.21	20.3	6.77	6.95
Sakhalin Oblast	39.94	58.51	11.36	17.28	19.01	18.04	7.79	7.1
Samara Oblast	51.67	50.23	18.79	17.57	10.73	13.22	4.24	5.36
Saratov Oblast	44.08	52.64	15.57	16.13	10.89	12.79	4.08	4.32
Smolensk Oblast	43.17	52.51	15.01	15.7	10.63	17.01	5.19	7.01
Stavropol Krai	41.86	45.46	16.96	16.37	10.72	12.86	5.3	5.5
Sverdlovsk Oblast	41.54	46.8	15.8	15.7	11.38	14.53	4	4.61
Tambov Oblast	39.57	42.41	14.88	12.92	12.09	12.32	5	3.67
Tatarstan. Republic of	42.5	47.71	13.77	13.65	11.11	15.73	2.87	3.79
Tomsk Oblast	42.9	51.32	18.78	16.52	16.61	19.56	7.09	7.06
Tula Oblast	46.82	51.32	18.75	16.23	11.28	15.15	5.83	6.34
Tuva. Republic of	33.41	32.11	10.21	7.09	27.54	24.07	6.24	12
Tver Oblast	42.8	47.86	17.64	16.38	17.14	18.49	7.38	6.39
Tyumen Oblast	37.63	45.68	14.59	12.81	15.93	17.38	4.34	4.48
Udmurt Republic	33.64	41	13.77	11.5	10.47	11.78	4.83	4.68
Ulyanovsk Oblast	41.37	48.43	15.84	16	14.38	15.68	4.49	4.3
Vladimir Oblast	38.24	42.39	19.63	15.92	9.82	14.15	5.6	5.14
Volgograd Oblast	40.53	47.16	18.41	14.43	16.15	16.99	6.38	7.01
Vologda Oblast	31.61	43.64	13.97	15.39	18.96	21.8	2.82	4.85
Voronezh Oblast	39.24	42.9	16.32	14.48	9.85	10.5	4.26	3.99

Yamalo-Nenets Autonomous Okrug **	-	29.33	-	18.39	-	11.41	-	4.15
Yaroslavl Oblast	47.1	46.58	16.39	13.84	11.81	16.54	3.71	4.91
Zabaykalsky Krai	41.75	48.87	16.99	15.89	24.92	29.23	5.43	8.57

*- Khanty–Mansi Autonomous Okrug-Yugra and Yamalo-Nenets Autonomous Okrug data were previously included in Tyumen oblast reported in 2008.

PUBLICATION
IV

Productivity losses associated with premature mortality due to cancer in Russia: a population-wide study covering 2001–2030

Barchuk, Anton, Aleksandr Bespalov, Heini Huhtala, Tuvshinjargal Chimed, Alexey Belyaev, Malcolm Moore, Ahti Anttila, Anssi Auvinen, Alison Pearce, and Isabelle Soerjomataram

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ORIGINAL ARTICLE

Productivity losses associated with premature mortality due to cancer in Russia: A population-wide study covering 2001–2030

ANTON BARCHUK[1,2], ALEXANDER BESPALOV[1,2], HEINI HUHTALA[1], TUVSHINJARGAL CHIMED[1], ALEXEY BELYAEV[2], MALCOLM MOORE[3], AHTI ANTTILA[4], ANSSI AUVINEN[1], ALISON PEARCE[5] & ISABELLE SOERJOMATARAM[6]

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Abstract

Aims: Productivity losses related to premature cancer mortality have been assessed for most developed countries but results for Russia are limited to cross-sectional reports. The aim of this study was to quantify productivity costs due to cancer mortality in Russia between 2001 and 2015 and project this to 2030. *Methods*: Cancer mortality data (2001–2015) were acquired from the State Cancer Registry, whereas population data, labour force participation rates and annual earnings were retrieved from the Federal State Statistics Service. Cancer mortality was projected to 2030 and the human capital approach was applied to estimate productivity losses. *Results*: The total annual losses increased from US6.5b in 2001–2005 to US$8.1b in 2011–2015, corresponding to 0.24% of the annual gross domestic product. The value is expected to remain high in 2030 (US$7.5b, 0.14% of gross domestic product). Productivity losses per cancer death are predicted to grow faster in women (from US$18,622 to US$22,386) than in men (from US$25,064 to US$28,459). Total losses were found to be highest for breast cancer in women (US$0.6b, 20% of overall losses in women) and lung cancer in men (US$1.2b, 24%). The absolute predicted change of annual losses between 2011–2015 and 2026–2030 was greatest for cervix uteri (+US$214m) in women and for lip, oral and pharyngeal cancers in men (+US$182m). ***Conclusions*: In Russia, productivity losses due to premature cancer mortality are substantial. Given the expected importance especially for potentially preventable cancers, steps to implement effective evidence-based national cancer control policies are urgently required.**

Keywords: *Cancer, premature mortality, productivity losses, Russia*

Background

Cancer is the second leading cause of death in Russia [1]. While information on incidence reflects the causes of cancer, data for mortality capture combined information on relative success of primary and secondary prevention as well as on cancer management. Such data can be applied to illustrate societal burden, including economic impact. This latter can be separated into two components, namely direct healthcare expenses and indirect costs associated with lost contribution to the economy due to absence from work, known as lost productivity. Though often dismissed, lost productivity through premature cancer mortality of the working population may exceed treatment expenses and contribute substantially to the overall cost of cancer to societies [2].

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Productivity losses related to premature cancer mortality have been assessed for most developed countries [3–10]. However, large-scale assessment of productivity losses has never been conducted in Russia and given recent efforts of the Ministry of Healthcare to implement cancer control strategies, such information is very necessary to guide design of national cancer control plans [11].

Aims

The aim of this study was to quantify this aspect of cancer burden by estimating years of life lost (YLL) and thereby calculate productivity losses due to premature cancer mortality in Russia in 2001–2015 and project this up to 2030.

Methods

General approach

We measured the YLL and the societal burden of cancer in Russia by assessing the impact of premature cancer mortality on productivity losses. Overall, YLL were calculated for six calendar periods (2001–2005, 2006–2010, …, and 2026–2030) by sex and 18 age groups for the following cancer sites, classified using ICD-10 (the International Statistical Classification of Diseases and Related Health Problems): lip, oral cavity and pharynx (C00–14), oesophagus (C15), stomach (C16), colorectum (C18–21), liver (C22), pancreas (C25), larynx (C32), trachea and lung (C33–34), bone (C40), skin (melanoma) (C43), soft tissues (C46.1,3,7–9,47,49), female breast (C50), cervix uteri (C53), corpus uteri (C54), ovaries (C56), prostate (C61), kidney (C64), bladder (C67), brain and central nervous system (C70–72, CNS), hematopoietic and lymphoid malignancies (C81–96) and all cancers combined including non-melanoma skin cancers (C00–96). The 'other' category included both cancer sites not mentioned earlier and unspecified cancer deaths. This was calculated as the difference between the number of all cancer deaths combined and the number of deaths from cancer-specific sites mentioned above. To estimate productivity losses due to cancer-related premature mortality in Russia in the period between 2001 and 2015 and projected until 2030 we applied an incidence-based method using the human capital approach (HCA).

Cancer mortality and population data

Age- and sex-specific cancer mortality data between 2001 and 2015 were acquired from the State Cancer Registry (SCR) based in the Herzen Research Institute of Oncology in Moscow [12]. A system of obligatory registration and lifetime follow-up of cancer patients was established in the USSR in 1953. Mortality data are collected by civil registration services and aggregated by the Federal State Statistics Service (FSSS). Population data, based on population censuses of 1989, 2002, 2010 and average population projections until 2031 were retrieved from the FSSS [13]. Age-standardized rates (ASRs) of cancer incidence and mortality per 100,000 person-years were calculated using the modified world standard population proposed by Segi [14]. In order to estimate trends over time log-transformed ASRs were calculated. To predict cancer mortality rates, we applied the Norpred prediction tool with a linear trend [15]. We derived age-specific YLL for each 5-year period calculated as a function of cancer deaths and life expectancy. Cause-deleted life-tables by period were generated based on data from the Human Mortality Database and forecasts with a functional demographic model [16, 17]. Methods and limitation of the analysis for data from the SCR were previously described [18].

All estimations were performed in open-source statistical software R (version 3.3.3, 2017-03-06)), using packages «nordpred» (accessed on 15 May 2016)[19] and «demography» (version 1.18) [20].

Economic data

The age- and sex-specific economic data were obtained from the FSSS: (a) labour-force participation rates (2001–2014); (b) averaged annual earnings (biennial, between 2002 and 2014); and (c) inflation rates (2001–2016). These data also included information on retirement and labour-force participation after retirement age (official retirement ages are 60 for men and 55 for women). Earnings were converted from Russian rubles to 2016 US dollars after adjustment for inflation based on yearly average currency exchange rates. We applied natural splines to interpolate employment rate integral and mean wages in 2001 and 2015, and also to project employment rates. For sensitivity analysis, wage growth was estimated based on two gross domestic product (GDP) scenarios: (a) GDP growth for 2016, 0.3%; 2018, 2.7%; 2022, 3.9%; 2024, 4.3%; 2027, 4.1%; 2030, 4%; and 2035, 3.8%, were used for base-case calculations, and (b) where GDP growth for 2016, 0.3%; 2018, 2.0%; 2022, 2.4%; 2024, 2.4%; 2027, 2.2%; 2030, 1.9%; and 2035, 1.7%, were used for sensitivity analysis.

Average age-specific wages weighted by age-specific labour force participation were then calculated. An annual discount rate of 2.5% was also applied for

base-case calculations [21]. For sensitivity analysis, we additionally applied discount rates of 0% and 5%. GDP based on purchasing power parity in 2011 international US dollars was acquired from the World Bank Database along with a deflator in order to transform the GPD to 2016 US dollars. In the base-case calculations, any earnings from work force participation were discontinued at the age of 70 as currently reported by FSSS. However, in the sensitivity analysis we also explored additional scenarios: where earnings were discontinued at an earlier age (65 and 55) and where earnings were not discontinued but projected to allow workforce participation until the end of life.

Estimation of lost productivity

The HCA assumes that economic output of an individual equates to wage rate, so that premature death, by cutting short the working life, produces economic losses to society equal to the lost earnings. To calculate productivity losses, we used age- and period-specific death and economic data. All results were expressed in 2016 US dollars. First (2001–2005), most recent (2011–2015) and last projected (2026–2030) periods for the base-case scenario were reported in Table I.

Ethical approval

This study utilized publicly available secondary aggregate data, and thus did not require, according to the current legislature, ethical approval.

Results

Trends in age-standardized mortality rates per 100,000 and YLL from cancer

Mortality for most cancer types was going down during the study period (Figure 1; Supplementary material Table S1). There was an upward trend between 2001 and 2015 for melanoma, pancreas, brain and CNS cancer mortality in both men and women, for lip, oral and pharynx, larynx and cervix uteri cancer mortality in women, and for prostate cancer mortality in men. Overall YLL increased for most cancer sites, except larynx in men, and stomach and bone in both men and women. The overall annual YLL due to premature cancer mortality in men increased from 11 million years in 2001–2005 to 12 million years in 2011–2015. It was predicted to further increase to 14 million years in 2026–2030.

Taking into account both relative and absolute changes in the overall YLL between 2001 and 2015, cervix uteri, pancreas and colorectal cancer showed the largest increases. Lip, oral and pharynx cancer showed the largest relative change, while cervix uteri cancer exhibited the largest absolute growth in women. Prostate cancer showed the highest absolute and relative increase in YLL in men, with major increases also in lip, oral and pharynx, colorectal and pancreas cancer in men in both relative and absolute terms (Supplementary material Figure S1).

Overall productivity losses and losses per one death

Annual productivity losses due to cancer mortality in Russia for the reported cancer types are presented in Table I. The annual overall productivity losses due to cancer mortality were reaching a peak of US$8.3b in 2006–2010 (US$3.2b in women and US$5.1b in men) (Figure 2).

Productivity losses per cancer death were higher in men (Table I). Yet, productivity losses per cancer death in women are predicted to grow faster than in men, from UD$18,622 in 2001–2005 to US$22,386 in 2026–2030. Productivity losses per cancer death were highest for bone, brain and CNS, cervix uteri, soft tissues cancer hematopoietic and lymphoid malignancies and melanoma of the skin (Supplementary material Figure S2).

In total, the estimated productivity losses decreased from 0.28% of GDP in 2001–2005 to 0.24% in 2011–2015 and are predicted to further decrease to 0.14% in 2026–2030. While this decline was seen for most cancer sites increases were found for lip, oral and pharyngeal, pancreatic, lung, cervix uteri in women; prostate in men; and oesophagus cancer in men and women.

Productivity losses by cancer type

Annual overall productivity losses were highest for breast cancer in women (US$0.6b or 20% of all losses in 2011–2015) and lung cancer in men ($1.2b or 24% in 2011–2015), which remain the highest-ranking cancers in the next two decades of the study period (Figure 2).

Relative change in productivity losses between 2011–2015 and 2026–2030 in women was highest for the larynx (174%), lip, oral and pharynx (152%), oesophagus (136%) and cervix uteri cancer (111%). During the same period, the absolute predicted change was highest for cervix uteri (+ US$214m) and lung cancer (+ US$61m) in women (Figure 3). In men, the relative change was highest for prostate cancer (111%), lip, oral and pharyngeal cancer (82%), oesophagus (64%), and liver cancer (69%), while the largest absolute increase was noted for lip,

Table I. Annual productivity losses due to cancer mortality, productivity losses per death (US$) and % of gross domestic product (GDP) adjusted for purchasing power parity by cancer, sex and period in Russia.

Cancer type (ICD-10)	Sex	Productivity losses 2016 US$m			Productivity losses per death, 2016 US$			% of GDP		
		2001–2005	2011–2015	2026–2030	2001–2005	2011–2015	2026–2030	2001–2005	2011–2015	2026–2030
Lip, oral cavity, pharynx (C00–14)	Women	27.0	50.5[a]	68.0	13,688	25,731	35,013	0.0011	0.0015	0.0013
	Men	222.5	322.8	405.3	26,251	38,871	49,033	0.0094	0.0094	0.0077
Oesophagus (C15)	Women	11.8	21.3	28.0	7734	13,672	18,155	0.0005	0.0006	0.0005
	Men	113.8	170.7	187.6	19,878	30,094	33,229	0.0048	0.005	0.0036
Stomach (C16)	Women	239.7	237.9	161.6	19,265	18,961	12,791	0.0102	0.0069	0.0031
	Men	518.5	522.8	362.4	31,149	30,640	21,094	0.022	0.0153	0.0069
Colorect al (C18–21)	Women	217.4	314.3	267.1	10,151	14,803	12,561	0.0092	0.0092	0.0051
	Men	257.8	402.7	361.5	13,971	22,124	19,972	0.0109	0.0117	0.0069
Liver (C22)	Women	53.2	70.1	73.9	12,798	17,047	18,029	0.0023	0.002	0.0014
	Men	113.3	165	180.4	20,669	30,440	33,737	0.0048	0.0048	0.0034
Pancreas (C25)	Women	71.9	122.9	115.9	8430	14,812	14,019	0.003	0.0036	0.0022
	Men	196.3	281.2	267.2	21,884	31,879	30,722	0.0083	0.0082	0.0051
Larynx (C32)	Women	4.8	7.9	13.1	15,885	26,697	44,887	0.0002	0.0002	0.0069
	Men	132.0	134.2	109.6	35,684	35,110	28,759	0.0056	0.0039	0.0021
Lung (C33, 34)	Women	115.8	174.4	177.0	12,273	18,589	18,938	0.0049	0.0051	0.0034
	Men	952.3	1206.5	968.0	23,259	29,094	23,378	0.0403	0.0352	0.0184
Bone (C40, 41)	Women	34.1	26.9	28.0	66,610	52,273	53,315	0.0014	0.0008	0.0005
	Men	70.8	61.6	58.9	107,636	93,561	87,423	0.003	0.0018	0.0011
Melanoma of skin (C43)	Women	47.8	62.9	60.2	25,092	33,306	31,854	0.002	0.0018	0.0011
	Men	61.9	83.3	81.9	37,198	51,050	50,186	0.0026	0.0024	0.0016
Soft tissues (C46.1,3,7–9,47,49)	Women	45.5	57.2	60.1	27,431	34,579	36,196	0.0019	0.0017	0.0011
	Men	70.9	91.5	99.0	45,857	59,415	64,514	0.003	0.0027	0.0019
Breast (C50)	Women	558.9	642.6	522.4	24,756	28,668	23,153	0.0237	0.0187	0.0099
Cervix uteri (C53)	Women	232.7	342.6	446.8	34,240	50,601	65,569	0.0099	0.01	0.0085
Corpus uteri (C54)	Women	99.0	145	137.9	14,426	21,358	20,272	0.0042	0.0042	0.0026
Ovary (C56)	Women	179.7	233.2	212.1	23,308	30,324	27,538	0.0076	0.0068	0.004

Table 1. (Continued)

Cancer type (ICD-10)	Sex	Productivity losses 2016 US$m			Productivity losses per death, 2016 US$			% of GDP		
		2001–2005	2011–2015	2026–2030	2001–2005	2011–2015	2026–2030	2001–2005	2011–2015	2026–2030
Prostate (C61)	Men	51.7	128.6	109.2	4332	12,151	10,589	0.0022	0.0038	0.0021
Kidney (C64)	Women	460	55.5	43.0	14,615	17,834	13,677	0.0019	0.0016	0.0008
	Men	135.4	173.2	132.6	25,632	33,180	25,398	0.0057	0.0051	0.0025
Bladder (C67)	Women	8.7	13.8	16.2	6150	9693	11,432	0.0004	0.0004	0.0003
	Men	66.6	88.8	64.3	13,183	17,197	12,404	0.0028	0.0026	0.0012
Brain, central nervous system (C70–72)	Women	140.0	165.7	186.3	37,720	45,747	52,049	0.0059	0.0048	0.0035
	Men	217.2	264.8	296.0	58,855	73,167	82,157	0.0092	0.0077	0.0056
Hematopoietic, lymphoid (C81–96)	Women	240.2	239	228.1	32,634	32,614	31,137	0.0102	0.007	0.0043
	Men	389.1	412.7	420.0	52,064	55,265	56,467	0.0165	0.012	0.008
Others[b]	Women	183.3	232.1	239.0	14,194	18,148	18,722	0.0078	0.0068	0.0045
	Men	341.3	426.3	408.7	28,867	36,447	35,031	0.0145	0.0124	0.0078
All cancer types combined (C00–96)	Women	2,547.8	3,204.4	3,053.4	18,622	23,492	22,386	0.1079	0.0935	0.0581
	Men	3,969.4	4,926.6	4,496.5	25,064	31,070	28,459	0.1681	0.1437	0.0855
Overall (sexes combined)	-	6,517.2	8,131.0	7,549.9	-	-	-	0.276	0.2372	0.1436

[a]Red cells represent increased losses compared with the previous period, green cells – reduced, grey – stable.
[b]Other cancer types includes all other cancers not specified above.

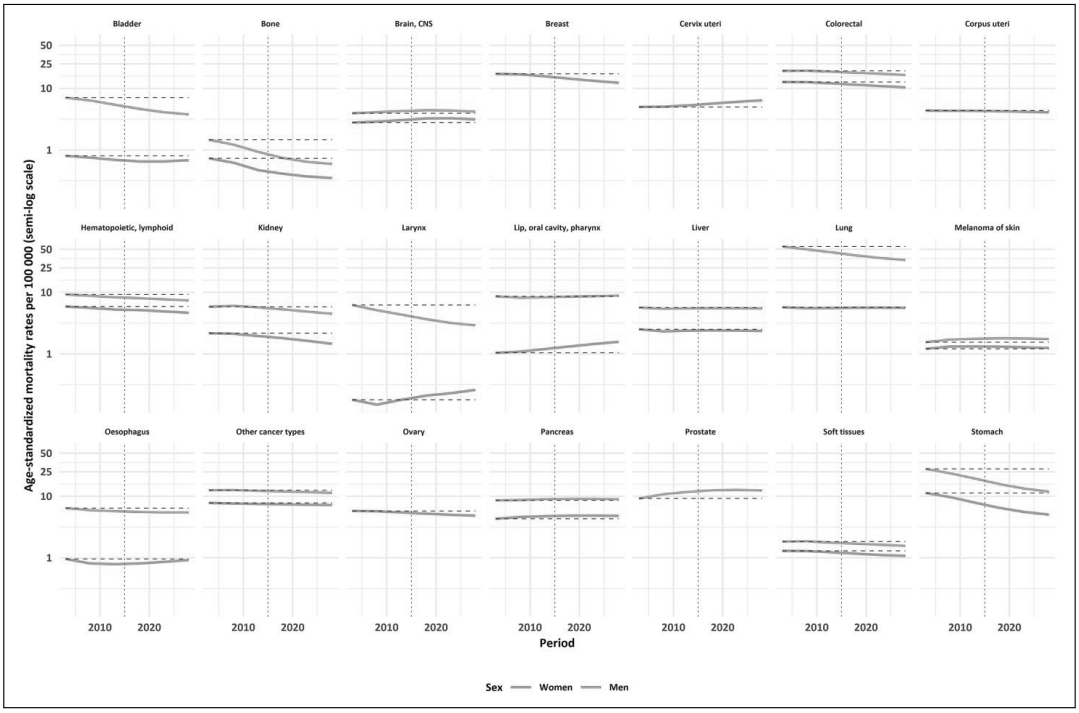

Figure 1. Age-standardized mortality rates per 100,000 (presented on a semi-log scale) according to cancer types and sex between 2001 and 2030 in Russia (dash–dot line separates recent and future predicted rates).

oral and pharyngeal (+ US$182m) and colorectal cancer (+ US$103m) (Figure 3).

Sensitivity analyses

Changing the discount rate affected the overall amount of annual productivity losses but did not affect the relative distribution of losses by cancer types (Supplementary material Figures S3 and S4). Cutting the earnings at a certain age decreased the amount of productivity losses. In the scenario, where earlier age at earnings was discontinued, more productivity losses were assigned to cancer types affecting younger age groups (e.g. cervix uteri) and less productivity losses to those with deaths at older age groups (e.g. prostate) (Supplementary material Figures S5–S7). However, the major findings reported for the base-case scenario remained. The maximum overall annual productivity losses for 2011–2015 were reached without discontinuation of earnings with 0% discount and the base-case GDP growth scenario – US$4.03b in women and US$6.04b in men – while the lowest figures were obtained with discontinuation at the age 55 with a 5% discount and the second GDP growth scenario – US$1.52b in women and US$2.11b in men (Supplementary material Figures S9–S10).

Discussion

To our knowledge, this is the first analysis of trends and prediction of cancer mortality related productivity costs in Russia. A large overall cost of cancer death in Russia was found amounting to US$8.1b or 0.24% of GDP in 2011–2015. It is expected to remain high in 2030 (US$7.5b or 0.14% of GDP). The result also provides a wide perspective of major contributors to these losses, the greatest cause being lung cancer (US$1.2b or 24% of the total loss) in men and breast cancer (US$0.6b or 20%) in women in 2011–2015. Quantitative assessment of the rising losses linked to cancers known to be related to human papilloma virus (HPV) infection, revealed a figure for cervical cancer in women of US$233m in 2001, which is expected to almost double to US$447m in 2030. This study provides an economic appraisal for the Russian government to set priorities in cancer control activities, including primary prevention (e.g. tobacco control or HPV control) and population-based cancer screening (cervical, breast and colorectal).

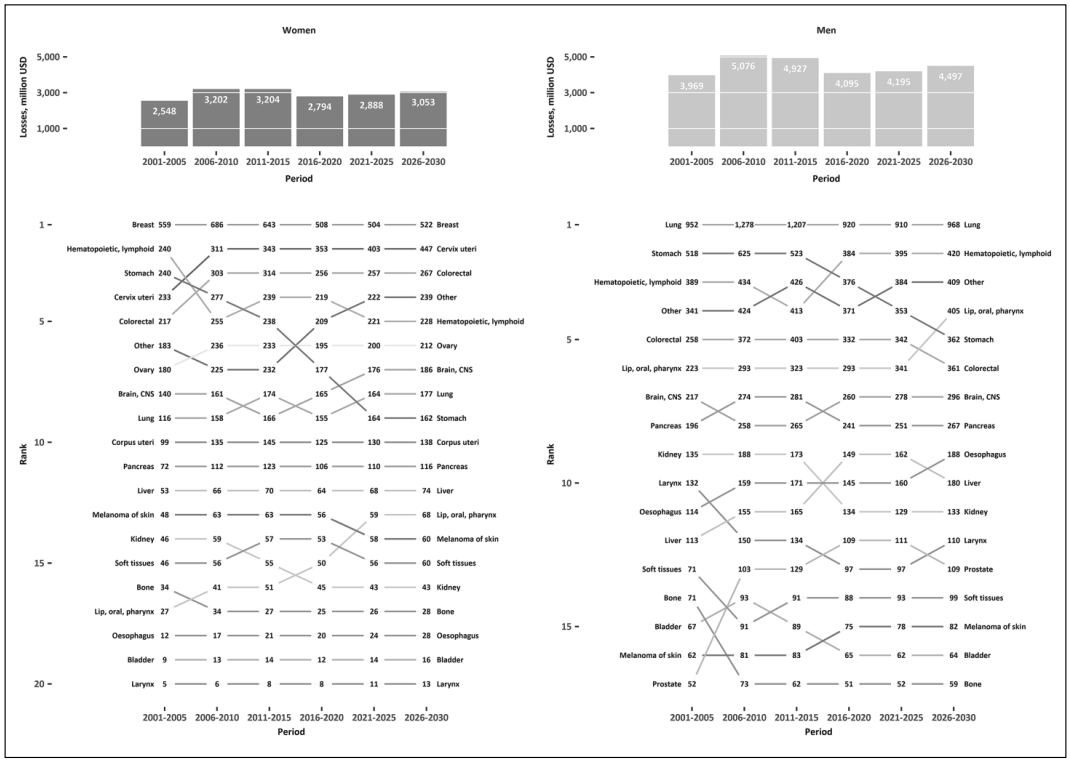

Figure 2. Overall observed and predicted average annual productivity losses due to premature cancer mortality in Russia in 2001–2030 and ranking according to cancer sites and sex.

Our findings can be compared with reports from other countries, which give similar relative estimates when costs are compared to GDP, taking into account differences in mortality and population size. In Europe, productivity losses due to cancer mortality in 2008 were 0.36% of total GDP ranging between 0.15 and 0.67% by country [22]. In the USA, productivity losses were higher: about 1.11% of GDP based on the 2000 estimates [3]. Cancer mortality related productivity costs in BRICS countries in 2008 were estimated as 0.21% GDP for Brazil, 0.25% for Russia, 0.34% GDP for China, 0.36% GDP for India and 0.49% for South Africa. Our results were consistent with these findings. [10].

We estimated an annual loss of US$8.1b due to premature deaths from cancer in Russia in 2011–2015. Extrapolating this estimate to total costs of cancer in Russia without high-quality data for direct medical costs related to cancers remains challenging. In a recent systematic review the proportion of cancer mortality related productivity losses was reported to be over 50% of the total cost [7]. However, in a large European study this proportion ranged from 24 to 54% for 27 countries [22, 23]. With some uncertainty, overall cancer costs in Russia can be estimated to be at least US$15b but probably more than US$20b per year based on extrapolation from our findings.

Productivity losses by cancer type

In general, we have observed a decline in the mortality from cancers in Russia with ASRs dropping between 2001 and 2015 from 94 to 87 per 100,000 in women (7%) and from 190 to 167 per 100,000 in men (12%), which reflected a decrease in the burden of cancer to the GDP from 0.27 to 0.24%. Some of this decrease can be related to the decline in smoking-related cancers in Russia as much of the productivity losses, particularly among men, are driven by smoking-related cancers such as lung cancer (24% of the total productivity loss in 2011–2015). The Russian Federation has been a Party to the WHO Framework Convention on Tobacco Control since 2008 and Federal Law on Health Protection from Exposure to Environmental Tobacco Smoke and the Consequences of Tobacco Consumption was adopted in 2013 – actions that

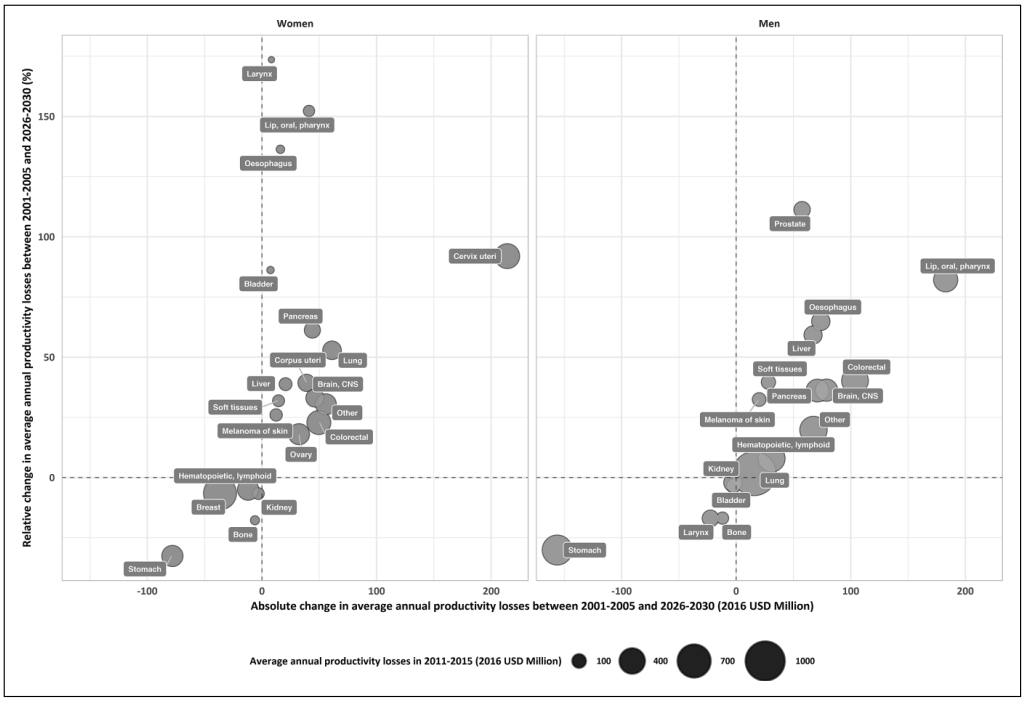

Figure 3. Change in in annual productivity losses due to premature cancer mortality in Russia between 2001–2005 and 2026–2030 according to cancer type and sex.

clearly will contribute to further mortality decline. Yet, the smoking prevalence remains high among men in Russia (daily smoking for 51% of men in 2015) [24]. Unlike many reports in other European countries, costs associated with women lung cancer deaths were moderate, ranking eighth of all costs in women probably related to a relatively low daily smoking prevalence (i.e. 15% in 2015) [24]. A slight increase in rates of lung cancer has been observed in women and continued increase in lung-cancer rates reported in other countries caution for a similar rise in Russia. Considering these factors, additional smoking cessation counselling might be implemented as part of screening programmes [25].

On the other hand, we saw a substantial increase in the contribution of HPV-related cancers (cervix uteri, oral and pharynx) to future productivity losses in Russia. At the moment, HPV vaccination is not available as a nationwide programme and cervical cancer screening remains opportunistic for a select proportion of the population [26]. Rising productivity losses from oral and pharynx cancers in both sexes adds additional motivation to put forward population-based HPV control activities at the national level.

We also saw a rapid rise in productivity losses from oesophagus, liver and pancreas cancer mortality, all traditionally related to smoking and alcohol consumption, that can also be partly explained by the increasing obesity prevalence in Russia and other lifestyle risk factors [27]. In addition, growing incidence and substantial losses from colorectal cancer mortality as well as a large contribution of breast cancer to the economic cost underline the need to assess the major risk factors for these cancers and also the effectiveness of early detection and management in order to adapt existing national control policies.

A few limitations of the study should be noted. Quality of the data used in the analysis may affect the result, and as such the data input for this study needs to be considered when interpreting reported results. The 'other cancer types' category in our analysis consisted of two groups: the first including unspecified tumors (C76–C80) with around 4% out of the total reported deaths. The second group is other specific cancer types (around 3%), for which data were not available for the whole study period. The HCA is only one of several approaches to estimate societal burden of cancer. The friction cost approach (FCA) is an alternative. As such, losses based on the HCA calculations are considerably higher than calculated by FCA [28]. Yet, the HCA has become widely used and the methodology has

become a standard to estimate productivity losses for calculating indirect non-medical costs due to mortality [23, 29]. This analysis includes only paid productivity losses, so other indirect and direct losses, like unpaid work such as caring for children or sick relatives, and volunteering work, as well as other payments, are not included. Additionally, our method does not consider productivity losses that occur due to illness and disability, and hence loss of income, related to cancer. Estimating individual losses is an optimal approach but it is rarely feasible and renders such results incomparable to other studies due to differences in data collection and availability [30]. Furthermore, projected losses need to be carefully interpreted due to uncertainty in the economic, population and cancer predictions.

The primary strength of our study is that we provide comprehensive analysis of the trends and changes in productivity losses over time while most similar studies report cross-sectional findings. That allowed us to capture how the changing cancer burden is affecting economic losses in Russia. We used combined economic and epidemiological data available for the whole period of the study. In the absence of the reliable individual-level data, results of our and similar studies must be used to approximate the overall cancer costs in Russia, but future research would benefit from having more detailed data to estimate the economic burden of cancer in Russia.

Conclusions

Productivity losses due to premature cancer mortality in Russia are substantial and amount to US$8b per year. The losses are expected to drop from 0.28% of GDP in 2001 to 0.14% in 2030 mostly due to a decline in the mortality from cancers in Russia. While the losses are highest for breast cancer in women and lung cancer in men, the relative growth in productivity losses was highest for HPV-related cancer mortality.

Conflict of interest

None declared.

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Supplemental material

Supplemental material for this article is available online.

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Productivity losses associated with premature mortality due to cancer in Russia: a population-wide study covering 2001-2030

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List of tables and figures

Table S1. Age-standardized mortality rates per 100 000 (ASR), years of life lost per death (YLL per death) and annual cumulative years of life lost (YLL) by cancer types, sex and period in Russia.

Cancer type (ICD-10)	Sex	ASRs per 100 000			YLL per death			YLL		
		2001-2005	2011-2015	2026-2030	2001-2005	2011-2015	2026-2030	2001-2005	2011-2015	2026- 2030
Lip, oral cavity, pharynx (C00–14)	Women	1.04	1.20**	1.57	14.58	18.17	20.75	111,411	163,931	270,376
	Men	8.61	8.30	8.84	13.38	15.91	18.74	475,557	607,466	907,046
Oesophagus (C15)	Women	0.96	0.79	0.92	11.45	14.2	18.23	93,988	100,591	158,864
	Men	6.43	5.73	5.46	11.88	14.33	16.94	314,590	378,845	526,760
Stomach (C16)	Women	11.29	7.87	5.03	13.95	15.12	17.77	1,199,824	1,020,813	879,956
	Men	27.86	19.40	11.88	11.78	13.5	15.7	1,371,965	1,219,906	1,116,713
Colorectal (C18–21)	Women	12.70	12.05	10.37	13.17	14.39	16.5	1,300,907	1,533,660	1,817,605
	Men	19.22	18.62	16.53	10.61	12.34	14.16	848,881	1,078,501	1,465,185
Liver (C22)	Women	2.51	2.38	2.35	14.44	15.08	17.36	263,045	303,177	404,545
	Men	5.65	5.48	5.47	12.14	14.07	16.15	284,024	355,495	515,232
Pancreas (C25)	Women	4.31	4.75	4.80	13.23	14.58	16.46	437,591	595,570	830,275
	Men	8.58	8.98	8.95	12.52	14.31	15.7	446,040	593,360	834,950
Larynx (C32)	Women	0.18	0.18	0.26	15.56	19.27	22.75	19,452	24,476	45,720
	Men	6.21	4.34	2.91	12.5	14.55	17.18	323,685	291,175	286,802
Lung (C33-34)	Women	5.69	5.55	5.59	14.08	15.94	18.38	597,605	717,842	966,260
	Men	55.33	44.66	33.47	11.97	14.08	16.23	2,767,761	2,905,787	3,199,607
Bone (C40-41)	Women	0.73	0.47	0.35	21.48	23.36	29.9	90,626	65,628	58,313
	Men	1.46	0.93	0.59	17.97	21.08	27.25	104,135	81,376	70,717
Melanoma of skin (C43)	Women	1.21	1.32	1.25	18.45	19.45	20.29	143,877	183,797	217,416
	Men	1.55	1.76	1.74	15.12	16.47	17.36	97,602	132,986	172,210
Soft tissues (C46.1,3,7-9,47,49)	Women	1.30	1.23	1.08	18.39	19.86	22.35	148,296	166,736	182,448
	Men	1.84	1.76	1.57	16.05	18.23	20.43	116,946	138,849	164,091
Breast (C50)	Women	17.21	15.69	12.30	17.75	18.74	19.99	1,971,514	2,149,205	2,159,309
Cervix uteri (C53)	Women	4.98	5.28	6.04	20.43	24.81	27.70	625,389	801,048	1,156,705
Corpus uteri (C54)	Women	4.36	4.31	4.17	15.08	16.86	18.92	464,296	560,533	703,748
Ovary (C56)	Women	5.77	5.46	4.83	17.56	19.5	21.55	655,834	750,770	835,540
Prostate (C61)	Men	9.22	11.79	12.42	8.95	10.2	11.82	341,101	570,305	984,388
Kidney (C64)	Women	2.17	1.95	1.46	14.85	15.28	16.92	227,314	247,074	252,227
	Men	5.82	5.68	4.48	12.74	14.26	15.57	305,892	372,958	414,909
Bladder (C67)	Women	0.80	0.69	0.68	10.77	12.18	15.5	75,970	84,469	117,532
	Men	7.05	5.42	3.77	9.78	11.23	13.27	285,615	288,508	319,099
Brain, CNS (C70–72)	Women	2.79	3.05	3.14	25.09	23.41	23.39	351,182	429,409	529,773
	Men	3.94	4.28	4.18	19.94	20.42	21.86	302,307	370,980	455,594
Hematopoietic, lymphoid (C81-96)	Women	5.88	5.25	4.65	20.08	19.53	20.93	704,438	713,004	785,339
	Men	9.23	8.29	7.37	16.9	17.68	19.33	614,810	638,860	755,466
Others *	Women	7.80	7.46	7.19	14.42	15.39	17.6	833,501	963,352	1,241,160
	Men	12.54	12.25	11.35	13.42	14.77	16.28	689,281	828,957	1,075,571
All cancer types combined (C00-96)	Women	93.52	86.78	78.12	16.49	18.02	20.02	10,789,362	12,192,138	14,115,270
	Men	190.25	167.50	137.90	13.24	15.33	17.47	10,427,951	11,844,558	14,180,163
Overall (sexes combined)*	-	129.35	116.63	99.86	-	-	-	21,217,313	24,036,696	28,295,433

* Other cancer types includes all other cancers not specified above

** Red cells represent increased rates compared with the previous period, green cells – reduced, grey – stable.

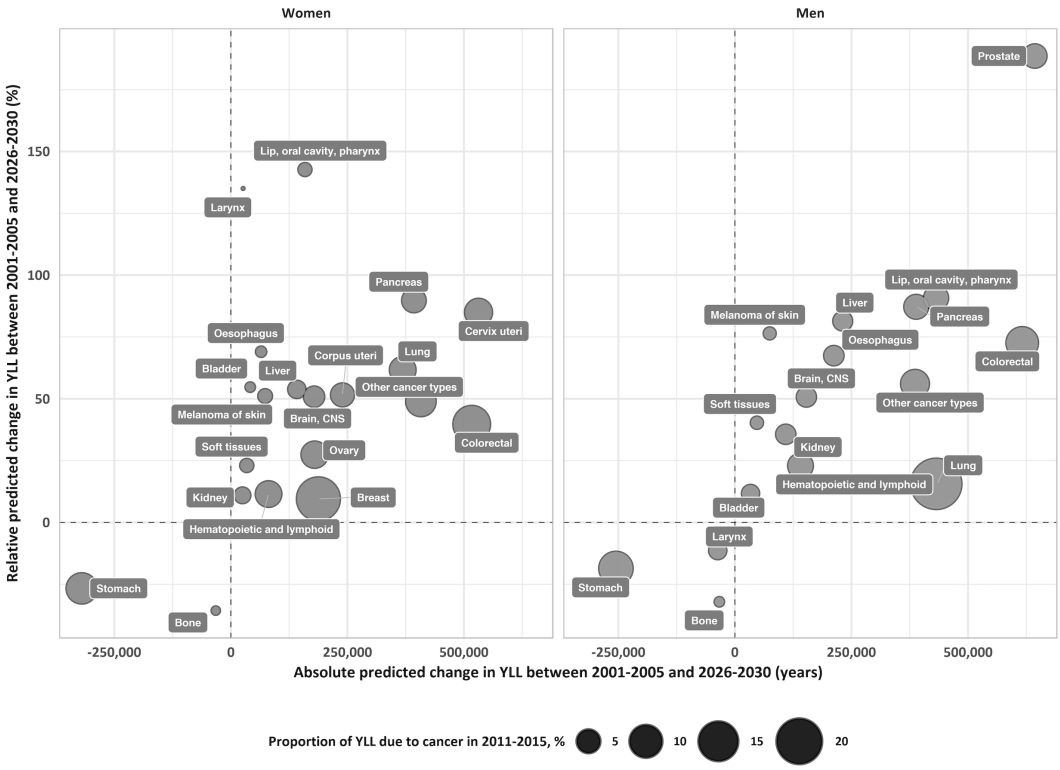

Figure S1. Predicted trends in number of years of life lost (YLL) due to premature cancer mortality in Russia between 2001-2005 and 2026-2030

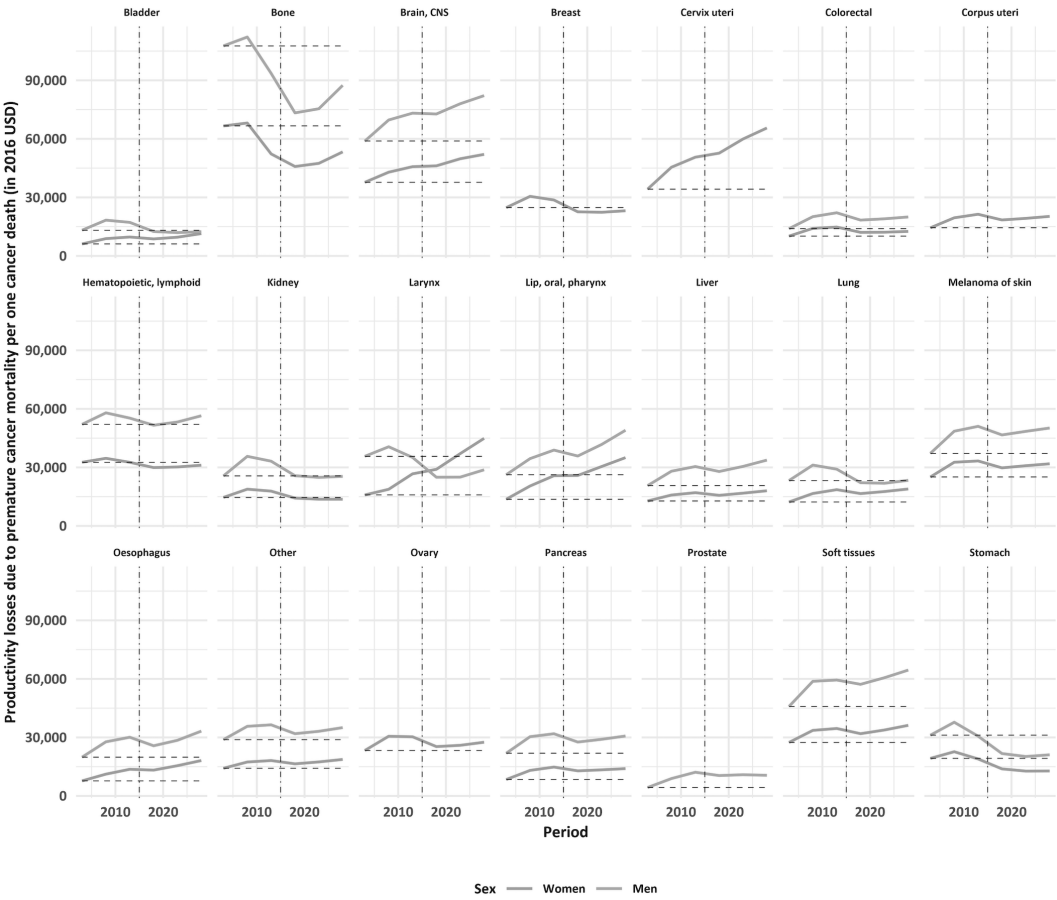

Figure S2. Observed and predicted annual productivity losses due to premature mortality per cancer death in Russia in 2001-2030 according to cancer site and sex

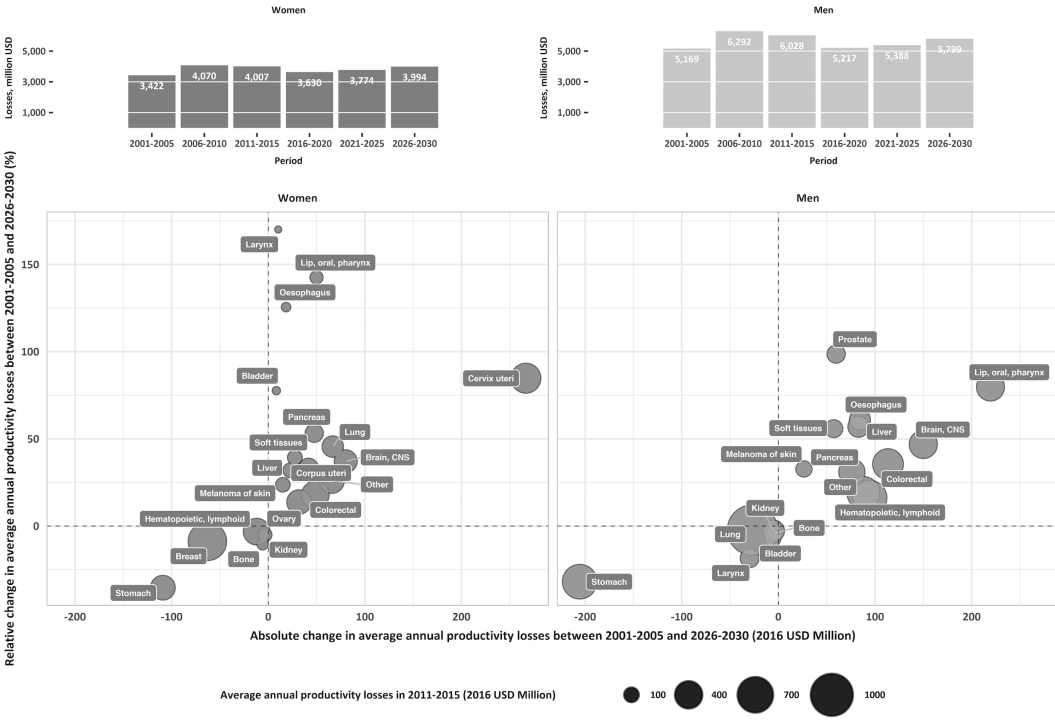

Figure S3. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 - base-case GDP growth scenario, earnings discontinued at the age 70, 0% annual discount rate.

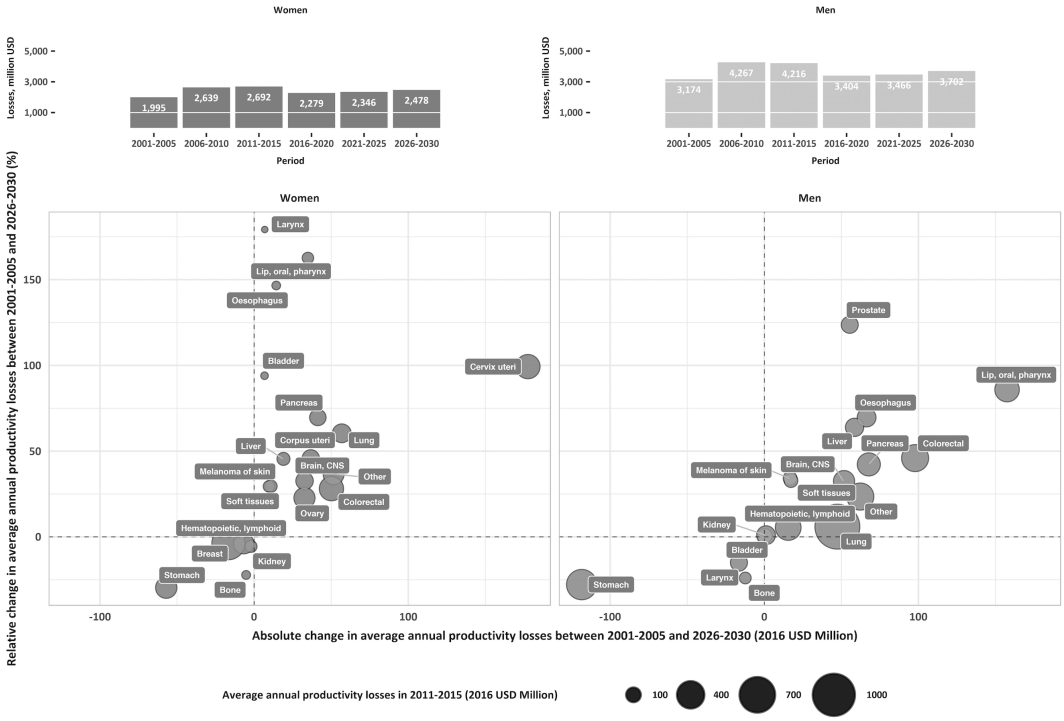

Figure S4. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – base-case GDP growth scenario, earnings discontinued at the age 70, 5% annual discount rate

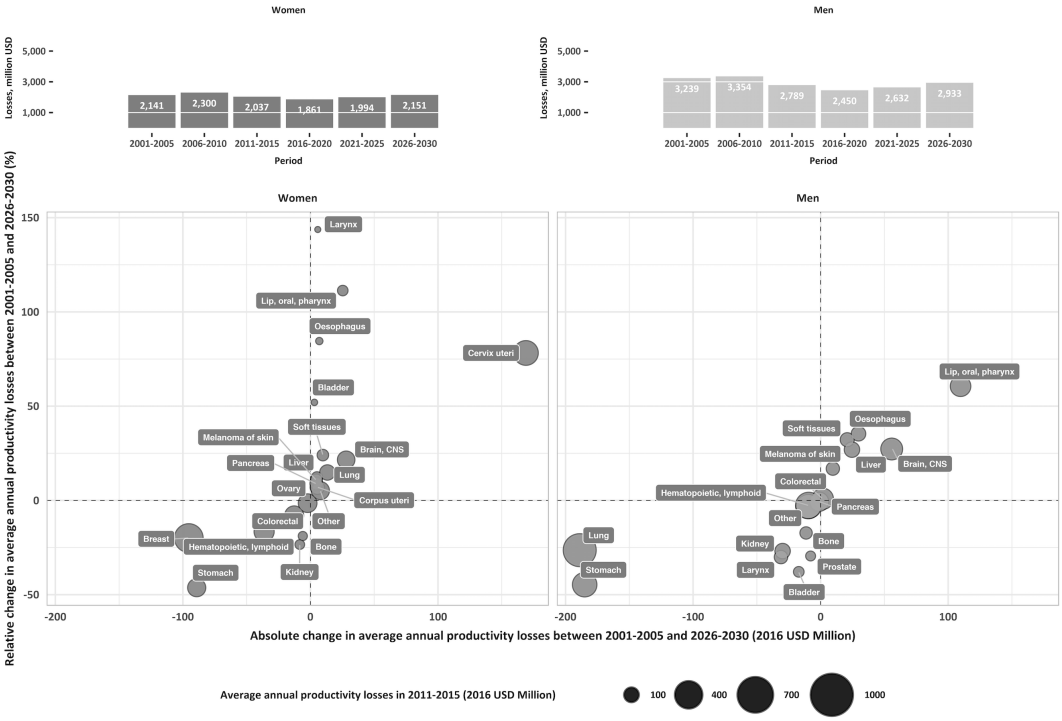

Figure S5. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – base-case GDP growth scenario, earnings discontinued at the age 55, annual discount rate 2,5%.

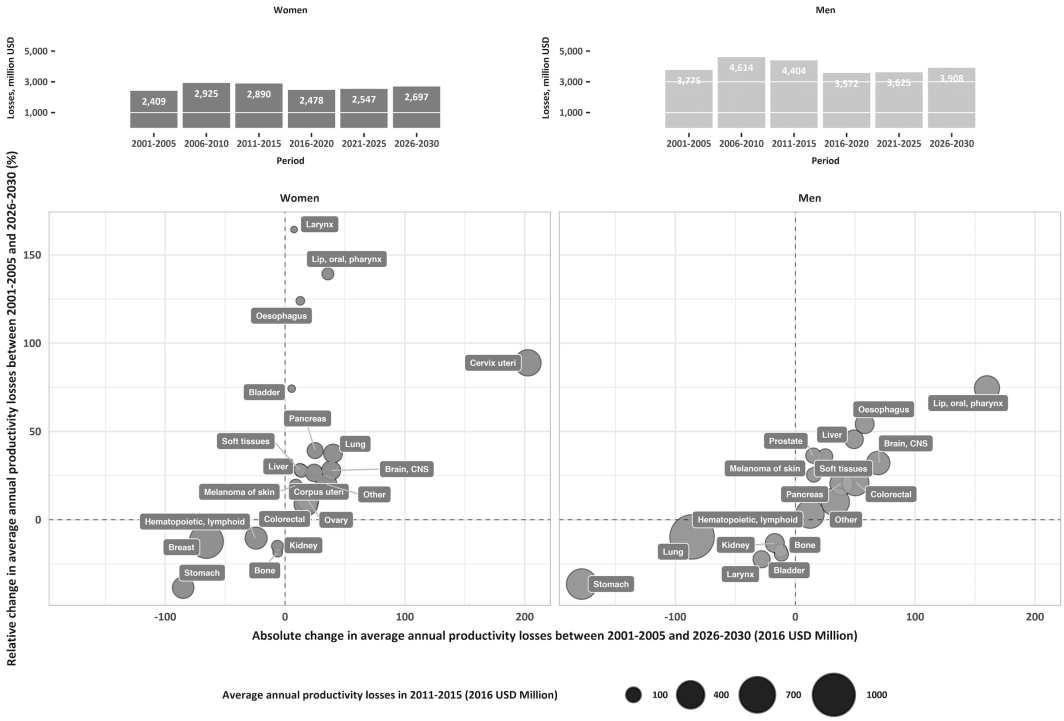

Figure S6. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – base-case GDP growth scenario, earnings discontinued at the age 65, annual discount rate 2,5%.

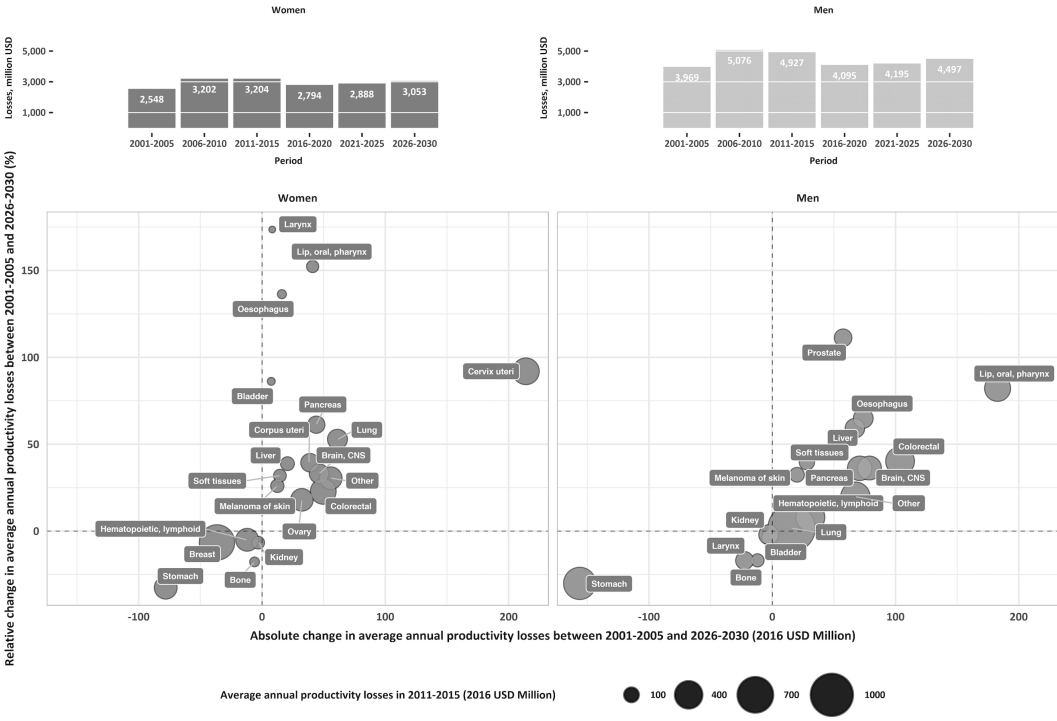

Figure S7. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – base-case GDP growth scenario, earnings projected to allow workforce participation until the end of life., annual discount rate 2,5%.

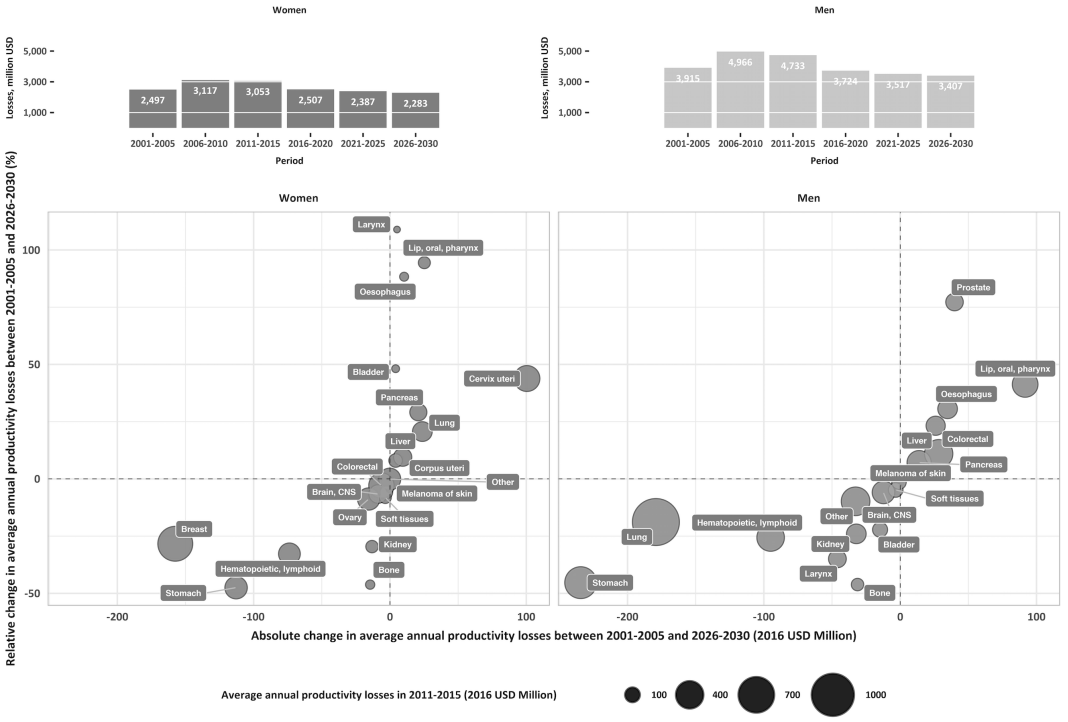

Figure S8. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – alternative GDP growth scenario, earnings discontinued at the age 70, 2,5% annual discount rate.

5. Scenarios with minimum and maximum amount of losses

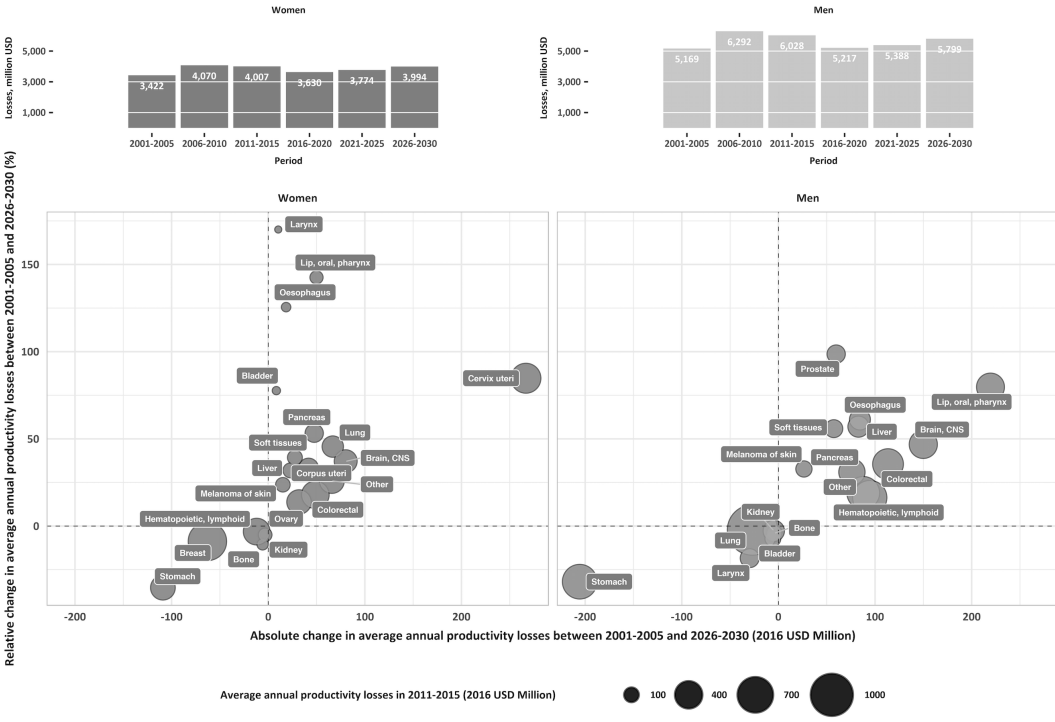

Figure S9. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – base-case GDP growth scenario, annual discount rate 0%, earnings projected to allow workforce participation until the end of life.

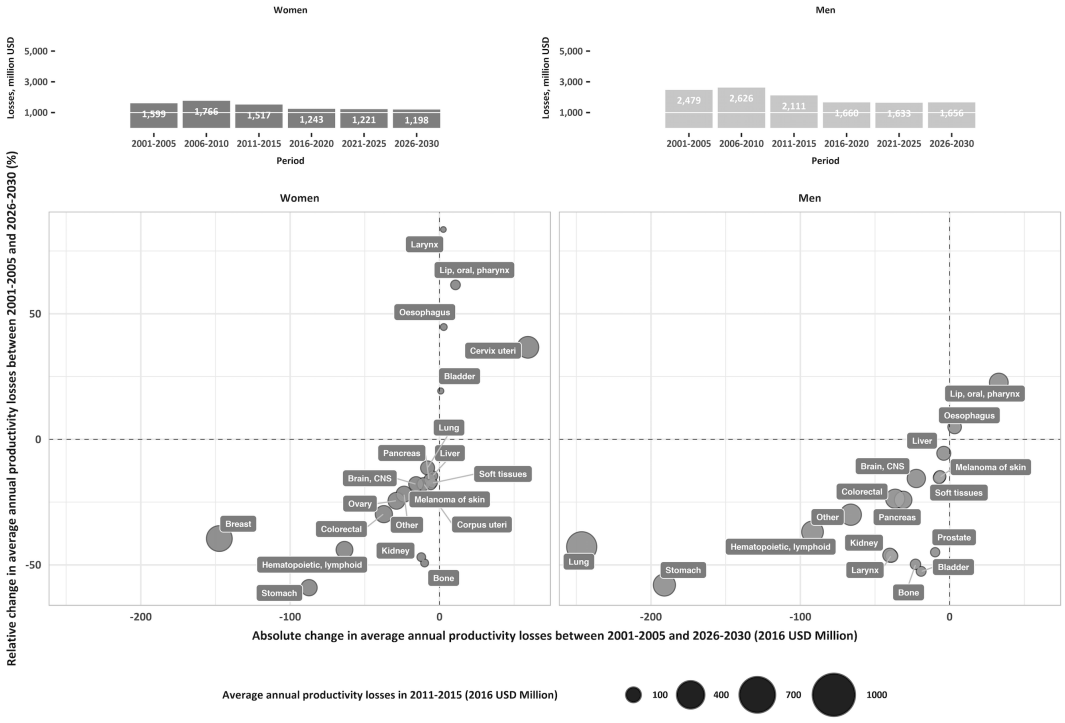

Figure S10. Overall observed and predicted annual productivity losses and predicted trends in annual productivity losses due to premature cancer mortality by cancer type in Russia between 2001-05 and 2026-30 – alternative GDP growth scenario, 5% annual discount rate, earnings cut at 55.