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IV. **Baburin, A.,** Aareleid, T., Padrik, P., & Valvere, V. (2014). Time trends in population-based breast cancer survival in Estonia: Analysis by age and stage. *Acta Oncologica,*53:226–234. https://doi.org/10.3109/0284186X.2013.806992

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Paper I: Study design, data analysis, interpretation of results, drafting the manuscript to which authors contributed, critically revised the manuscript for intellectual content and approved the final manuscript.

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Paper III: Data analysis, interpretation of results, critically revised the manuscript for intellectual content and approved the final manuscript.

Paper IV: Data analysis, interpretation of results, drafting the manuscript to which authors contributed, critically revised the manuscript for intellectual content and approved the final manuscript.

2. ABBREVIATIONS

APC	annual percentage change
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
ASR	age-standardized rate
BC	breast cancer
CI	confidence interval
CoDR	Causes of Death Registry
ECR	Estonian Cancer Registry
EoD	extent of disease
HDI	Human Development Index
IB	incidence-based
ICD-10	International Classification of Diseases 10th revision
ICD-O-3	International Classification of Diseases for Oncology, third edition
IR	incidence rate
MIR	mortality-to-incidence ratio
RCT	randomized controlled trial
RR	rate ratio
RSR	relative survival ratio
WHO	World Health Organization
TNM	tumor, nodules, metastases staging system

3. INTRODUCTION

Breast cancer (BC) represents a huge public health challenge being the leading cause of cancer morbidity and mortality among women worldwide (Ferlay et al., 2024). It is a significant contributor to the global burden of disease and a primary threat to women's health (Arnold et al., 2022; Bray et al., 2004; Huang et al., 2021; Xu et al., 2023). The incidence of BC is strongly correlated with human development with the highest rates observed in the most developed regions in the world (Wilkinson et al., 2022). The death rates, however, are higher in regions undergoing economic transition (Łukasiewicz et al., 2021). These global inequities have been addressed by the World Health Organization's (WHO) Global Breast Cancer Initiative, the goal of which is to save 2.5 million lives over a 20-year period (WHO, 2024). The key strategies to achieve these objectives are health promotion and early detection, timely diagnosis and comprehensive BC management (WHO, 2024). Evidence suggests that in countries where comprehensive cancer plans include these strategies there is potential to change the trajectory of BC mortality trends (Trapani et al., 2022).

BC etiology is complex and includes several non-modifiable risk factors (e.g., age, genetic, and hormonal factors), but also several modifiable factors such as obesity, alcohol consumption, and the use of hormonal replacement therapy (Łukasiewicz et al., 2021). For early detection of BC, organized population-based mammography screening has been recommended by the European Commission (The Council of the European Union, 2003; European Commission, 2022) and the WHO (WHO, 2014). Implementing screening, however, is a complex endeavor requiring substantial investments and screening programs entail an increased risk of overdiagnosis and subsequent overtreatment (Jørgensen et al., 2009; Trapani et al., 2022). Early diagnosis is also important outside of the screening program for symptomatic cases and this concept includes awareness, timely access to clinical diagnosis and treatment (WHO, 2017). Comprehensive BC management including resource-appropriate, person-centered and multidisciplinary cancer care is crucial for achieving optimal survival (Harbeck et al., 2019; Wilkinson et al., 2022).

The Estonian National Cancer Control Plan for 2021–2030 has set three major goals: fewer people develop cancer; people live longer and healthier lives after cancer diagnosis and people living with cancer have a better quality of life (Ministry of Social Affairs & National Institute for Health Development, 2021). For successful implementation, cancer control initiatives need to be informed by epidemiological research. Assessing overall progress against cancer requires concurrent analysis of all three trends – incidence, mortality, and survival as none of the indicators are interpretable alone in isolation from the others (Dickman et al., 2006).

Historically, BC mortality in Estonia has exceeded that of the neighboring Finland, although BC incidence has been nearly two times lower (Ferlay et al., 2024). In early EUROCARE studies, there was a 20% survival gap between

Estonia and Western and Northern Europe that have the highest survival rates (Berrino et al., 1995, 1999; Coleman et al., 2003). Along with the political and economic transition, major changes occurred in health-care system during the 1990s, followed by the adoption of international guidelines and modern therapeutic modalities becoming increasingly available. Increasing availability of mammography was accompanied by first early detection efforts in late 1990s, which led to the initiation of organized population-based screening program in 2004. However, the targeted age range has not been in accordance with international recommendations due to financial constraints and participation has remained low.

The aim of this thesis was to provide a comprehensive overview of long-term trends in BC incidence, mortality, and survival with a focus on understanding the impact of societal changes and cancer control activities, including organized mammography screening, on the burden of BC in Estonia. This thesis takes advantage of the long-term high-quality data collected by the Estonian Cancer Registry (ECR) and applies a variety of methodological approaches to achieve its goals. The study results have important implications for cancer control policy in Estonia and other regions with similar recent history.

4. REVIEW OF THE LITERATURE

4.1. Breast cancer epidemiology

BC is the leading cancer in women, with 2.3 million new cases diagnosed worldwide in 2022 according to GLOBOCAN estimates. It accounts for a quarter of all cancers diagnosed in women and 12% of cancers in both sexes combined. BC is also the leading cause of cancer death among women, with over 666,000 deaths globally in 2022. (Ferlay et al., 2024). BC is the most frequently diagnosed cancer in 159 countries and the leading cause of cancer-related death in 110 countries (Sung et al., 2021). An estimated 8.1 million women were alive in 2022 who had been diagnosed with BC within five years (Ferlay et al., 2024). BC has a significant public health impact with a loss of 14.8 million disability adjusted life years (Huang et al., 2021). By 2040, the burden from BC is predicted to increase to over 3 million new cases and one million deaths every year because of population growth and ageing alone (Arnold et al., 2022).

4.1.1. Incidence

BC incidence rates, which indicate how often individuals within a population are diagnosed with cancer, are affected by changes in risk factors, along with advancements in diagnostics and early detection methods, including screening (Kalager et al., 2021).

On the global scale, the number of new cases of BC rose approximately 2.6 times from 1990 to 2020 (from 877,000 to 2.26 million cases) (Ferlay et al., 2021; Xu et al., 2023). However, age-standardized (by world standard population) rates (ASR) are changing at a much slower pace, increasing just 14% during the 30-year period from 1990 to 2019 (40.1 vs 45.9 per 100,000) (Xu et al., 2023; Zhang et al., 2023). A systematic analysis of worldwide cancer burden revealed that of the global rise of 43% in BC incidence between 2005 and 2015, population growth accounted for 12.6%, population aging for 15.5%, and changes in age-specific incidence rates for 14.9% (Fitzmaurice et al., 2017).

BC incidence varies by the country level of economic development. Typically, BC incidence has been relatively high in economically developed countries, which exhibit higher income levels and consequently a higher Human Development Index (HDI) (Wilkinson et al., 2022; Lei et al., 2021). Evidence has shown a linear relationship between BC rates and HDI, showing that as country HDI levels increase, there is a corresponding rise in BC incidence (Lei et al., 2021).

In 2020 the age-standardized incidence rate (ASIR) of BC in countries with high or very high HDI was approximately two times higher than in countries with low to medium HDI (55.9 vs 29.7 per 100,000) and this ratio persisted in 2022 (Arnold et al., 2022; Ferlay et al., 2024; Sung et al., 2021). A comparable effect can also be observed with social development index, a comprehensive metric that combines fertility rate, income, and education (Xu et al., 2023). This clearly indicates that the level of economic development determines the resources available

for anti-cancer initiatives, while also influencing the general trends of disease occurrences. A country's gross domestic product represents the economic impact on the health of its inhabitants that may exert a dual influence on incidence and mortality trends (Peng et al., 2022). Rapid economic growth is usually accompanied by a rise in BC incidence attributed to factors such as obesity, declining fertility rates, reduced breastfeeding, and increased workloads (Arnold et al., 2022; Lei et al., 2021; Peng et al., 2022). At the same time, countries may channel acquired wealth into development of healthcare, cancer prevention and public awareness, prompting early diagnosis and effective treatment of BC (Arnold et al., 2022; Peng et al., 2022). Apart from age-related and other demographic changes within countries, the influx of migrants from regions with lower BC incidence to high-risk countries can impact the burden of BC in the host country (Arnold et al., 2010; DeSantis et al., 2015; Nilsson et al., 1997). This leads to the realization that significant geographic and demographic diversity exists in the levels of BC burden across countries and regions, owing to differing socio-economic, and environmental conditions (Arnold et al., 2022). If BC incidence trends continue with the same pace, the estimated number of new cases could be about 3 million by the year 2040 (Arnold et al., 2022). This forecast primarily relies on the aging and growth of population in transitioning countries, which contribute a proportionally larger share to the rise in BC incidence (Arnold et al., 2022). However, the incidence of BC in Nordic countries, representing regions with very high HDI, is projected to increase by approximately 85% (Larønningen et al., 2023) as a result of reproductive, hormonal and lifestyle risk factors and detection of early-stage tumors by widespread use of organized and opportunistic mammography screening (Arnold et al., 2022; Srivastava et al., 2019; Sung et al., 2021). Likewise, in previous years, rise in prevalence of these factors coupled with increased awareness and improvements in early detection was also behind the elevation in BC rates in Western countries during the 1980s and 1990s (Sung et al., 2021; Torre et al., 2017). After a period of stabilization in the early 2000s, BC incidence began to increase again, particularly for estrogen receptor-positive cancers as opposed to estrogen receptor-negative cancers (Sung et al., 2021). In addition to its association with the prevalence of obesity, estrogen receptor-positive cancers are more readily detectable through mammography screening than estrogen receptor-negative cancers (Han et al., 2023; Sung et al., 2021). As population-based screening aims at detecting tumors at an early stage, the introduction of screening can be assumed to bring along increasing incidence rates of localized tumors and a shift in stage distribution, particularly in age groups targeted by screening. There have been studies reporting an accompanying decrease in the incidence of later stage BC (de Glas et al., 2014; Katalinic et al., 2019; Larsen et al., 2018), but also studies reporting no such decrease (Autier et al., 2011; Bleyer and Welch, 2012; Jacklyn et al., 2017; Lousdal et al., 2016).

4.1.2. Mortality

Mortality quantifies the number of cancer-related deaths across the entire population and is dependent on factors that influence incidence as well as those affecting survival (Kalager et al., 2021).

In 1990, there were about 337,000 deaths from BC globally (Sharma et al., 2019), a figure that rose to approximately 375,000 by 2000 (Arnold et al., 2022; Bray et al., 2004). In 2016, BC-related deaths amounted to 535,341 (Sharma et al., 2019), and by 2020, they surged to a staggering 685,000 (Arnold et al., 2022; Lei et al., 2021), doubling over a span of 30 years. On average, this translates into approximately 15,500 deaths annually. At the same time, the age-standardized (world) mortality rate (ASMR) of BC per 100,000 women decreased from 17.2 in 1990 to 14.6 in 2016 (Sharma et al., 2019), and further dropped to 12.7 in 2022 (Ferlay et al., 2024). Once more, as demonstrated in the case of ASIR, the difference in the direction of trends in absolute numbers and age-standardized rates indicates a significant influence of aging and population growth on BC mortality. If current BC mortality rates persist, projections suggest an increase to approximately one million deaths by 2040 (Arnold et al., 2022) or to 1.5 million deaths by the year 2050 (Xu et al., 2023).

Historically, BC mortality has been on the rise in most countries since the 1950s. High-income countries have succeeded in turning BC mortality downwards since the 1980s, and today, the trend continues with a 2% decrease per year (Trapani et al., 2022). The decrease has been most evident among women under 50 years of age (Bray et al., 2004). There is a clear pattern that mortality decreases in countries with high HDI or high income (Lei et al., 2021).

Currently, the highest mortality rates are recorded in parts of Oceania (ASMR 27.5 per 100,000), Africa (ASMR 22.3 per 100,000), and the Caribbean region (ASMR 18.9 per 100,000) (Arnold et al., 2022) with fastest-growing mortality trends observed in the Philippines and Thailand (AAPC over 4%) (Huang et al., 2021). Other countries experiencing slower but still significant increases include Colombia and Brazil (AAPC < 1%) (Huang et al., 2021). The steepest declining trends were shown in Denmark, Norway, Estonia, Belgium, Canada and the UK (AAPC lower than -2%) (Huang et al., 2021) i.e. countries belonging to both high HDI and high-income group.

In Europe, age-standardized BC mortality rates have decreased in many countries over the past three decades (Carioli et al., 2017; Malvezzi et al., 2019; Woityla et al., 2021). Despite the favorable trend in mortality, BC remains the leading cause of cancer death in women in the EU (Joint Research Centre, 2020). Furthermore, the number of BC deaths is not decreasing, primarily due to the aging of the population (Malvezzi et al., 2019). Recently, the situation where mortality rates were higher in Western and Northern Europe compared to Central and Eastern Europe has reversed (Santucci et al., 2020; Woityla et al., 2021). According to 2022 estimates, BC mortality in Europe is the highest in Cyprus, Slovakia and Poland and the lowest in Spain, Sweden and Finland (Joint Research Centre, 2020).

4.1.3. Survival

Population-based cancer survival is one of the most important measures of the overall effectiveness of national health systems in managing the cancer burden (Coleman, 2014). Survival represents the rate at which patients with a cancer diagnosis die of that cancer. Survival is influenced by the characteristics of the patients and their tumors as well as by the effectiveness of cancer care (Kalager et al., 2021). Relative survival is used to estimate net survival or the probability of dying of cancer before a given time in the hypothetical scenario where cancer is the only possible cause of death (Brenner et al., 2004; Kalager et al., 2021; Mariotto et al., 2014). Population lifetables are used to account for survival in the underlying population. Relative survival may be confounded by the differences in the age distribution of cancer patients, which requires age-standardization if cancer survival rates are to be compared (Brenner et al., 2004; Corazziari et al., 2004).

The first worldwide comparison of cancer survival by the CONCORD study for patients diagnosed in the beginning of 1990s revealed wide disparities in relative survival of BC patients between high-income and low-income countries (Coleman et al., 2008). Five-year relative survival from BC ranged from 84% in the US and 85% in Japan and Sweden to 58% in Brazil and Slovakia and 61% in Estonia (Coleman et al., 2008). Early EUROCARE studies including patients diagnosed in the late 1980s showed a difference of over 20% between European countries showing the highest and lowest survival (80% in Sweden, France and Switzerland versus below 60% in Slovakia, Poland and Estonia) (Berrino et al., 1999).

A high-resolution study on patients diagnosed in 1990–1992 suggested that late stage at diagnosis was the main explanation for survival differences observed across Europe, although considerable differences were also observed in stage-specific survival and in diagnostic and treatment practices (Sant et al., 2003). Among patients diagnosed in late 1990s, overall five-year relative survival from BC was 84% in the US and 81% in Europe, but the differences were due to low survival in Eastern European countries (69%) (Allemani et al., 2013). Again, patients in Eastern European countries were characterized by later stage at diagnosis, but also by considerably lower use of recommended diagnostic practices such as the examination of lymph nodes as well as recommended treatment such as breast-conserving surgery combined with radiation therapy in early BC (Allemani et al., 2010; Allemani et al., 2013).

Among women diagnosed with BC in 2005–2009 and included in the CONCORD-2 study, five-year relative survival exceeded 85% in several high-income countries of North America, Oceania and Western and Northern Europe, but remained below 75% in several Eastern European and Baltic countries and below 70% in some countries in Asia and Africa (Allemani et al., 2014). By 2010–2014, five-year survival had increased in most countries in Central and South America, East and West Asia, and in all of Europe and reached 85% or higher in 35 countries across the world with Eastern Europe and Estonia and Lithuania still

lagging behind with estimates below 80% (Allemani et al., 2018). The latest estimates from the Nordic countries are 90% or higher (Larønningen et al., 2023).

A study using EUROCARE data for 2000–2007 indicated that late stage at diagnosis only marginally explained the poorer prognosis of Eastern European BC patients compared to their counterparts in other European regions and suggested less effective care as the main explanation (Minicozzi et al., 2018). A high-resolution study showed large increase in the use of recommended treatment in early BC in Estonia and Poland, but also higher frequency of comorbidities affecting patients in these countries compared to countries of Western Europe (Minicozzi et al., 2019).

4.2. Screening

Cancer screening is based on two principles: early detection and prevention (Bretthauer & Kalager, 2013). BC screening by mammography is aimed at early detection of already invasive cancer in the entire population, assuming that a proportion of cancers are curable with screening, but without screening would progress to an incurable stage (Adami et al., 2019). The objective of screening is to detect cancer in the preclinical phase before the emergence of symptoms when treatment is most effective, thereby preventing fatal outcomes (Hakama & Auvinen, 2008; Bretthauer & Kalager, 2013). Thus, the primary aim of early detection screening is to reduce cancer mortality (Hakama & Auvinen, 2008; International Agency for Research on Cancer Working Group on the Evaluation of Cancer-Preventive Strategies, 2016; Marmot et al., 2013). It cannot lower BC incidence and screening with mammography may in fact increase incidence, firstly because of early detection and secondly because of overdiagnosis (Bretthauer & Kalager, 2013). Overdiagnosis is defined as the detection of a disease or condition that would not cause symptoms or death during an individuals' lifetime (Adami et al., 2019) and is the most significant and difficult to avoid adverse effect associated with mammography (Jørgensen et al., 2009). The effect of mammography screening on BC incidence is first manifested by immediate increase in cancer incidence due to early detection (Boer et al., 1994; Ripping et al., 2017). Without overdiagnosis the initial increase would be compensated by a comparable drop in the incidence among older age groups, because these cancers were already diagnosed in previous age groups (Figure 1) (Boer et al., 1994; Jørgensen et al., 2009; Ripping et al., 2017). Overdiagnosed cancers on the other hand are not balanced out in age groups where screening is no longer offered. As a result, the excess incidence after screening is the combination of overdiagnosed and "real" cancer cases with partial compensatory drop after the conclusion of screening (Ripping et al., 2017).

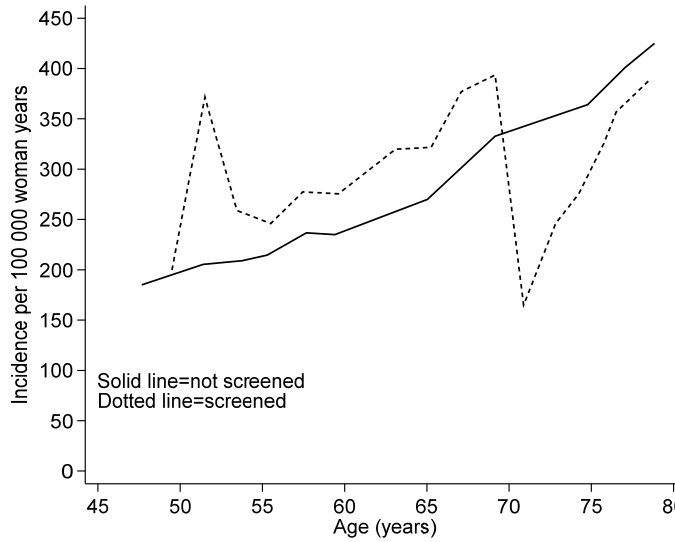

Figure 1. Expected breast cancer incidence associated with screening in age groups 51–69 by two-year age categories (adapted from Boer et al., 1994).

There is significant heterogeneity between studies estimating overdiagnosis, depending on the methodology used (Chaltiel et al., 2021; Gøtzche et al., 2013; Marmot et al., 2013; Richman et al., 2023).

The effect of screening on survival estimates is complex, as the survival increase includes true prolongation of survival time due to improved prognosis, but also the effects of lead time and overdiagnosis. Lead time is defined as the time interval between the diagnosis of screen-detected cancer and the potential clinical detection of the tumor (Figure 2) (Bretthauer & Kalager, 2013; Dickman & Adami, 2006). If early detection does not improve the chances of cure and the patient's time of death remains the same whether the cancer is detected clinically or through screening, then lead-time bias will cause the patient's survival time to appear longer with no actual benefit for the screen-detected patient. Survival estimates in cancer screening settings are additionally affected by selection bias, self-selection bias and overdiagnosis and therefore, survival cannot be considered as a valid endpoint to evaluate the effect of cancer screening (Bretthauer & Kalager, 2013). Self-selection or the healthy screened effect refers to the phenomenon where women participating in BC screening differ in background factors from those who do not attend (Marmot et al., 2013).

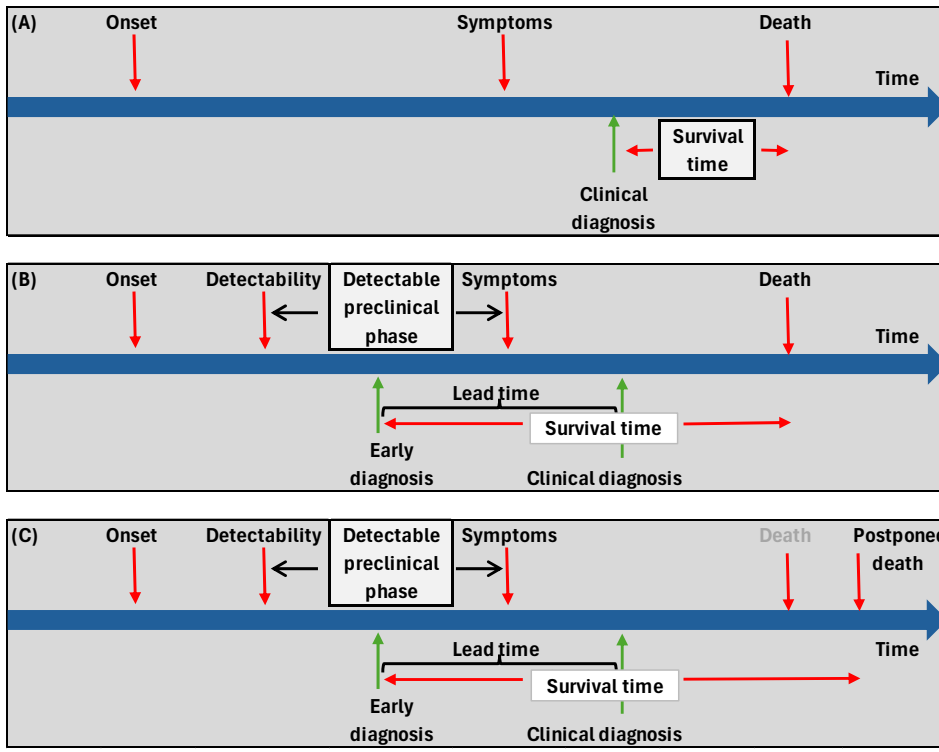

Figure 2. Calculation of survival time in three scenarios. (A) Survival time of a symptomatic, clinically diagnosed BC patient; (B) Survival time of an asymptomatic screen-detected BC patient where early detection has not postponed the time of death; (C) Survival time of an asymptomatic screen-detected BC patient where early detection has postponed the time of death (adapted from Dickman & Adami, 2006).

4.2.1. Impact of screening on breast cancer mortality

Since the 1930s, the design of randomized controlled trials (RCT) has developed into the gold standard for demonstrating the effectiveness of interventions or treatments in comparison with control groups (Miller et al., 2020; Zabor et al., 2020). Randomization aims to reduce the impact of confounding variables and equalizes the characteristics in compared groups, enabling conclusions to be drawn about the cause of outcome differences following exposure or the intervention (Hariton et al., 2018; Miller et al., 2020; Zabor et al., 2020). Because of these properties, RCTs are considered the most reliable method for accurately estimating the effectiveness of screening (Gøtzche et al., 2013).

First BC screening trials were conducted in the 1960s in the US, followed by trials in Scotland, Sweden, Canada and elsewhere (Gøtzche et al., 2013; Koning et al., 2003; Sarkeala, 2008). First trials showed consistent reduction of mortality in the range of 20–35% among women aged 50–69 with number needed to screen values for preventing one death varying from 1000 to 10,000 at 10 years (Hakama & Auvinen, 2008). With longer follow-up periods, the reduction in mortality

decreased to between 13% and 17% (Gøtzche et al., 2013; Sarkeala, 2008). As a result of significant reductions in mortality observed in initial RCTs from the 1970s and 1980s, many Western countries began implementing population-based mammography screening programs during the 1980s and 1990s (Broeders et al., 2012; Dibden et al., 2020; Heggland et al., 2022). Majority of screening trials were conducted over 30 years ago and thus do not account for more recent changes in incidence, mortality, treatment, and screening methods; the previous findings of these studies may not accurately reflect the true effectiveness of present-day screening programs (Dibden et al., 2020). Besides, the only RCTs that demonstrated a negative impact of mammography screening programs, the Canadian National Breast Screening Study, are currently undergoing revision, and their inclusion in systematic reviews is being questioned (Duffy et al., 2022; Harvey, 2022; Yaffe et al., 2021). Currently, the most recent RCTs explore different BC screening strategies, for example comparing digital breast tomosynthesis mammography screening with digital mammography alone. Those studies are not completed yet and results are therefore inconclusive (Henderson et al., 2024).

Once the screening program has started, randomizing individuals to a non-intervention group is deemed unethical, and therefore, the effectiveness of screening can only be evaluated through observational studies (Dibden et al., 2020). Observational studies may be less controversial but are more susceptible to bias, as groups compared may not be identical and some confounders cannot be accounted for. After the introduction of mammography screening programs in several countries, some observational studies failed to demonstrate the mortality reducing effect (Autier et al., 2011; Haukka et al., 2011; Kalager et al., 2014). However, studies utilizing refined BC mortality that excluded prescreened diagnoses, displayed outcomes comparable to those of randomized trials (Broeders et al., 2012; Heggland et al., 2022). Cancers diagnosed before screening was initiated cannot experience the same advantages in treatment as screened cases. Hence the beneficial effect from early detection can be assessed from the mortality of cases diagnosed after the first invitation to screening (Marmot et al., 2013; Njor et al., 2012).

The concept of incidence-based (IB) mortality entails the assessment of mortality based on BC deaths in persons previously diagnosed with BC and reported to the cancer registry (Chu et al., 1994). Individual linkage of cancer deaths and cases allows the analysis of mortality by variables related to disease onset, like the time of diagnosis or age and stage at diagnosis or other clinical variables (National Cancer Institute, 2024). The effects shown by IB mortality studies are summarized in several systematic reviews and meta-analyses. A review of 20 studies found that the most methodologically robust IB mortality designs demonstrated BC mortality reduction around 26% (Njor et al., 2012). Broeders et al. reported a similar reduction of 25% (Broeders et al., 2012). A most recent meta-analysis of 27 studies showed significant reductions in BC mortality: 22% for those invited to screening and 33% for those who attended screening (Dibden et al., 2020).

A case-control study can be an effective tool to estimate the benefits of cancer screening as constant changes in baseline risk factors, improvement in methods of detection and cancer treatment require frequent reassessments of screening effectiveness (Paap et al., 2011; Verbeek et al., 2010). The main problem with this type of studies is high probability for selection bias and confounding bias of the odds ratio (Verbeek et al., 2010). Additional methodological challenges are presented by selection of cases and controls, specification of screening exposure and self-selection bias (Cronin et al., 1998). In general, case-control studies have demonstrated a greater reduction in BC mortality following screening compared to previous trials and cohort studies, thereby confirming their findings (Marmot et al., 2013; Paap et al., 2011). However, the range of obtained mortality reduction varied significantly across the studies, extending from 25% to 76% after correction for self-selection (Heinävaara et al., 2016; Massat et al., 2015; Paap et al., 2011).

A recent systematic review of RCTs and observational studies showed consistent mortality reduction in all European regions where mammography screening was implemented and monitored, while the difference in estimates was suggested to be the result of evaluation design rather than screening effectiveness (Zielonke et al., 2020). The authors also pointed out the lack of relevant studies from Eastern Europe (Zielonke et al., 2020).

Screening recommendations

In the US, the first BC screening recommendations were issued in 1976 by American Cancer Society (Mack & Lapane, 2019). Screening programs were initiated in many European countries during 1980s and 1990s with Eastern European and Baltic countries starting during 2000s.

In its recommendations, the WHO suggests that organized, population-based mammography screening be accessible every two years for women aged 50–69, provided that adequate resources are available to support such efforts (WHO, 2014).

Current screening recommendations in Europe for women who are not at high risk for BC are mammograms every two years for ages 50–69 and every three years for women aged 45–49 and 70–74 (European Commission, 2024). The US Preventive Task Force recommends biennial mammography for women aged 40–74 (Nicholson et al., 2024).

4.2.2. Screening in Estonia

By the 1990s, Estonia had developed adequate technical infrastructure and trained personnel to start mammography screening. Since resources were not sufficient to fully launch the screening program all at once, it was decided to begin with pilot projects in larger centers and then gradually expand nationwide, increasing the scale gradually (Ulp et al., 2010). The initial pilot projects of BC screening in Estonia were started in two largest cities of Tallinn and Tartu in 1996 and 1998,

respectively (Ulp et al., 2010; Võrno et al., 2013). Estonian Cancer Foundation in cooperation with Tartu University Hospital and Estonian Health Insurance Fund started the preparations for the introduction of population-based screening program in 2002 (Võrno et al., 2013). The first invitations were distributed through media, targeting women aged 45–59 with valid health insurance (Ulp et al., 2010). In 2003, first invitations were sent to women from target birth cohorts, but self-referred women were also screened and as a result, almost half of screened women were self-referred (Aasma et al., 2007).

Starting from 2004, the screening program has been solely invitation based (Aasmaa, 2007). Initially, the main age group invited was 50–59 years, which was extended up to age 63 in 2007 (Figure 3). Women up to the age of 69 were included only in 2018. Currently, the upper age limit is being gradually extended to 74 years. Up to 2021, only women with valid health insurance could attend screening free of charge. The proportion of adults in Estonia covered by health insurance is around 95%.

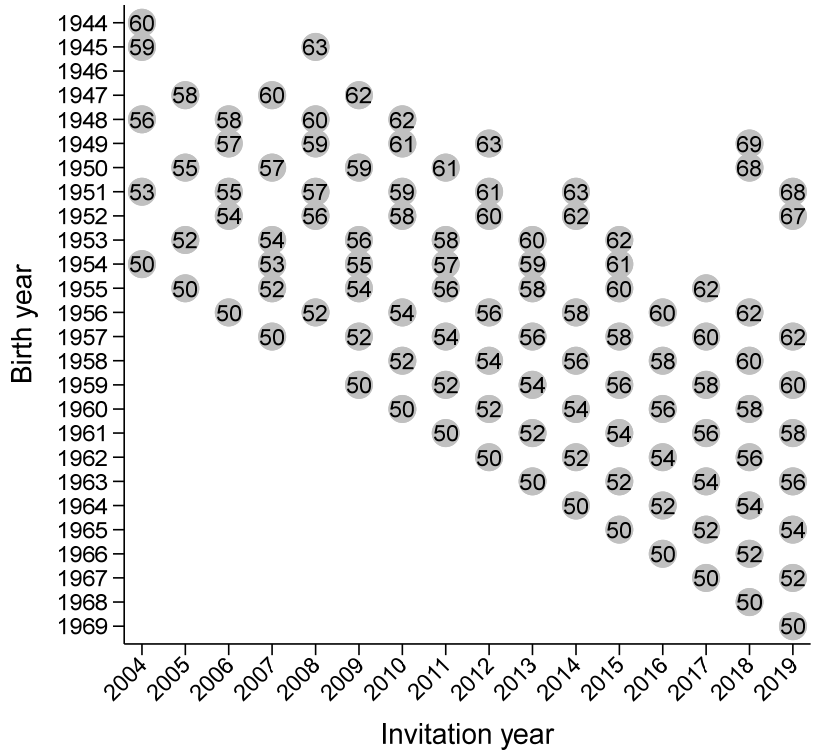

Figure 3. Birth cohorts invited to mammography screening, Estonia 2004–2019. The dots indicate age at the time of invitation.

Participation of women in BC screening has been below the recommended 70%. In 2004, approximately 47% of invited women participated in screening (Aasmaa et al., 2007). By 2009, participation had increased to 52% (Ulp et al., 2010), and by 2023 to 64.5% (National Institute for Health Development, 2024). As the data from the Estonian Cancer Screening Registry are available from 2015 (National Institute for Health Development, 2024), information on BC screening participation rate in interim years is sporadic. A study analyzing organized screening participation trajectories in 17 EU countries estimated that participation rate increased at a rate of 1.7% per year in Estonia from 41% in 2004 to 58% in 2014 (Gianino et al., 2018). Self-reported data from a survey of Estonian adult population indicated that the percentage of women aged 55–64 who had not had a mammography during the past 2 years decreased from 89% in 2000 to 65% in 2004 and to 30% in 2020 (Reile & Veideman, 2021; Tekkel & Veideman, 2013, 2016).

4.3. Summary of the literature review

BC incidence and mortality have showed varying patterns across countries with different levels of social and economic development. Globally, HDI shows a strong positive correlation with age-standardized incidence, but a negative correlation with BC mortality. In most European countries, BC incidence is increasing, while mortality rates are declining. The increasing incidence rates are related to changes in population age structure, but also to increasing exposure to risk factors and wide use of screening mammography, while declining mortality may be attributed to early detection and improved BC management.

BC survival is consistently increasing and has reached 90% in several high-income countries but remains considerably lower in some regions of the world. Increased survival can be attributed to the combination of early diagnosis and improved treatment methods.

Mammography screening is recommended to facilitate early detection and there is ample evidence of BC mortality reduction associated with population-based screening. However, early detection screening is also associated with accompanying harms and therefore, the benefits of screening have been questioned as the effectiveness of treating symptomatic BC has increased considerably.

Previous studies have identified shortcomings in the early detection and mortality outcomes of BC in Estonia. Despite low incidence, BC mortality is relatively high and considerable survival deficit has been observed in international studies, likely related to late stage at diagnosis and shortcomings in the use of recommended diagnostic and treatment practices. Screening coverage has been low both in terms of narrow age range and poor attendance. Evidence on the effect of screening on BC mortality from the Eastern part of Europe is lacking.

Thus, there has been a need for a comprehensive overview of long-term BC incidence, mortality and survival trends in Estonia to better understand the impact of societal and health care changes on the burden of BC in Estonia and to inform cancer policy.

5. AIMS OF THE STUDY

The general purpose of this study was to evaluate long-term trends in BC incidence, mortality and survival in Estonia in the context of societal and health care system changes and the implementation of organized mammography screening.

The specific aims of the study were:

1. To examine long-term trends of BC incidence and mortality in Estonia and compare the pattern of these trends with selected European countries.
2. To evaluate incidence-based BC mortality in Estonia before and after the introduction of mammography screening program.
3. To examine BC relative survival trends in Estonia with special emphasis on age and stage.

6. MATERIALS AND METHODS

6.1. Data sources

Incident cases

Information on incident cases of BC were obtained from the ECR, a population-based cancer registry with nationwide coverage that has been collecting data since 1968, providing a thorough overview of cancer incidence over the decades and excellent opportunities for cancer research (Rahu, 1997). Reporting to the ECR is mandatory for all physicians and pathologists who diagnose or treat reportable tumors: all malignant tumors, *in situ* tumors, benign tumors and tumors of uncertain or unknown behavior of the brain and central nervous system as well as of the endocrine organs, that are located in the area of the brain, and other tumors of lymphoid, hematopoietic and related tissue (Zimmermann et al., 2024). Multiple sources are used for case ascertainment. Notifications are sent by health-care institutions where cancer is diagnosed or treated, and by pathologists or forensic experts when the cancer diagnosis is confirmed by a tissue sample (National Institute for Health Development, 2024). Additionally, cases are ascertained through linkages with the patient files of three cancer centers and trace-back of cases first identified from death certificates. The ECR uses the third edition of the International Classification of Diseases for Oncology (ICD-O-3) for coding and adheres to international definitions and rules issued by the International Association of Cancer Registries and the European Network of Cancer Registries. Follow-up for vital status is conducted via linkages with the Causes of Death Registry and Population Registry. Data quality of the ECR is evaluated routinely using data quality indicators published in annual reports (Zimmermann et al, 2024) and by special studies (Innos et al., 2015; Orumaa et al., 2015; Paapsi et al., 2017).

The Estonian Cancer Screening Registry was used to obtain information on the detection mode of BC for a subset of cases. Cancer Screening Registry has been in operation since 2015 and collects information on all organized cancer screening programs in Estonia (National Institute for Health Development, 2024).

Cancer deaths

Information on cancer deaths was obtained from the Estonian Causes of Death Registry (CoDR), which includes data on death certificates issued in Estonia since 1985. The CoDR collects data from death notifications, causes of death notifications, and perinatal death cause notifications. The underlying cause of death is determined according to WHO rules (National Institute for Health Development, 2024). The obligation to submit data lies with all physicians and forensic experts identifying death cases.

Population data

Follow-up for vital status of cancer patients was conducted by the ECR through the Estonian Population Register, a database that contains the primary personal information of Estonian citizens and residents. It is managed and developed by the Ministry of the Interior (as the data controller) and the IT and Development Centre of the Ministry of the Interior (as the data processor) (Ministry of the Interior, 2024).

Population denominator data, average annual population numbers by five-year age groups were obtained from Statistics Estonia database (Statistics Estonia, 2024).

6.2. Data definitions

BC cases

Data on all cases of invasive BC (ICD-O-3 topography codes C500–C509) diagnosed in women in Estonia during 1968–2021 (regardless of cancer sequence) were obtained from the ECR. The ECR also provided data on *in situ* BC (International Classification of Diseases 10th revision (ICD-10) code D05) diagnosed in women in Estonia during 1994–2021. Percentage of microscopically verified cases, percentage of death certificate only cases and percentage of cases discovered at autopsy were used as data quality indicators. Age at diagnosis was categorized into following age-groups: 30–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years.

Stage information was available for cases diagnosed from 1995. Stage was coded according to the Union for International Cancer Control tumor, node, metastasis (TNM) classification, 7th edition. Stage information is reported to the ECR according to one or more of the three following classifications: 1) component T, N and M codes (pathological or clinical); 2) grouped TNM stage (pathological or clinical); 3) extent of disease (EoD), categorized as local, spread to neighboring tissues, regional lymph nodes, distant metastasis, unknown. Starting from 2012, TNM variables are routinely recorded at the ECR, and quality control procedures are applied. In case of conflicting information, component TNM codes take priority, and grouped stage and/or EoD are corrected accordingly. For 1995–2011, TNM stage was coded as part of this study from information entered in text format and similar rules were applied. If EoD was reported as distant metastasis and TNM variables were missing, stage IV was assumed. If grouped TNM stage was reported, but all or some component TNM values were missing, and the reported TNM values were not in conflict with the stage grouping, the grouped TNM stage was assumed to be correct. Category "unknown" includes cases with no or incomplete information on stage. In paper IV, summary stage was compiled as localized (T1–3 N0 M0); local/regional spread (T1–3 N1–3 M0 or T4 Nany M0), distant (Tany Nany M1) or unknown.

For Paper III, a subset of BC cases aged 50–64 diagnosed in 2015–2018 were individually linked with Estonian Cancer Screening Registry to identify the mode

of detection, which was categorized as detected at screening or diagnosed by other modes of detection.

Survival analysis included BC cases diagnosed in adults (age ≥15 years), excluding death certificate only and autopsy cases, diagnosed from 1995–2021. Survival was examined by five-year time periods, with 2017–2021 as the most recent presented in this thesis.

BC deaths

For death-certificate-based BC mortality analysis, data on all deaths among women in Estonia with BC registered as the underlying cause of death (ICD-10 code C50) were obtained from the CoDR for 1985–2022 (Papers I and III).

IB deaths were defined as BC deaths (the underlying cause of death ICD-10 code C50) occurring in 1974–2019 in women who had a first-time invasive BC diagnosis during the same period. The ECR provided data on incident cases of invasive BC diagnosed in women in Estonia in 1974–2019 individually linked to causes of death (Paper II).

Age at death was categorized into age-groups 30–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years. IB mortality trends were shown for birth cohorts born in 1909–1913, 1914–1918, 1919–1923, 1924–1928, 1929–1933, 1934–1938, 1939–1943, 1944–1948, 1949–1953, 1958–1963, 1964–1968, 1969–1973 and 1974–1978 (Paper II).

6.3. Statistical methods

6.3.1. Descriptive statistics

Descriptive statistics are represented by counts and percentages. For categorical variables the significance of the difference between groups was tested with the chi-squared test. The equality of proportions was tested with two-sample tests of proportions. A p-value of less than 0.05 was regarded as statistically significant, indicating that there is less than a 5% probability that the observed results occurred by chance. This threshold was used to determine whether the results provided sufficient evidence to reject the null hypothesis, suggesting that the findings were unlikely to be due to random variation alone.

6.3.2. Incidence

Crude incidence rates were calculated for BC age-specific and age-stage-specific categories using annual incidence cases as numerators and average annual population of Estonia for corresponding age-groups as denominators. For all ages combined the annual incidence rates were age-standardized using world standard population (Waterhouse et al., 1976). All rates were expressed per 100,000 person-years. Age-specific, stage-specific and age-standardized rates were modeled with joinpoint regression to determine instances of significant change in

time-trends with corresponding annual percentage change (APC). The uncertainty of APC values was assessed with 95% confidence intervals (CI). Joinpoint regression was performed with the Joinpoint Regression Program (version 4.9.1.0.) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/). Permutation test was used to find the number of significant joinpoints (Kim et al., 2000).

6.3.3. Mortality

Mortality rates were calculated using annual BC deaths as numerators and average annual population of Estonia for corresponding five-year age-groups as denominators. For all ages, mortality rates were age-standardized to world standard population (Waterhouse et al., 1976). All rates were expressed per 100,000 person-years.

IB mortality trend, based on BC deaths occurring in 1974–2019 in women who had a first-time invasive BC diagnosis during the same period, was restricted to 1979–2019 to allow for a five-year burn-in period (Paper II). Similarly to incidence analysis, overall BC mortality and age-specific IB mortality trends were modeled with joinpoint regression using a permutation test to find statistically significant joinpoints in the trends and to calculate annual percentage change (APC) and corresponding 95% CI.

Additionally, trends in IB mortality were analyzed using age-period-cohort regression. This analysis utilized five-year age groups, five-year periods and corresponding synthetic birth cohorts, allowing for a detailed examination of how age, time period, and birth cohort influenced mortality rates.

Similarly organized data were used for comparison of IB mortality by five-year birth cohorts (born from 1909 to 1978). Mortality rates per 100,000 person-years were calculated using the number of IB deaths in five-year age groups and five-year periods, divided by population numbers in the same categories. Obtained rates were assigned to respective birth cohorts. IB mortality trends for birth cohorts were smoothed by applying the LOESS (locally estimated scatterplot smoothing) technique (Paper II).

IB mortality by age groups was also compared during periods of equal length, specifically 1993–2003 and 2004–2014 (before and after the introduction of screening, respectively). IB deaths for 10-year age-groups and periods were totaled and corresponding national population figures were used as exposure in stratified Poisson regression analysis to calculate relevant IB mortality rates and risk ratios with 95% CI. For the stratified Poisson regression analysis, IB deaths were restricted to those where both the diagnosis and death from BC occurred within the same period and age group. This restriction was applied to minimize potential bias due to lead time and overdiagnosis. Because only women aged 50–63 were invited to screening during 2004–2014 (Figure 3), women aged 64 were excluded due to irregular and infrequent invitation schemes.

For international comparison (Paper I), the age-standardized BC incidence and mortality rates were acquired from the currently inactive EUREG database

(http://eu-cancer.iarc.fr/ EUREG/Default.aspx) for selected European countries and regions that had equal time series of incidence and mortality data available. EUREG data was pooled into groups representing Western, Southern, Northern and Eastern Europe (Paper I, Supplementary Table I). Data for Russia were available from annual reports (Chissov et al., 2010).

For international comparison of BC burden, two different approaches were used for simultaneous analysis of BC incidence and mortality trends (Paper I). First, the annual age-standardized BC incidence and mortality rates for selected countries and regions were conjointly displayed on scatterplot as point coordinates. Around resulting datapoint clusters the 95% confidence ellipses were drawn, and Spearman rank correlation was calculated to examine the association between BC incidence and mortality, complementing visual analysis of the trends. Estonian data was divided into two periods (1985–1995 and 1996–2012) to demonstrate the changes in BC incidence and mortality. Second method for joint analysis of BC was calculation of mortality to incidence ratios (MIR) and corresponding proxy survival probability 1-MIR (Asadzadeh-Vostakolaei, 2011).

Trend smoothing, Poisson regression analysis, and graphs were performed with Stata 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). For the analysis and graphing of the acquired curves, the R package Epi modules apc.fit and apc.lines were used (Carstensen https://bendixcarstensen.com/APC/, https://cran.r-project.org/web/packages/Epi/Epi.pdf). Confidence ellipses and Spearman's rank correlation coefficients were calculated with Stata 12.1.

6.3.4. Survival

BC patients were followed up from the date of BC diagnosis until death, emigration or until the end of study period (for survival analysis in paper IV that included years 1995–2007 and 2002–2021 in current analysis). Follow-up was conducted by the ECR at the Estonian Population Registry using unique personal identification numbers. In case of death or emigration, respective dates were provided. Patients who were diagnosed and died on the same day were included with one day of survival time. We used the relative survival approach which captures both direct and indirect mortality due to cancer (Dickman & Coviello, 2015). Relative survival ratios (RSR) were obtained by dividing the observed survival of the cancer patients by the expected survival derived from the underlying general population. For calculation of expected survival, the Ederer II method and national life tables for the female population, stratified by age and calendar year were used (Ederer et al., 1961). Cohort method was applied for patients diagnosed in earlier periods who had full five-year follow-up. To obtain the most recent survival estimates, the period method (Brenner et al., 2004) was used. Period estimates are considered to be very similar to actual survival rates observed in the future for patients who were at risk and diagnosed during this specific period (Talbäck and Dickman, 2012). In paper IV, a modification of period analysis, called hybrid analysis was used, to account for delays in cancer

incidence registration (Brenner & Rachet, 2004). The International Cancer Survival Standard population was used for age-standardization of overall survival estimates (Corazziari et al., 2004). Survival analysis was performed using the module *strs* in Stata 12.1 (Paper IV) and Stata 17.0 (Dickman & Coviello, 2015)

6.4. Ethics approval

The studies described in papers I and IV were conducted with the support by Estonian Science Foundation (grant no ETF8881), Estonian Ministry of Education and Research (SF0940026s07) and Estonian Research Council (IUT5-1), approved by the Tallinn Medical Research Ethics Committee (Decision no 1656, April 16, 2009).

For papers II and III the support came from the grant no PRG722, the study protocol of which was approved by the Tallinn Medical Research Ethics Committee (Decision no 2636, February 14, 2019).

7. RESULTS

7.1. Incidence

Total number of BC incident cases registered during 1968 to 2021 was 27,571. During this period, the average annual number of new cases increased over three-fold from 258 in 1968–1974 to 807 in 2017–2021. The data quality indicators and age distribution are shown separately for 1968–1994 and 1995–2021 (Tables 1 and 2). The proportion of microscopically verified cases increased significantly over the study period from 79% to 97%. The proportion of death certificate only and autopsy cases varied from 0.1% to 1.2% and 0.1% to 0.4%, respectively.

The age distribution indicates that the majority of cases (around 85%) occurred in the age range 40–79 years. In the later period there appears to be a shift in age distribution with proportions increasing in ages 70 and older and decreasing in ages 30–59 years.

The distribution of stage at diagnosis (available since 1995) shows an increase in the percentage of stage I BC while the percentages of stages II, III and IV have decreased (Table 2). There has been an increase in the percentage of cases with unknown stage. During the first 10 years of the studied period (from 1995–1999 to 2005–2007), the proportion of cases diagnosed at localized stage increased the most in age-groups 50–59 and 60–69 and exceeded the percentage seen in the youngest age-group (Paper IV, Figure 2). The updated analysis based on TNM stage grouping showed that the proportion of stage I tumors has reached 40% in age-groups 50–59 and 60–69, while it has remained below 30% in age-groups <50 and 70–79 and below 20% in women age ≥80 years. The analysis of the stage distribution of cases in age-group 50–64 diagnosed in 2015–2018 showed that the proportion of stage I cases was 49% and 30% among cases detected at screening and diagnosed by other means of detection, respectively (Paper III). The respective proportions of stage IV cases were 3% and 10% (Paper III).

Stage distribution by age and period of diagnosis showed significant increase in stage I BC in age-groups 50–59, 60–69 and 70–79 during the study period (Table 3). In addition, the proportion of stage III BC declined significantly between 2002–2006 and 2017–2021 in age-group 60–69.

Table 1. Incident cases of breast cancer, Estonia 1968–1994

	Total		1968–1974		1975–1979		1980–1984		1985–1989		1990–1994		
	No	%	No	%	No	%	No	%	No	%	No	%	p-value[a]
Total	9523	100	1804	100.0	1574	100.0	1827	100.0	2037	100.0	2280	100.0	
Microscopically verified	8442	88.7	1430	79.3	1333	84.7	1675	91.7	1899	93.2	2105	92.3	<0.001
Death certificate only	23	0.2	7	0.4	5	0.3	2	0.1	1	0.1	8	0.4	0.110
Autopsy cases	32	0.3	5	0.3	7	0.4	6	0.3	8	0.4	6	0.3	0.861
Age at diagnosis (years)													
<30	65	0.7	9	0.5	9	0.6	19	1.0	17	0.8	11	0.5	0.940
30–39	687	7.2	151	8.4	118	7.5	125	6.8	151	7.4	142	6.2	0.008
40–49	2073	21.8	445	24.7	360	22.9	390	21.3	430	21.1	448	19.6	<0.001
50–59	2446	25.7	405	22.5	415	26.4	516	28.2	552	27.1	558	24.5	0.132
60–69	2131	22.4	395	21.9	337	21.4	377	20.6	436	21.4	586	25.7	0.005
70–79	1569	16.5	306	17.0	244	15.5	314	17.2	344	16.9	361	15.8	0.330
≥80	552	5.8	93	5.2	91	5.8	86	4.7	107	5.3	175	7.7	0.001

[a] chi-square test; for age and stage categories comparison of proportions in the first and last period

Table 2. Incident cases of breast cancer, Estonia 1995–2021

	Total		1995–2001		2002–2006		2007–2011		2012–2016		2017–2021		
	No	%	No	%	No	%	No	%	No	%	No	%	p-value[a]
Total	18048	100.0	3832	100.0	3042	100.0	3407	100.0	3734	100.0	4033	100.0	
Microscopically verified	17231	95.5	3581	93.4	2897	95.2	3253	95.5	3609	96.7	3891	96.5	<0.001
Death certificate only	173	1.0	23	0.6	35	1.2	39	1.1	36	1.0	40	1.0	0.105
Autopsy cases	41	0.2	11	0.3	7	0.2	2	0.1	11	0.3	10	0.2	0.223
Age at diagnosis (years)													
<30	87	0.5	17	0.4	14	0.5	17	0.5	21	0.6	18	0.4	0.986
30–39	736	4.1	196	5.1	101	3.3	138	4.1	149	4.0	152	3.8	0.004
40–49	2722	15.1	725	18.9	508	16.7	463	13.6	482	12.9	544	13.5	<0.001
50–59	4173	23.1	913	23.8	794	26.1	834	24.5	851	22.8	781	19.4	<0.001
60–69	4423	24.5	981	25.6	724	23.8	795	23.3	843	22.6	1080	26.8	0.235
70–79	3872	21.5	722	18.8	632	20.8	796	23.4	863	23.1	859	21.3	0.007
≥80	2035	11.3	278	7.3	269	8.8	364	10.7	525	14.1	599	14.9	<0.001
Stage at diagnosis[b]													
I	4547	25.5	592	15.6	692	23.1	898	26.7	1073	29.1	1292	32.4	<0.001
II	6863	38.5	1529	40.3	1264	42.1	1273	37.8	1346	36.5	1451	36.4	<0.001
III	3465	19.4	965	25.4	663	22.1	646	19.2	630	17.1	561	14.1	<0.001
IV	1595	8.9	454	12.0	267	8.9	259	7.7	298	8.1	317	8.0	<0.001
Unknown	1364	7.6	258	6.8	114	3.8	290	8.6	340	9.2	362	9.1	<0.001

[a] chi-square test; for age and stage categories comparison of proportions in the first and last period

[b] excluding death certificate only and autopsy cases

Table 3. Breast cancer stage distribution by age and period, Estonia 2002–2021

Age	Stage at diagnosis	Total		2002–2006	2007–2011	2012–2016	2017–2021	
		No	%	%	%	%	%	p-value[a]
<50	Total	2620	100.0	100.0	100.0	100.0	100.0	
	I	645	24.6	23.3	23.9	23.9	27.0	0.438
	II	1123	42.9	47.1	40.5	41.8	42.2	0.228
	III	505	19.3	21.9	22.1	17.5	16.2	0.252
	IV	133	5.1	4.6	5.5	4.6	5.6	0.853
	Unknown	214	8.2	3	8.1	12.2	9.1	0.381
50–59	Total	3270	100.0	100.0	100.0	100.0	100.0	
	I	1114	42.5	31.2	31.2	34.3	39.8	0.035
	II	1186	45.3	38.6	38.8	33.3	34.4	0.297
	III	547	20.9	19.5	16.6	16.7	14.1	0.252
	IV	215	8.2	6.9	6.3	7.6	5.4	0.762
	Unknown	208	7.9	3.9	7	8.1	6.3	0.643
60–69	Total	3473	100.0	100.0	100.0	100.0	100.0	
	I	1152	44.0	21.8	30.4	35.5	41.0	<0.001
	II	1244	47.5	40.7	35.4	34.8	33.7	0.063
	III	553	21.1	22.9	17.4	14.3	11.4	0.012
	IV	287	11.0	11.1	8.6	8.1	6.2	0.295
	Unknown	237	9.0	3.4	8.2	7.3	7.7	0.451
70–79	Total	3181	100.0	100.0	100.0	100.0	100.0	
	I	766	29.2	16.5	24	26.8	27.0	0.036
	II	1224	46.7	44.3	36.6	35.8	38.6	0.152
	III	584	22.3	21.1	20.9	18.1	14.3	0.154
	IV	305	11.6	11	7.7	9.5	10.4	0.903
	Unknown	302	11.5	7.1	10.7	9.8	9.8	0.606
80+	Total	1772	100.0	100.0	100.0	100.0	100.0	
	I	295	11.3	12.5	15.3	17.4	18.7	0.402
	II	584	22.3	30.6	33.5	36	31.0	0.948
	III	331	12.6	25.8	18	19.1	15.6	0.106
	IV	223	8.5	13.7	12	11.1	13.7	1.000
	Unknown	339	12.9	17.3	21.3	16.4	21.0	0.588

[a]Comparison of proportions in the first and last period

Incidence trends

Age-standardized incidence rates increased continuously during 1968–2021 with a slight yet statistically significant leveling after 1998 (from APC 2.3% to APC 1.4%) (Figure 4).

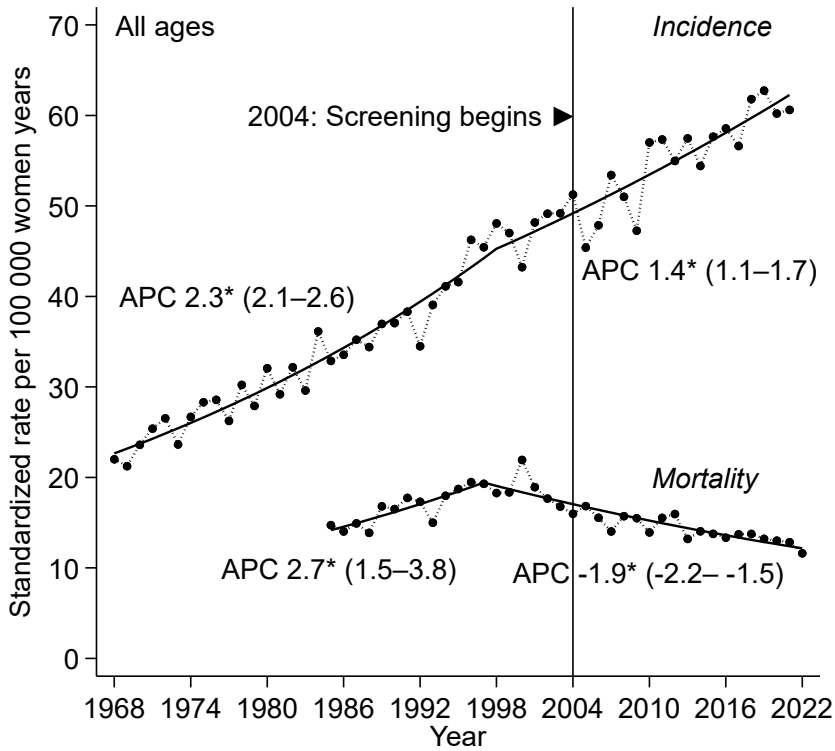

Figure 4. Observed (connected dots) and joinpoint regression modeled (solid line) age-standardized BC incidence (1968–2021) and mortality (1985–2022) in Estonia with annual percentage change (APC) and 95% confidence intervals (CI). * Indicates that the APC is significantly different from zero at the alpha=0.05 level.

Age-standardized incidence of *in situ* BC increased very rapidly until 2004 and the rise continued afterwards with APC of 3% (Figure 5A). The age distribution of *in situ* cases indicated that the proportion of the youngest age group (<50) remained stable around 20%, doubled in age group 50–59 to 30% and decreased in age group 70 years and older (Figure 5B).

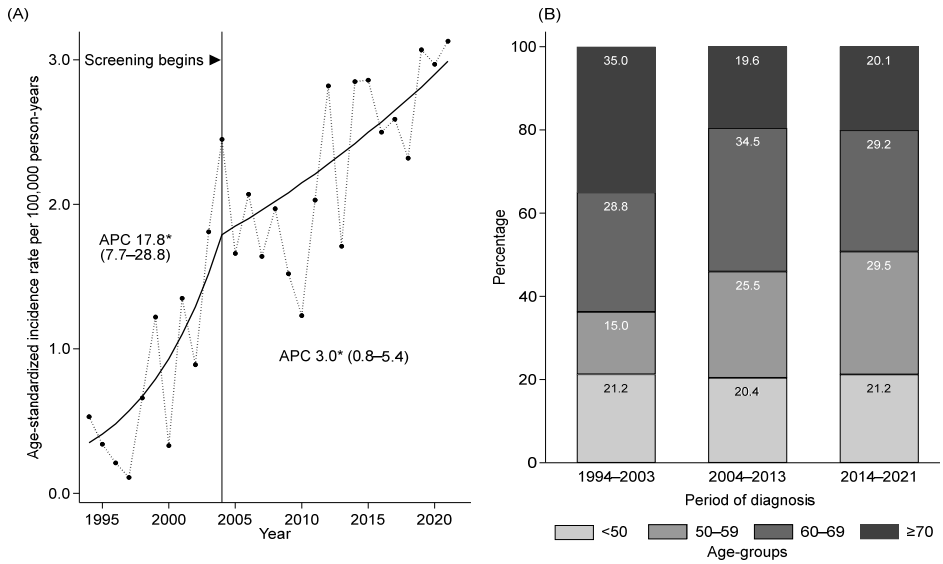

Figure 5. (A) Observed (connected dots) and joinpoint regression modeled (solid line) age-standardized *in situ* breast cancer incidence (1994–2021) in Estonia with annual percentage change (APC) and 95% confidence intervals (CI). (B) Age distribution of *in situ* breast cancer by period of diagnosis. * Indicates that the APC is significantly different from zero at the alpha=0.05 level.

Age-specific incidence rates of invasive BC showed an increasing trend with statistically significant APC values for all age-groups (Figure 6). The highest rates were seen in women aged ≥80 years. The incidence trend in this group is complex, showing an initially significant but rather level increase (APC 1.1). After 1992, the trend surged substantially upwards (APC 7.6) with subsequent flattening and decrease in recent years. Age-groups 60–69 and 70–79 showed continuous and statistically significant incidence increases at a rate of 2.5% per year. The rates in these groups are half of those observed in individuals aged 80 and over. In age-group 50–59, incidence increased at a rate of 2.5% until 2004 and 0.5% thereafter. Youngest age-groups demonstrated a slow but significant incidence increase. While the trend has been constantly rising with a significant APC of 0.9% in age group 30–39, the increase in age-group 40–49 slowed in the 1990s (from APC 2.3 to 0.9).

The analysis of stage-specific incidence indicates that in the youngest age-group (<50 years), a significant incidence increase has been apparent in stages I, II and IV with no change in stage III (Figure 7). In age-groups targeted by screening (50–59 and 60–69), there has been a rapid increase in stage I incidence and the rates have exceeded those of stage II. At the same time, there has been a significant decrease in the incidence of stage III and IV BC. In older age-groups (70–79 and ≥80), a significant increase has been apparent for stages I and II, with no change in stages III and IV.

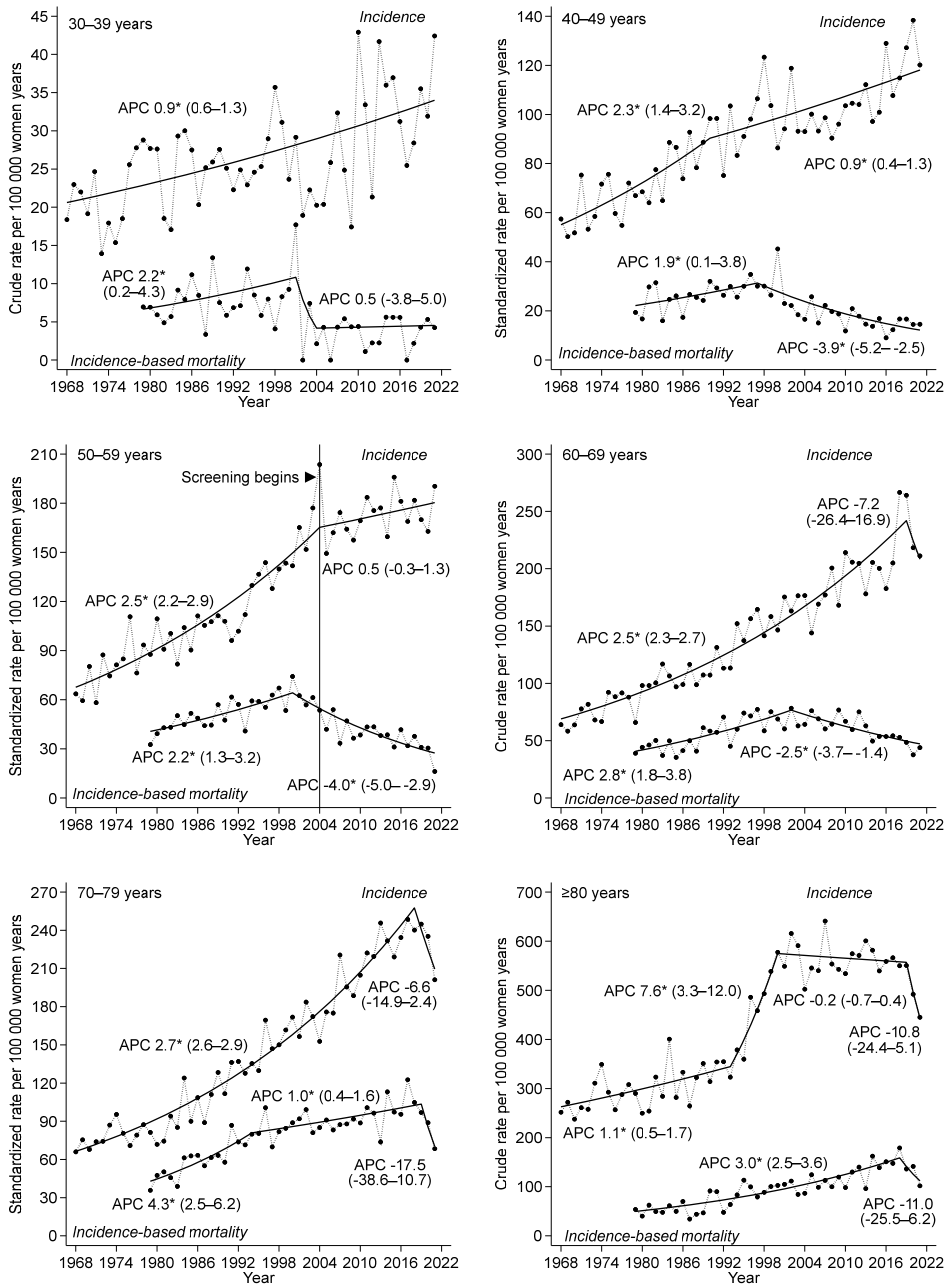

Figure 6. Observed (connected dots) and joinpoint regression modeled (solid line) age-specific breast cancer incidence (1968–2021) and incidence-based mortality 1979–2022 in Estonia with annual percentage change (APC) and 95% confidence intervals (CI). * Indicates that the APC is significantly different from zero at the alpha=0.05 level.

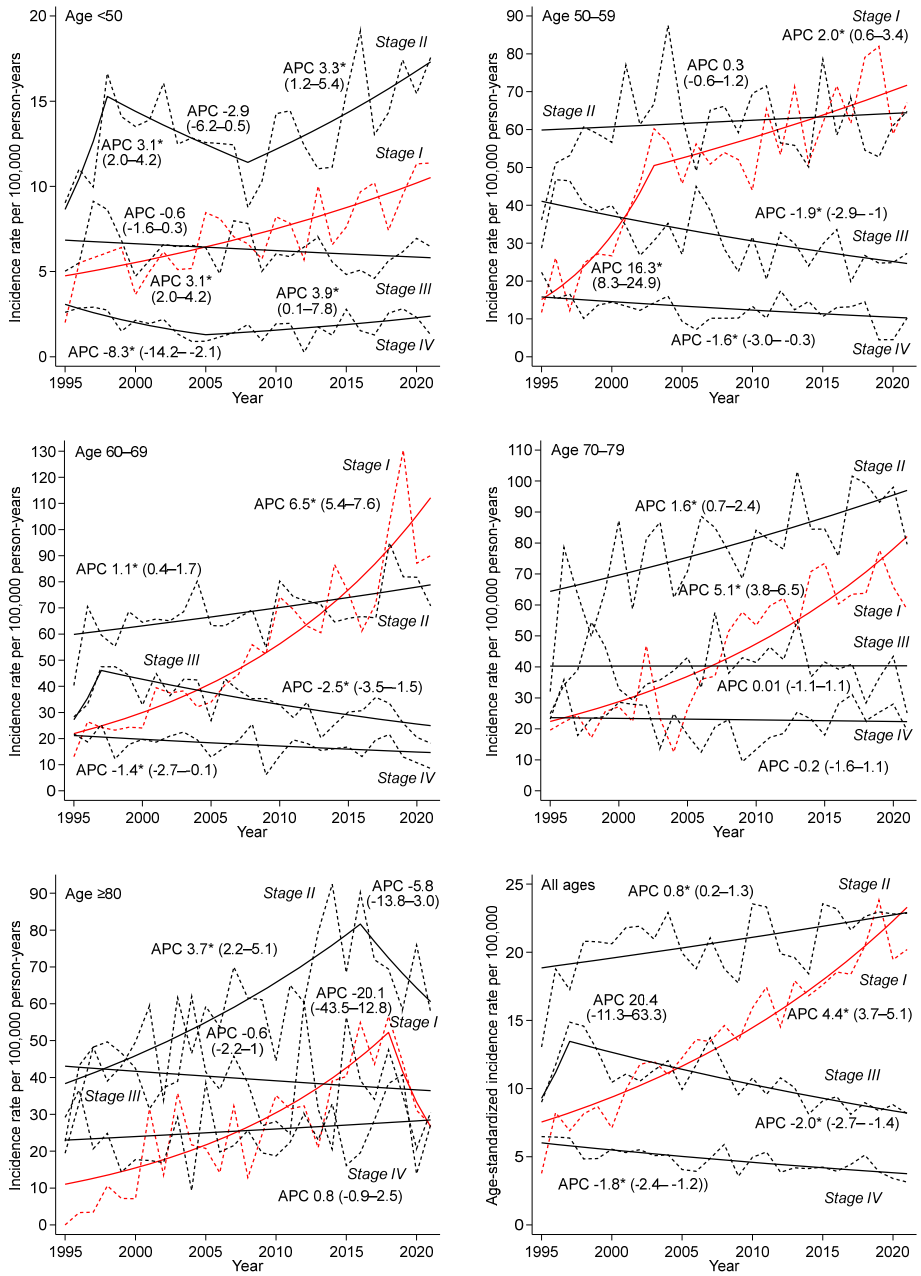

Figure 7. Observed (dashed line) and joinpoint regression modeled (solid line) stage-specific breast cancer incidence in Estonia (1995–2021) with annual percentage change (APC) and 95% confidence intervals (CI). * Indicates that the APC is significantly different from zero at the alpha=0.05 level.

7.2. Mortality

The joinpoint modeled age-standardized BC mortality trend showed a significant increase until 1997 (APC 2.7) with significant decline thereafter (APC -1.9) (Figure 4). A similar pattern was seen in age-groups 40–49, 50–59 and 60–69, while a continuous decline was seen in women aged 30–39 and a continuous increase among women aged 70 years and older (Paper III, Figure 1B).

Age-standardized IB mortality trend showed an increase of 2.3% per year during 1979–1997 and a decrease of 2.1% per year thereafter (Paper III, Figure 2). In age-groups below 70 years of age, age-specific IB mortality trends exhibit a pattern similar to overall age-standardized trend, although the joinpoints indicating the start of the decline vary across age-groups between late 1990s and early 2000s (Figure 6). In women aged 70–79 years, there has been no change in IB mortality since 1992 and for women aged ≥80 years, IB mortality increased until 2019 (APC 3.0)

IB mortality trends analyzed by five-year birth cohorts showed a continuous increase with age for cohorts born from 1909 to 1943 that were never invited to organized screening (Paper II, Figure 3). Cohorts exposed to organized screening display a distinctly different pattern indicating an immediate (1949–1953, 1964–1968) or delayed (1944–1948) stabilization or decline of mortality rates after the age of first invitation. The cohort born in 1974–1978 has not yet been invited to mammography screening and showed a steep increase in mortality with age (Paper II, Figure 3).

IB mortality trends were also analyzed using age-period cohort regression to identify simultaneous mortality changes by age at death, period of death and by birth cohort (Figure 8). The age effect shows increasing BC mortality on a log scale. Without intervention, we would expect mortality to increase on a straight diagonal line with advancing age. Instead, the trend deviates to the right after the age of 50–54, continues at a slower rate and resumes faster upward movement in older ages. The period effect on the right side of the plot, expressed as rate ratios, indicates that mortality decreased significantly in 2004–2008 compared to the previous period and continued to slowly decline thereafter. The birth cohort effect in the center is also expressed as RRs, with the 1944–1948 birth cohort as a reference. IB mortality is consistently lower in successive birth cohorts born later than the reference cohort.

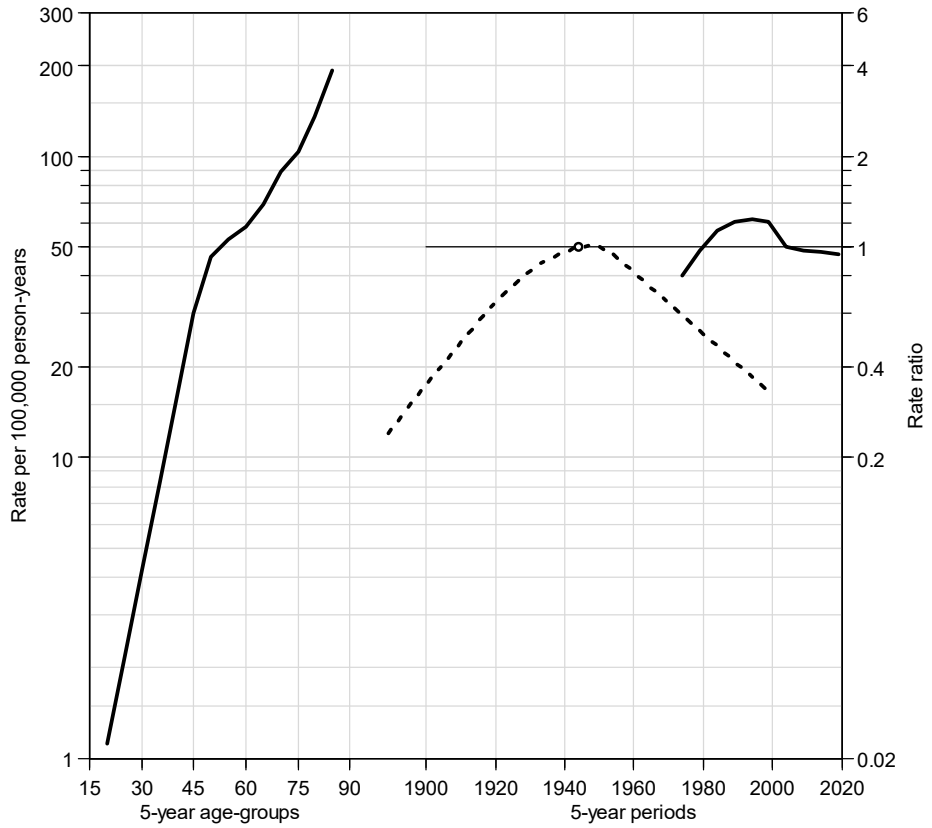

Figure 8. Age, period, and cohort effects (dashed line) of incidence-based breast cancer mortality in Estonia, 1974–2019. Age represents five-year age groups and calendar time five-year periods.

Comparison of IB mortality rates between two periods (1993–2003 and 2004–2014) in age-groups stratified by exposure to screening revealed a significant decline in mortality in age-groups 30–49 (age-standardized RR 0.51, 95% CI 90.42–0.63) and 50–63 (RR 0.65, 95% CI 0.56–0.74) (Paper II, Table 1). No decrease in mortality was observed for the older age-groups 65–69 and 70+.

The pattern of BC burden in Estonia changed from a strong positive correlation (rho = +0.8) between increasing incidence and increasing mortality rates observed during 1985–1995 to a moderate negative correlation (rho = -0.68) between declining mortality and increasing incidence since 1996, denoting a shift from the pattern seen in Eastern Europe to that seen in Western and Northern Europe (Paper I, Figure 2).

7.3. Survival

Age-standardized five-year RSR increased by 18.5% units from 62.5% in 1995–1999 to 81.0% in 2017–2021 (Paper IV, Table 2; Table 4). During the first 10 years of the study period (from 1995–1999 to 2005–2009), the largest survival increases by more than 15% units were seen in age-groups <50 years and 50–59 years (Paper IV, Table 2). By stage, five-year survival increased by more than 11% units for locally/regionally spread BC, mainly T1–3 N1–3 M0 cancers (Paper IV, Table 2). Five-year RSR exceeding 95% was seen for localized tumors in all age-groups, while a pronounced age gradient was seen at more advanced stages (Paper IV, Table 3).

Updated analysis for 2002–2021 included a total of 14,136 BC cases and demonstrated an 8% survival increase in age standardized five-year RSR from 73% to 81% (Table 4). The largest change occurred between 2007–2011 and 2012–2016 with a significant increase of 4.6% units (from 76.7% to 81.3% respectively) and there was no change between the two last periods. The highest age-specific five-year RSR was seen in age-group 50–59 years, but survival improved the most in age-groups 60–69 and 70–79 with 12% and 10%-unit increase, respectively. While the survival improvement for age-group 60–69 was more gradual, a significant 8%-unit increase occurred in age-group 70–79 between 2007–2011 and 2012–2016 comprising the majority of the 10% improvement mentioned above. By stage, an 18.4%-unit increase was seen from 2002–2006 to 2017–2021 for stage III cancers, followed by a 9.4%-unit increase for stage IV cancers (Table 4).

Table 4. Relative survival from breast cancer in Estonia, 2002–2021

	2002–2006 cohort estimate			2007–2011 cohort estimate			2012–2016 cohort estimate			2017–2021 period estimate			
	1-year RSR	5-year RSR	95% CI	1-year RSR	5-year RSR	95% CI	1-year RSR	5-year RSR	95% CI	1-year RSR	5-year RSR	95% CI	Change[a]
Total	92.3	75.4	73.5–77.2	93.0	78.6	76.9–80.2	95.2	82.5	80.9–84.1	94.4	82.1	80.5–83.6	+**6.7**
Age-standardized	90.9	73.0	70.5–75.3	91.8	76.7	74.6–78.6	94.6	81.3	79.4–83.0	93.7	81	79.3–82.7	+**8.0**
Age at diagnosis (years)													
<50	96.9	81.2	77.8–84.2	97.6	83.8	80.5–86.5	98.6	87.0	84.0–89.4	98.9	86.4	83.5–88.9	+5.2
50–59	94.2	79.4	76.1–82.3	95.4	84.7	81.8–87.2	97.9	87.1	84.5–89.4	97.5	87.3	84.6-89.6	**+7.9**
60–69	92.4	74.6	70.8–78.1	93.9	79.7	76.3–82.7	95.2	83.8	80.8–86.5	97.0	86.6	83.9–89.1	+**12.0**
70–79	88.3	69.8	64.9–74.5	90.6	71.8	67.6–75.7	93.3	79.7	76.0–83.2	93.3	79.8	76.1–83.3	+**10.0**
≥80	83.1	59.7	48.8–70.9	81.3	65.4	56.5–74.2	88.8	68.4	61.0–75.8	80.9	62.3	55.6–69.0	+2.6
Stage													
I	98.9	98.6	59.8–100.0	99.5	97.7	90.1–99.5	100.7	99.6	10.6–100.0	100.0	99.8	0.0–100.0	+1.2
II	99.1	86.6	82.8–89.6	99.0	90.6	87.0–93.2	100.2	93.2	90.0–95.4	99.7	91.1	88.2–93.4	+4.5
III	90.2	54.0	49.0–58.8	92.9	60.3	55.5–64.7	94.2	67.7	63.0–71.9	96.4	72.4	67.5–76.6	+**18.4**
IV	48.2	10.6	7.0–15.1	49.9	11.8	7.9–16.4	63.8	19.0	19.0–23.9	62.5	20.0	15.5–24.9	+**9.4**
Unknown	83.2	57.7	45.5–68.1	79.6	56.9	49.9–63.3	86.1	63.8	57.5–69.5	78.2	53.8	47.6–59.5	-3.9

[a] Difference in RSR between first and last periods

For stage I BC, five-year RSR for 2017–2021 was close to 100% for all ages (Table 5). For stage II, five-year RSR exceeded 90% for all age-groups except for women 80 years and older. The RSR ranged from 75% to 52% for stage III and from 27% to 11% for stage IV.

Table 5. Five-year relative survival ratio (RSR) from breast cancer by stage and age, Estonia 2017–2021

Stage at diagnosis	Age at diagnosis (years)	5-year RSR	95% CI
Stage I	<50	97	93–99
	50–59	98	96–100
	60–69	101	98–102
	70–79	101	94–105
	≥80	102	85–116
Stage II	<50	96	92–98
	50–59	95	91–97
	60–69	93	88–96
	70–79	91	85–96
	≥80	79	67–91
Stage III	<50	75	65–82
	50–59	81	73–87
	60–69	76	67–83
	70–79	74	64–83
	≥80	53	38–69
Stage IV	<50	27	15–41
	50–59	16	8–26
	60–69	19	10–31
	70–79	24	15–35
	≥80	11	5–22

8. DISCUSSION

This thesis provides a comprehensive overview of BC incidence and mortality trends in Estonia, using different methodological approaches, including stage-specific incidence and IB mortality analysis.

The incidence of BC has continuously increased since the beginning of cancer registration in Estonia with a mid-trend slowdown around 1998. The introduction of screening in 2004 did not induce any surge in overall incidence rates. Stage-specific BC incidence analysis revealed increasing rates of stage I cancer in all age groups, accompanied by a decrease in stage III and IV incidence in age groups 50–59 and 60–69.

Overall BC mortality increased until late 1990s and has continuously declined thereafter. Substantial mortality reduction has been apparent in women below 70 years of age. Analysis of IB mortality indicated that age-specific BC mortality curve flattened or started to decline after entering screening age in birth cohorts invited to screening, whereas mortality continued to increase with age in earlier birth cohorts. Poisson regression of IB mortality before and after the introduction of screening indicated a significant reduction in young women not yet invited to screening as well as women invited to screening suggesting the screening effect of around 19% in age group 50–63.

This thesis also examined survival from BC. During the past 30 years the age-standardized RS from BC has increased by 18.5% units with the largest change occurring between 1995–1999 and 2000–2004. After initial gain the improvements in relative survival gradually slowed down although overall RS has continued to increase. In the beginning of the study period, the largest survival gains were seen in younger age groups, but in later periods survival increased the most in age groups 60–79 years. By stage, survival improvement has been most pronounced for locally/regionally spread cancers.

8.1. Strengths and limitations

This is the first and most comprehensive study of BC incidence, mortality and survival trends in Estonia covering five decades including the period of political, social, economic and healthcare transition that provides context for interpreting the trends and comparing them with those of other European countries.

The main strengths of the thesis were the use of high-quality data and the application of various methodological approaches and analytical techniques to better understand factors behind the observed trends. Data were mainly obtained from a high-quality population-based cancer registry that collects data since 1968, utilizing thorough data collection and quality control procedures, which ensure the completeness of case ascertainment and follow-up for vital status. Data quality is evidenced by consistently low proportion of death certificate only cases and increasing microscopic verification rate. Cancer incidence data individually linked to causes of death enabled IB mortality analysis that allowed a partitioning

of mortality by variables associated with disease onset such as age at and time of cancer diagnosis, which is crucial for evaluating the impact of screening. Using data on diagnosis and death occurring in the same period minimized the possibility of lead time bias and reduced errors caused by competing causes of death. The availability of data on TNM stage since 1995 enabled stage-specific incidence and survival analyses that help interpret the trends in early detection and survival. In addition to joinpoint regression analysis to identify changes in incidence and mortality trends, age-period-cohort analysis was used to separate the effects of age, birth cohort and time period, and Poisson regression modelling to compare IB mortality before and after the initiation of screening program. Confidence ellipses and correlation coefficients were used in international comparison. In analyzing relative survival, cohort, hybrid and period approaches were used to detect the most recent trends.

The study also had some limitations. BC incidence and mortality data available from the EUREG database covered time periods of various lengths restricting concurrent international comparisons. However, sufficient overlap in time and overall trends observed in our study permitted us to draw conclusions that concur with pertinent trends described in other studies (Arnold et al., 2015). Small population of Estonia makes BC rates susceptible to considerable variation, particularly at younger ages. To facilitate interpretation, joinpoint regression was used to smooth out these random fluctuations and identify significant changes in trends.

The study period included two years (2020 and 2021) of COVID-19 pandemic, which may have had some effect on the incidence and mortality rates. The impact of the pandemic will be subject to further investigations when more data become available.

Reporting of *in situ* BC cases did not cover the whole study period and may have been incomplete during the first years of registration affecting the trend.

We were not able to identify women who were invited to or participated in screening during the study period, as this information has been collected only since 2015. Data on cancer cases linked to cancer screening registry were therefore used only in a small subgroup analysis to describe stage at diagnosis.

The interpretation of survival estimates was to a certain extent hindered by the lack of clinical information beyond stage at diagnosis, such as mode of detection, comorbidities or diagnostic and treatment procedures. As for stage, data were missing for 8% of the patients and this proportion increased slightly over the study period. Patients with unknown stage may differ by their clinical profiles across registries which may compromise stage-specific comparisons between the countries. Improved diagnostic procedures and the resulting more accurate determination of cancer stage may have affected some stage-specific trends and produced the effect of stage migration in stage-specific survival estimates. Overall survival improvement is likely to include some effect of lead-time due to the rise in mammography coverage and the initiation of a mass screening program during the study period.

Analyses of BC deaths may have been affected by misclassification of the underlying cause of death, which is more likely among older patients with multiple comorbidities. A recent analysis revealed a notable over-reporting of prostate cancer as a cause of death among older men in Estonia who had been diagnosed with prostate cancer during their lifetime but ultimately died from other causes (Innos et al., 2022). This could also be applicable to other cancers with a good prognosis, such as BC, potentially masking the impact of improved treatment in older women.

8.2. Incidence and mortality

The pattern of BC burden in Estonia observed in this study presents a clear divergence of incidence and mortality trends in the late 1990s and early 2000s, a shift towards the pattern seen in Western, Northern and Southern Europe rather than in Eastern Europe. A weak positive correlation between BC mortality and incidence was observed in a European study using GLOBOCAN 2008 data, with a notable differentiation between Eastern and Western Europe along the diagonal that denotes low incidence-high mortality and high incidence-low mortality rates (Ades et al., 2013). More recent data from GLOBOCAN 2022 showed that this distinction between East and West still exists, but for women aged 40–74 the association between mortality and incidence has become negative (Spearman rho = -0.403, p=0.01) (Ferlay et al., 2024). Trends analogous to Estonia for the equivalent period were also seen in other Eastern European countries, such as Czech Republic, Poland, and Lithuania (Paper I; Everatt & Gudavičienė, 2022).

BC incidence has increased in Estonia since 1968, although it remains lower than in Western and Northern European countries and according to the 2022 estimates, the age-standardized incidence of BC in Estonia is the third lowest in Europe (Joint Research Centre, 2020). The upward trend is likely associated with the same determinants that have been suggested to affect the trends for other European countries (Arnold et al., 2015; Karim-Kos et al., 2008). Gradual adoption of western lifestyle has brought along increasing impact of reproductive risk factors such as declining fertility rates and rising age at first birth (Statistics Estonia, 2024), but also behavioral risk factors such as obesity and low physical activity (Tekkel & Veideman, 2013; Reile & Veideman, 2021). Alcohol consumption is particularly on the rise among young women (Baburin et al., 2020). However, the observation that incidence increase has largely been limited to early-stage BC in all age groups suggests a role of mammography use, both within and outside the screening program as well as better symptom awareness among women in Estonia. The incidence of *in situ* BC that can be considered an indirect indicator of screening activity has risen steadily during the study period, but remains four times lower than in Finland, for example (Finnish Cancer Registry, 2024). The lack of typical screening-induced incidence surges is probably related to low screening coverage, both in terms of narrow age range and poor attendance, as until 2018, only women aged 50–63 years were invited and the participation rate exceeded 60% for the first time in 2022 (Zimmermann et al., 2024).

Nevertheless, it is likely that a certain amount of overdiagnosis is present. Overdiagnosis represents the major harm of early detection screening (Adami et al., 2019; Marmot et al., 2013). According to recent estimates from England, a country where mammography screening started in 1988 and participation has been relatively stable around 70–73%, about 35% of BC detected by screening would represent overdiagnosis, which translates into 18% of all BC diagnosed in women invited to screening (Autier et al., 2024). The magnitude of overdiagnosis in Estonia will remain the subject of future research.

While BC incidence in Estonia is 25% lower than the estimate for EU27, the mortality estimate is much closer to EU27, being just 12% lower (Joint Research Centre, 2020). After a steady increase until 1997, overall BC mortality in Estonia has been in significant decline, a trend that was not yet apparent in the earlier analysis until 2013 (Paper I). The observed magnitude of the decrease of around 2% per year is similar to that seen in the US, Australia and the UK over a comparable period (Lei et al., 2021). In the earlier analysis, the age group 50–59 was the only one to show a significant mortality decrease since around 2000. In the updated IB mortality analysis, however, a significant decline is apparent in ages 40–69 years. In particular, the decline of nearly 4% per year in age group 60–69 is considerably larger than that observed in several Western countries during a similar period (Lei, 2021). Our birth cohort analysis showed that in birth cohorts that received multiple screening invitations, the IB mortality curve flattened with increasing age after entering screening age, in contrast to earlier cohorts where mortality continued to rise. Previous research on the Dutch screening program, which began in 1989, showed that uninvited cohorts experienced a continuous increase in mortality with age, while invited cohorts presented a diverging trend within five years after screening invitation (Ripping et al., 2013). The shape of the period effect clearly indicates that IB mortality dropped dramatically in 2004–2008 compared to previous periods and together with cohort effect also implies that screening have contributed to the drop in mortality. Very similar pattern of BC mortality has been observed in Lithuania, where BC screening program was initiated in 2006 for women aged 50–69 and mortality has been decreasing since 1996 (Everatt & Gudavičienė, 2022). Their data have shown cohort effects that may be linked with risk factor changes, particularly among younger generations, but also period effects suggesting the beneficial impact of increased mammography testing, along with overall improvements in early detection and the introduction of new treatments (Everatt & Gudavičienė, 2022).

When comparing IB mortality before and after the beginning of mammography screening, accounting only for BC deaths where diagnosis and death had occurred within the specified period and age range, a 35% IB mortality reduction was seen in women aged 50–63 years. A meta-analysis of BC cohort studies estimated that exposure to screening invitation decreased IB mortality in women over 50 by 20%, which after adjustment for self-selection increased to 26% (Dibden et al., 2020). A systematic review found that after 11 years of follow-up of women invited to screening, the impact of mammography screening was around 26% (Njor et al., 2012). Based on the data from a Norwegian population-based

cohort study, researchers hypothesized that the effect of BC treatment on IB mortality might be about 16% (Møller et al., 2019). By applying this hypothetical value, we can estimate that the possible screening effect in Estonia may be around 19%. Our somewhat smaller result fits well within the magnitude of screening benefits shown by other studies. Since we did not see any mortality reduction in the 65–69 age group in similar analysis, we may speculate that the role of screening may be more significant. A recent study from the United States using simulations and modeling of cohort and randomized trial data on screening and treatment of BC stages I to IV between 1975 and 2019 estimated that of the 58% reduction in BC mortality, 25% can be attributed to screening (Caswell-Jin et al., 2019). The authors also emphasized that BC cases diagnosed outside of the screening program may result in poorer outcomes that even modern treatments are unable to change (Caswell-Jin et al., 2019). Typically, screening detects small, less aggressive, and slowly growing tumors, leading to increased incidence rates. It has been suggested that given the later adoption of mammography screening in Eastern Europe, it has the potential to prevent 23% of BC deaths (Zielonke et al., 2020; Zielonke et al., 2021).

In age group 30–49 not included in screening, the mortality reduction was nearly 50% comparing periods before and after the introduction of screening. Such a large reduction may partly result from earlier diagnosis through increased awareness and better symptom recognition, as an indirect consequence of widespread screening-related BC communication measures (Hermann et al., 2018). Earlier diagnosis may also have been facilitated by the opening of offices dedicated to breast health at Estonian cancer centers that can be visited without a referral. Earlier detection is evidenced by increasing incidence of stage I and II BC in this age group, but it has not been paralleled by a drop in the incidence of late-stage BC. Therefore, it is likely that improved treatment is mostly responsible for mortality reduction in young women, also supported by the results of survival analysis. Evidence suggests that significant improvements in BC treatment may benefit younger age groups to a larger extent (Beral et al., 1995).

In the comparison of two time periods, no decline in IB mortality was observed in age groups 65–69 and ≥70 years. The lack of mortality decline in women 70 years and older is in contrast to other countries (Kalager et al., 2014; Møller et al., 2019; Marmot et al., 2013). This can probably be attributed to later detection as well as poorer treatment results. Women 70 years and older have consistently had 10% of more new cases diagnosed at stage IV, the proportion of T4 tumors has been higher and the proportion of stage I lower than in other age groups. At the same time, stage-specific survival estimates have also been lower in older women.

8.3. Survival

Five-year relative survival from BC has increased considerably in Estonia over the study period. In early 1990s, the survival estimates for Estonia were among the lowest in Europe according to EUROCARE-3 (Coleman et al., 2003). The gap of nearly 20% compared with Nordic countries observed in late 1990s has narrowed by half as the latest five-year survival estimate for Estonia was around 80% and those for Nordic countries around 90% (Larønningen et al., 2023). In these comparisons, the component of lead time and overdiagnosis in countries with a large proportion of female population routinely covered by screening should be considered.

Both age and stage were highly important prognostic factors as reported elsewhere (Holleczek et al., 2011; Innos et al., 2015; Minicozzi et al., 2018). Survival increased in all age and stage categories, but the extent of the increase as well as the timing of it varied. During the first half of the study period survival gain was largest in younger age groups (below 60 years), but age groups 60–79 years showed larger gains during the second half. The age difference is likely mainly due to different stage distribution at diagnosis. In stage-specific survival, considerably lower estimates were seen only for women aged 80 years and older for stages II–IV. While overall survival trends are affected by both early detection (including screening-induced lead-time effect) and improved treatment, the analysis of stage-specific survival trends enables to evaluate the effect of cancer care. Localized early-stage tumors showed excellent survival throughout the study period, consistently with previous high-resolution studies (Sant et al., 2003) and across all age groups. In earlier analysis (Paper IV), a considerable survival deficit of patients in Estonia with locally/regionally spread and metastasized BC was apparent compared to the US and Germany. The latest stage-specific estimates presented in this thesis are similar to those shown for England in 2013–2017 (Office for National Statistics, 2024), but lower than the latest data for Norway (Cancer Registry of Norway, 2023) and Australia (National Breast Cancer Foundation, 2024): stage III survival Estonia 72%, Norway 80%, Australia 81%; stage IV survival Estonia 20%, Norway 39%, Australia 32%. Nevertheless, a very large survival increase among stage III cancers in Estonia is evident over the study period, consistent with the considerable evolvement of BC treatment. In late 1990s, chemotherapy and hormonal treatment were more widely used than more expensive surgery and radiotherapy, which was suggested to be related to low healthcare expenditure (Allemani et al., 2013). The use of breast-conserving surgery combined with radiotherapy in early BC increased from 9% to 75% from 1997 to 2011 (Minicozzi et al., 2019). The use of radiotherapy was severely hindered by low availability of radiotherapy equipment with 3.0 megavoltage units per million population compared to the median of 5.3 of 28 European countries in 2012 (Grau et al., 2014). The number of megavoltage units increased in 2016 and according to a previous analysis, receipt of radiotherapy was nearly 40% higher among BC patients in Estonia in 2016–2018

than in 2007–2009 (Shahrabi Faharani et al., 2021). New anticancer drugs have become increasingly available.

On the other hand, Estonian BC patients have been shown to have higher levels of comorbidities, which may restrict the choice of therapeutic options or necessitate dose reductions (Minicozzi et al., 2019). Supportive care for frail patients and psychosocial support throughout the cancer journey have not been well established in Estonia. There is evidence of sociodemographic inequalities in receipt of cancer treatment (Innos & Paapsi, 2023; Shahrabi Faharani et al., 2021) despite solidarity-based health insurance system, which should guarantee access to standard treatment to all patients. As another possible factor contributing to deficits in BC management, no routine monitoring of quality of care has been established. These shortcomings have also been highlighted by the National Cancer Control Plan (Ministry of Social Affairs & National Institute for Health Development, 2021).

9. CONCLUSIONS

This thesis provides an in-depth analysis of long-term trends in BC incidence, mortality, and survival in Estonia, using a variety of methodological approaches and covering a period of social and health care transition and introduction of organized screening. The results consistently indicated that the introduction of organized screening program combined with early detection beyond screening and improvements in cancer care have significantly influenced observed patterns in incidence, mortality, and survival.

1. BC incidence in Estonia has been increasing steadily over the past decades, at a rate of 1.4% per year since 1998. Increase has been apparent in all age groups, but the patterns have differed, and the most rapid rise was observed in women aged 60–79 years. Since 1995, most of the increase has been due to increasing rate of stage I BC (4% per year), followed by stage II BC (1% per year). In parallel, the incidence of stage III and stage IV cancer has declined (both 2% per year). The incidence of stage I BC has increased in all age groups, but the decrease of stage III and IV incidence has occurred only in women aged 50–69. BC mortality has been declining since 1997 at a rate of 2% per year. Mortality has been decreasing rapidly in age groups 40–69 years, while it has increased in women 70 years and older. The observed clear divergence of incidence and mortality trends in the late 1990s and early 2000s represents a shift towards the pattern seen in Western, Northern and Southern Europe rather than in Eastern Europe.

2. The age-specific IB mortality curves of birth cohorts invited to screening distinctly differed from those of younger and older cohorts, as their curves flattened or started to decline after entering screening age, while a continuous increase with age was seen in earlier birth cohorts. The comparison of IB mortality during 11-year periods before and after the introduction of screening revealed a substantial reduction in young women not yet invited to screening (mortality decline 49%) and women aged 50–63 years invited to screening (mortality drop 35%). No mortality decline was seen in women 65 years and older who were not invited during that period. These findings support the beneficial effect of screening on BC mortality, despite low participation.

3. Five-year relative survival from BC has increased by 18.5% over a 27-year period, with considerable heterogeneity across age and stage. The survival gap between young women and those aged 70–79 years has narrowed considerably, both overall and for stage-specific survival. Despite rapid improvements, the survival of stage III and IV remains lower than in countries showing the highest survival. While the persistent 10% deficit in age-standardized five-year relative survival is probably mainly due to later stage at diagnosis of Estonian patients, the inferior survival of advanced stage cancers suggests deficits in BC care.

10. IMPLICATIONS FOR FUTURE RESEARCH AND HEALTH POLICY

To further reduce BC mortality, efforts are necessary to tackle modifiable risk factors through primary prevention, ensure high-quality screening program according to the recommendations of the European Commission, reduce patient and provider delay in symptomatic cases, and ensure availability of up-to-date treatment modalities and support for BC patients. The results thus support the goals of Estonian National Cancer Control Plan for 2021–2030. Primary prevention to reduce exposure to alcohol consumption, obesity and low physical activity is particularly important in view of slow but steady BC incidence increase in young women. Study results support the recent decision to expand the screening invitation up to age 74 in 2024, also recommended by the European Commission. At the same time the results do not support the inclusion of younger age groups to mammography screening. Further investigation is warranted to elaborate whether the increase in stage IV incidence in the youngest age group could be due to improved diagnostic accuracy or other factors. In addition to efforts to increase screening participation in target groups, continuous monitoring of quality indicators of mammography screening is crucial, and the screening program should be accompanied by clear communication of the benefits and harms. As more data become available from the cancer screening registry, more detailed analysis of the diagnostic and treatment practices of BC cases detected by screening or by other means of detection is warranted, including the effects of COVID-19 pandemic. Routine monitoring of quality-of-care indicators would help pinpoint shortcomings in cancer diagnostics and care that may hinder survival improvement.

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12. SUMMARY IN ESTONIAN

Rinnavähihaigestumus, -suremus ja -elulemus Eestis tervishoiusüsteemi muutuste ja sõeluuringu kontekstis

Taust

Rinnavähk on peamine vähihaigestumuse ja vähisurmade põhjus maailmas ja seega keeruline rahvatervishoiu probleem. Rinnavähihaigestumuse ja -suremuse mustrid varieeruvad tulenevalt riikide sotsiaalsest ja majanduslikust arengutasemest. Globaalses vaates on inimarengu indeks tugevas positiivses korrelatsioonis rinnavähi vanusestandarditud haigestumusega, ent korrelatsioon rinnavähisuremusega on negatiivne. Enamikus Euroopa riikides on rinnavähihaigestumus suurenemas. Taoline trend on tingitud muutustest rahvastiku vanuselises struktuuris, ent ka üha kasvavast ekspositsioonist riskiteguritele ja mammograafilise sõeluuringu laialdasest levikust. Suremuse vähenemine on omakorda seotud varasema avastamise ja üha tõhustuva vähiraviga.

Rinnavähi viie aasta elulemus suureneb pidevalt ja ulatub paljudes jõukates riikides 90%-ni, ent madalama arengutasemega riikides jääb mitmekümne protsendi võrra madalamaks. Parem elulemus tuleneb varasema avastamise ja tõhusama ravi kombineeritud mõjust. Rinnavähi varaseks avastamiseks soovitavad rahvusvahelised organisatsioonid mammograafilist sõeluuringut. Tõendusmaterjali selle kohta, et rahvastikupõhine sõeluuring vähendab suremust, on rohkelt. Siiski kaasnevad rinnavähi varase avastamisega ka kahjulikud mõjud ning sõeluuringu kasulikkus on mitmete autorite poolt küsimuse alla seatud. Viimastel aastakümnetel on märkimisväärselt paranenud sümptomaatilise rinnavähi ravi tõhusus, mistõttu ei pruugi asümptomaatiliste juhtude avastamine sõeluuringul enam avaldada sama suurt mõju kui varem.

Varasemad uuringud on näidanud Eesti mahajäämust seoses rinnavähi varase avastamise, elulemuse ja suremusega. Kuigi haigestumus on võrdlemisi väike, püsib suremus suhteliselt kõrgel tasemel. Rahvusvahelised uuringud on näidanud madalamat elulemust võrreldes teiste riikidega, peamiselt tingituna hilisest avastamisest ja puudujääkidest soovitatavate diagnostika- ja ravimeetodite rakendamises. Sõeluuringuga hõlmatus on olnud madal nii kitsa vanusevahemiku kui madala osalusmäära tõttu. Euroopa idapoolse osa riikides napib sõeluuringu efektiivsuse hindamisele suunatud uuringuid.

Eesmärgid

Uuringu üldeesmärk oli hinnata rinnavähihaigestumuse, -suremuse ja -elulemuse pikaajalisi trende ühiskonnas ja tervishoiusüsteemis toimunud muutuste ning organiseeritud sõeluuringu rakendamise kontekstis.

Alaeesmärgid olid:

1. Uurida rinnavähihaigestumuse ja suremuse pikaajalisi trende Eestis ja võrrelda neid valitud Euroopa riikides esinevate mustritega.
2. Hinnata rinnavähi haigestumuspõhist suremust Eestis enne ja pärast mammograafilise sõeluuringuprogrammi käivitamist.
3. Hinnata rinnavähi suhtelise elulemuse trende Eestis rõhuasetusega vanusel ja staadiumil.

Metoodika

Eesti Vähiregistrist päriti andmed kõigi Eestis ajavahemikul 1968–2021 diagnoositud invasiivsete rinnavähijuhtude kohta naistel (Rahvusvahelise Haiguste Klassifikatsiooni (RHK) Onkoloogia osa kolmanda versiooni (RKH-O-3) topograafiakoodid C500–C509). Lisaks saadi vähiregistrist andmed aastatel 1994–2021 diagnoositud *in situ* rinnavähijuhtude kohta (RHK10 kood D05. Staadiumiandmed olid kättesaadavad alates 1995. Staadium kodeeriti vastavalt TNM klassifikatsioonile. Elulemusanalüüsi kaasati aastatel 1995–2021 elupuhuselt diagnoositud rinnavähijuhud vanuses ≥15 aastat, keda jälgiti surma või Eestist lahkumise suhtes kuni 2021. aasta lõpuni.

Surmatunnistustel põhineva rinnavähisuremuse analüüsi kaasati kõik surma põhjuste registris aastatel 1985–2022 registreeritud surmajuhud naistel, mille puhul peamiseks surmapõhjuseks oli märgitud rinnavähk (RHK-10 C50). Haigestumuspõhise suremuse analüüsis defineeriti rinnavähisurmana surmajuhud aastatel 1974–2019, kus peamine surmapõhjus oli rinnavähk (C50) naistel, kellel oli samal ajavahemikul diagnoositud rinnavähk. Andmed Eestis naistel diagnoositud rinnavähijuhtude kohta, mis olid individuaalselt lingitud surmapõhjustega, saadi vähiregistrist. Haigestumuspõhise suremuse trend näidati perioodi 1979–2019 kohta, et oleks võimalik võtta arvesse eelneva viie aasta jooksul diagnoositud juhud.

Haigestumus- ja suremuskordajad arvutati kasutades aastakeskmist rahvastikku ja väljendati 100 000 inimaasta kohta. Vanusestandardimiseks kasutati maailma standardrahvastikku. Kordajaid modelleeriti muutuspunkti regressiooni abil ja leiti aastane protsentuaalne muutus (ingl k *annual percentage change*, APC) koos 95% usaldusvahemikuga (UV). Haigestumuspõhist suremust analüüsiti viieaastastes sünnikohortides (sünniaasta 1909–1978) ning vanus-periood-kohort-regressioonanalüüsi abil. Lisaks võrreldi haigestumuspõhist suremust kahel võrdse pikkusega perioodil (1993–2003 *vs* 2004–2014) enne ja pärast sõeluuringu käivitamist, kasutades *Poissoni* regressioonanalüüsi. Analüüsi kaasati ainult need haigestumuspõhised surmajuhud, mille puhul nii diagnoos kui surm leidsid aset samal ajaperioodil ja samas vanuserühmas (<50, 50–63, 65–69, ≥70).

Euroopa riikide võrdlusanalüüsiks saadi valitud Euroopa riikide rinnavähi haigestumus- ja suremusandmed EUREG andmebaasist. Riigid koondati nelja rühma: Lääne-, Lõuna-, Põhja- ja Ida-Euroopa. Vanusestandarditud haigestumus- ja suremuskordajate ühise varieeruvuse hindamiseks kasutati hajuvusdiagrammi ning Spearmani astakkorrelatsioonikordajaid. Eesti andmed jagati kaheks, et võrrelda perioode 1985–1995 ja 1996–2012.

Elulemusanalüüsis kasutati suhtelise elulemuse metoodikat. Viie aasta suhteline elulemusmäär koos 95% UVga leiti tegeliku elulemuse jagamisel eeldatava elulemusega, viimane leiti Ederer II meetodil rahvastiku elutabelite põhjal. Varasemate perioodide puhul kasutati kohortmeetodit, hilisemate perioodide korral, kui patsiendid ei olnud veel läbinud viieaastast jälgimisperioodi, kasutati perioodmeetodit. Vanusele kohandatud elulemusmäärade arvutamiseks kasutati rahvusvahelisi standardeid.

Andmete analüüsimiseks kasutati programme Stata ja R. Uuringuprotokolli kooskõlastas Tallinna Meditsiiniuuringute Eetikakomitee.

Tulemused ja arutelu

Kokku diagnoositi aastatel 1968–2021 Eestis naistel 27 571 rinnavähijuhtu. Kui aastatel 1968–1974 diagnoositi aastas keskmiselt 258 juhtu, siis aastatel 2017–2021 oli see arv üle kolme korra suurem ehk 807 juhtu aastas. Vanusestandarditud rinnavähihaigestumus suurenes kuni 1998. aastani 2,3% aastas ja seejärel 1,4% aastas. Haigestumus suurenes üldjoontes kõigis vanuserühmades, kõige kiiremini 50–79aastaste naiste seas. Vaadeldes haigestumust staadiumite lõikes selgus, et vanusestandarditud haigestumuskordaja suurenes kõige kiiremini I staadiumi puhul (4,4% aastas), samal ajal kui nii III kui IV staadiumi haigestumus vähenes umbes 2% aastas. I staadiumi haigestumus suurenes märkimisväärselt kõigis vanuserühmades, kuid III ja IV staadiumi haigestumuse vähenemine ilmnes ainult vanuserühmades 50–59 ja 60–69. Üldine rinnavähihaigestumuse suurenemine on tõenäoliselt seotud järkjärgulise üleminekuga läänelikule eluviisile, millega kaasnevad rinnavähi riski suurendavad reproduktiivkäitumise muutused, aga samuti rasvumine ja vähene kehaline aktiivsus. Teisalt viitab varase rinnavähi haigestumuse kiire kasv ka mammograafia laialdasele kasutuselevõtmisele nii sõeluuringu raames kui selle väliselt ning teadlikkuse kasvust tingitud sümptomite paremale äratundmisele. Haigestumustrendides ei ole siiski näha n-ö tüüpilist sõeluuringukõverat, mis võib olla tingitud suhteliselt kitsast vanuserühmast ja samuti madalast osalusmäärast, kuna 2018. aastani kutsuti sõeluuringule ainult naisi vanuses 50–63 aastat ja osalusmäär jõudis 60%ni esmakordselt 2022. aastal. Eesti rinnavähihaigestumus on siiski 25% madalam kui Euroopa Liidus keskmiselt.

Vanusestandarditud rinnavähisuremus suurenes Eestis kuni 1990. aastate teise pooleni ja on seejärel pidevalt vähenenud 1,9% aastas. Enim on suremus vähenenud vanuserühmades 40–69 aastat, ent 70aastaste ja vanemate naiste seas on suremus endiselt tõusutrendis. Haigestumuspõhise suremuse analüüs näitas, et sõeluuringule kutsutud sünnikohortides lamenesid vanusekõverad pärast sõeluuringuvanusesse jõudmist, kuid vanemates sünnikohortides suurenes suremus koos vanusega. Vanus-periood-kohort analüüs näitas samuti haigestumuspõhise suremuse aeglasemat tõusu vanuserühmades 50–69. Ühtlasi täheldati madalamat suremust nooremates sünnikohortides ja alates perioodist 2004–2008. Haigestumuspõhise suremuse võrdlus enne ja pärast sõeluuringuprogrammi käivitamist näitas olulist suremuse vähenemist noortel naistel (vanusele kohandatud riski-

suhe 0,51, 95% UV 0,42–0,63) ja sõeluuringu vanuserühmas 50–63 aastat (vanusele kohandatud riskisuhe 0,65, 95% UV 0,56–0,74), samal ajal kui 65–69aastastel ning 70aastastel ja vanematel naistel suremus ei vähenenud. Eesti rinnavähisuremus on Euroopa Liidu keskmisest vaid 12% väiksem. Üldine suremuse vähenemise kiirus sarnaneb mitmetele kõrge arengutasemega riikidele. Haigestumuspõhise suremuse vanusekõverad sünnikohortides viitavad sõeluuringu positiivsele mõjule, sarnaselt mitmetele teistele riikidele, kus on tehtud analoogseid uuringuid. Suremuse võrdlus kahel perioodil enne ja pärast sõeluuringu käivitamist näitas sõeluuringu vanuserühmas suremuse 35%st vähenemist. Eeldades, et ravi tõhustumise mõju suremuse vähenemisele on umbes 16% (tuginedes Norra andmetele), siis võib sõeluuringu mõju Eestis hinnata 19%le.

Rinnavähi viie aasta suhteline elulemus on Eestis viimase 27 aasta jooksul suurenenud 18,5% võrra (62,5% aastatel 1995–1999 ja 81,0% aastatel 2017–2021). Uuringuperioodi alguses kogesid suuremat elulemuse paranemist nooremad vanuserühmad, kuid viimastel aastatel pigem naised vanuses 60–79 aastat. Perioodide 2002–2006 ja 2017–2021 võrdluses suurenes viie aasta suhteline elulemus 60–69aastastel naistel 12% võrra ja 70–79aastastel naistel 10% võrra. Staadiumide lõikes oli viie aasta suhteline elulemus viimastel andmetel järgmine: I staadium 100%, II staadium 91%, III staadium 72%, IV staadium 20%, teadmata staadium 54%. Perioodide 2002–2006 ja 2017–2021 võrdluses suurenes III staadiumi elulemus 18,4% võrra ja IV staadiumi elulemus 9,4% võrra.

Kui 1990. aastate teises pooles jäi Eesti rinnavähipatsientide elulemus Põhjamaade tulemustest maha ligi 20% võrra, siis praeguseks on vahe poole võrra vähenenud ja erinevus on ligi 10%. Varases staadiumis diagnoositud rinnavähi elulemus on Eestis olnud väga hea juba mõnikümmend aastat, ent III ja IV staadiumi elulemuses püsib teatav mahajäämus. Uuringud on näidanud, et diagnostika ja ravi on Eestis väga palju edasi arenenud. Samas on Eesti rinnavähipatsientidel rohkem kaasuvaid haigusi, võib täheldada sotsiaalset ebavõrdsust teatud raviviiside rakendamises ning probleeme on psühhosotsiaalse toe pakkumisega vähiteekonnal. Eestis puudub ka süsteem ravikvaliteedi indikaatorite pidevaks monitoorimiseks. Kõik need probleemid on välja toodud kehtivas vähitõrje tegevuskavas.

Järeldused

Doktoritöö annab põhjaliku ülevaate rinnavähi pikaajalistest haigestumuse, suremuse ja elulemuse trendidest Eestis, kasutades eri metodoloogilisi lähenemisi ja hõlmates ajaperioodi, mille jooksul toimusid suured muutused ühiskonnas ja tervishoiusüsteemis ning alustati organiseeritud sõeluuringuga. Tulemused näitavad läbivalt, et organiseeritud sõeluuringu käivitamine koosmõjus sõeluuringuvälise varase avastamise ja vähiravi tõhustumisega on märkimisväärselt mõjutanud rinnavähi haigestumust, suremust ja elulemust Eestis.

1. Rinnavähihaigestumus on Eestis viimastel aastakümnetel jätkuvalt suurenenud. Haigestumuse suurenemine ilmnes vanuserühmades erineval määral,

enim naistel vanuses 60–79 aastat. Alates 1995. aastast on haigestumus peamiselt suurenenud I staadiumi arvelt, vähemal määral II staadiumi arvel. Samal ajal on vähenenud nii III kui IV staadiumi haigestumus. Kui I staadiumi haigestumus suurenes kõigis vanustes, siis III ja IV staadiumi langustrend ilmnes ainult naistel vanuses 50–69. Rinnavähisuremus on vähenenud alates 1997. aastast. Kiire suremuse langus on ilmnenud vanuserühmades 40–69 aastat, kuid 70aastastel ja vanematel naistel on suremus endiselt suurenenud. Haigestumus- ja suremustrendi ilmne lahknemine sajandivahetuse ümbruses näitab, et Eesti rinnavähimustrid on muutunud sarnaseks Lääne-, Põhja- ja Lõuna-Euroopa mustritega.

2. Sõeluuringule kutsutud sünnikohortides ilmnenud haigestumuspõhise suremuse vanuskõverad erinesid märgatavalt nii nooremates kui vanemates sünnikohortides täheldatust, kuna need lamenesid või hakkasid langema pärast sõeluuringu vanusesse jõudmist. Haigestumuspõhise suremuse võrdlus sõeluuringu käivitamisele eelnenud ja järgnenud 11aastase perioodi vältel näitas suurt suremuse langust noortel naistel (49%) ja 50–63aastastel naistel, keda kutsuti sõeluuringule (35%). 65aastastel ja vanematel naistel, keda tol perioodil sõeluuringule ei kutsutud, suremus ei vähenenud. Tulemused viitavad, et hoolimata madalast osalusmäärast on sõeluuring avaldanud kasulikku mõju rinnavähisuremusele Eestis.

3. Vaadeldud 27aastase uuringuperioodi jooksul suurenes rinnavähi viie aasta suhteline elulemus 18,5% võrra, kuid vanuseti ja staadiumiti trendid varieerusid. Elulemuse erinevus noorte naiste ja 70–79aastaste vahel vähenes märgatavalt. Kiirest kasvust hoolimata jääb III ja IV staadiumi elulemus alla parimaid tulemusi näitavatele riikidele. Kui koguelulemuse mahajäämus 10% võrra on tõenäoliselt tingitud hilisemast avastamisest, siis kaugelearenenud kasvajate kehvem elulemus viitab puudujääkidele rinnavähi ravis.

Edasised uurimissuunad ja poliitikasoovitused

Rinnavähisuremuse edasiseks vähendamiseks on vaja rakendada mõjutatavatele riskiteguritele suunatud esmase ennetuse meetmeid, tagada kvaliteetse sõeluuringuprogrammi läbiviimine vastavalt Euroopa Komisjoni soovitustele, vähendada viivitusi sümptomaatiliste patsientide diagnoosimisel ning tagada kaasaegsete ravimeetodite ja psühhosotsiaalse toe kättesaadavus vähipatsientidele. Uuringu tulemused toetavad seega Vähitõrje Tegevuskava 2021–2030 eesmärke. Arvestades rinnavähihaigestumuse aeglast, kuid püsivat suurenemist noortel naistel on esmases ennetuses eriti tähtis vähendada ekspositsiooni alkoholile, rasvumisele ja vähesele kehalisele aktiivsusele. Uuringutulemused toetavad hiljutist otsust laiendada sõeluuringu sihtrühma kuni 74. eluaastani, mis on kooskõlas Euroopa Komisjoni soovitusega. Samal ajal ei toeta tulemused nooremate vanusrühmade kaasamist mammograafilisse sõeluuringusse. Vajalikud on täiendavad uuringud, et selgitada, kas IV staadiumi haigestumuse tõus noorimas vanuserühmas on tingitud tõhusamast diagnostikast või muudest teguritest. Lisaks jätku-

vatele pingutustele sõeluuringu osalusmäära suurendamiseks on võtmetähtsusega sõeluuringu kvaliteediindikaatorite pidev jälgimine ning sõeluuringuprogrammiga peavad kaasnema selged sõnumid sõeluuringu võimaliku kasu ja kahjude kohta. Sõeluuringuregistri andmetele tuginedes on vajalik detailselt uurida sõeluuringul või muul viisil avastatud rinnavähijuhtude puhul rakendatud diagnostika ja ravimeetodeid, sh COVID-19 pandeemia mõjusid. Ravikvaliteedi indikaatorite pidev jälgimine aitaks tuvastada puudujääke diagnostikas ja ravis, mis võivad takistada elulemuse paranemist.

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14. PUBLICATIONS

15. CURRICULUM VITAE

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Education:

2020–	University of Tartu, Faculty of Medicine, PhD studies
1994–1995	Erasmus University Rotterdam, Master of Science in Epidemiology
1987–1992	University of Tartu, Department of Geography
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Work Experience:

2003–	National Institute for Health Development, Researcher (1,00)
2023–2024	University of Tartu, Faculty of Medicine, Institute of Family Medicine and Public Health, Junior Research Fellow in Epidemiology (0,50)
1995–2003	Institute of Experimental and Clinical Medicine, Researcher
1992–1994	Institute of Experimental and Clinical Medicine, Research assistant

Honours and Awards:

2023	National Research Award in Social Studies
2006	Research Award of the Estonian Society of Cardiology
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Main field of research: cancer epidemiology, statistical data analysis

Publications related to the thesis:

Baburin, A., Veerus, P., Lang, K., & Innos, K. (2024). Incidence-Based Breast Cancer Mortality Trends in Estonia Before and After the Introduction of Organized Mammography Screening: A Register-Based Study. *Cancer Control*, 31: 10732748241266491. https://doi.org/10.1177/10732748241266491

Innos, K., **Baburin, A.,** Hallik, R., & Veerus, P. (2022). Rinna-, emakakaela- ja jämesoolevähi sõeluuringute tulemused Eestis. *Eesti Arst*, 101, 281–290.

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Haridus:

2020–	Tartu Ülikool, Arstiteaduste osakond, doktoriõpe
1994–1995	Erasmuse Ülikool Rotterdam, magistriõpe epidemioloogias
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1973–1984	Tallinna 43. keskkool

Teenistuskäik:

2003–	Tervise Arengu Instituut, teadur (1,00)
2023–2024	Tartu Ülikool, Meditsiiniteaduste valdkond, Peremeditsiini ja rahvatervise instituut, epidemioloogia nooremteadur (0,50)
1995–2003	Researcher, Eksperimentaalse ja Kliinilise Meditsiini Instituut, teadur
1992–1994	Researcher, Eksperimentaalse ja Kliinilise Meditsiini Instituut, laborant

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2023	Riigi teaduspreemia sotsiaalteaduste valdkonnas
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Väitekirjaga seotud publikatsioonid:

Baburin, A., Veerus, P., Lang, K., & Innos, K. (2024). Incidence-Based Breast Cancer Mortality Trends in Estonia Before and After the Introduction of Organized Mammography Screening: A Register-Based Study. *Cancer Control*, 31: 10732748241266491. https://doi.org/10.1177/10732748241266491

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