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The Impact of Sociodemographic Factors on the Utilization of Radiation Therapy in Breast Cancer Patients in Estonia: a register-based study

Master thesis extended research article set

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Sotsiaaldemograafiliste tegurite mõju kiiritusravi kasutamisele rinnavähipatsientide seas: registripõhine uuring

Magistritöö

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Author’s declaration of originality

I hereby certify that I am the sole author of this work. All the used materials, references to the literature and the work of others have been referred to. This work submitted for thesis defence is based on the scientific article which is original work and has not been published before presenting to the publisher.

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Abstract

Radiation therapy is an important part of multimodal breast cancer treatment. The aim was to examine the impact of sociodemographic factors on radiation therapy use in breast cancer patients in Estonia, linking cancer registry data to administrative databases.

Estonian Cancer Registry provided data on women diagnosed with breast cancer in Estonia in 2007–2018. Use of radiation therapy within 12 months of diagnosis was determined from Estonian Health Insurance Funds claims, and sociodemographic characteristics from population registry. Receipt of radiation therapy was evaluated over time and by clinical and sociodemographic factors using Poisson regression with robust variance.

Overall, of 8637 women included in the study, 4310 (50%) received radiation therapy within 12 months of diagnosis. Compared to women with stage I breast cancer, those with more advanced stage were less likely to receive radiation therapy (for stage II, PRR 0.79, 95% CI 0.75–0.82; for stage III, PRR 0.93, 95% CI 0.88–0.97). Receipt of radiation therapy increased significantly over time. Use of radiation therapy was significantly lower for women with the lowest level of education compared to those with a university degree, and for divorced/widowed women compared to married women. Age at diagnosis, nationality and place of residence were not associated with receipt of radiation therapy.

The study showed considerable increase in the use of radiation therapy in Estonia over the study period. The lack of geographic variations suggests equal access to therapy for patients living in remote regions. However, educational level and marital status were significantly associated with receipt of radiation therapy, highlighting the importance of psychosocial support in ensuring equal access to care.

The thesis work is written in English and is in 60 pages, which includes 65 references and 1 appendix. The article word count is 3838 and contains 2 tables and 1 figure.

Keywords**:** breast cancer, radiation therapy, stage, sociodemographic factors, education, marital status, Estonia

Annotatsioon

Kiiritusravi moodustab tähtsa osa rinnavähi multimodaalsest ravist. Uuringu eesmärk oli hinnata sotsiaaldemograafiliste tegurite mõju kiiritusravi kasutamisele rinnavähipatsientide seas, kasutades vähiregistri andmete linkimist administratiivsete andmebaasidega.

Eesti Vähiregistrist saadi andmed naiste kohta, kellel diagnoositi Eestis aastatel 2007–2018 rinnavähk. Andmed kiiritusravi kohta, mis tehti 12 kuu jooksul alates diagnoosist, päriti Eesti Haigekassa raviarvete andmebaasist. Sotsiaaldemograafilised andmed saadi rahvastikuregistrist. Kiiritusravi kasutuse hindamiseks eri ajaperioodidel ning kliiniliste ja sotsiaaldemograafiliste tegurite lõikes arvutati riskisuhe (PRR) koos 95% usalduspiiridega (CI), kasutades robustse dispersiooniga Poissoni regressioonanalüüsi.

Uuringusse kaasatud 8637 naisest sai 12 kuu jooksul alates diagnoosist kiiritusravi 4310 naist (50%). Võrreldes naistega, kelle vähk oli diagnoosimisel I staadiumis, said hilisemas staadiumis rinnavähiga naised oluliselt vähem kiiritusravi (II staadiumi puhul PRR 0,79; 95% CI 0,75–0,82; III staadiumi puhul PRR 0,93; 95% CI 0,88–0,97). Kiiritusravi kasutamine suurenes uuringuperioodi vältel olulisel määral (40%). Madalama haridustasemega naised said oluliselt vähem kiiritusravi võrreldes kõrgharidusega naistega, samuti lahutatud/lesestunud naised võrreldes abielus naistega. Vanus diagnoosimisel, rahvus ja elukoht ei olnud seotud kiiritusravi kasutamisega.

Uuringutulemused näitasid, et kiiritusravi kasutus rinnavähi ravis suurenes Eestis uuringuperioodi vältel märkimisväärselt. Piirkondlike erinevuste puudumine viitab, et kiiritusravi on võrdselt kättesaadav ka nendele patsientidele, kes elavad keskustest kaugel. Küll aga oli kiiritusravi kasutamine olulisel määral seotud haridustaseme ja perekonnaseisuga, mis viitab vajadusele võimaldada patsientidele psühhosotsiaalset tuge, et ebasoodsamas olukorras inimestele oleks tagatud kvaliteetse ravi kättesaadavus.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 60 leheküljel, 65 kirjandusallikat ja 1 lisa. Artiklis sisaldub 3838 sõna, 2 tabelit ja 1 joonis.

Võtmesõnad: rinnavähk, kiiritusravi, staadium, sotsiodemograafilised tegurid, haridus, perekonnaseis, Eesti

List of abbreviations and terms

AJCC	American Joint Committee on Cancer
BC	Breast cancer
BCS	Breast conserving surgery
CI	Confidence intervals
DCO	Death certificate only
ECR	Estonian Cancer Registry
EHIF	Estonian Health Insurance Fund
ICD-O-3	3rd Edition of International Classification of Disease for Oncology
ICD-10	International Statistical Classification of Diseases and Health Problems 10th Revision
IGRT	Image-guided radiation therapy
IMRT	Intensity modulated radiation therapy
MV	Megavoltage
PRR	Prevalence rate ratio
RT	Radiation therapy
TNM	Tumour, Node and Metastasis

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Extension of Article

Fereshteh Shahrabi Farahani (2021). The impact of sociodemographic factors on the utilization of radiation therapy in breast cancer patients in Estonia: a register-based study. Extensions of research article as master thesis. Tallinn University of Technology. Healthcare Technology.

Background

The main subject field of this study is breast cancer (BC) which is a major health burden among women worldwide as well as in Estonia. Estimated BC incidence in Estonia was 109.6 per 100,000 in 2020, the fifth lowest in Europe [1]. However, estimated mortality from BC was 31.3 per 100,000, the ninth lowest in Europe in 2020 [1]. In 2018, 840 new cases of BC were diagnosed in Estonia [2]. The subcategory of this study is radiation therapy (RT) which is a cancer treatment in which high doses of radiation are used in order to destroy cancer cells.

Cancer stage at diagnosis is one of the most important determinants of cancer survival. Different systems are used to stage BC. One of the most common staging systems is the American Joint Committee on Cancer (AJCC) TNM system. TNM stands for Tumour, Node and Metastasis and refers to the extent (size) of tumour, spread to nearby lymph nodes and spread (metastasis) to distant sites [3]. Furthermore, BC has 5 general stages which are expressed as a number on a scale of 0 through IV with stage 0 indicating non-invasive BC and stage IV indicating advanced BC that has spread to distant body parts [3].

BC treatments can be various combinations of surgery, RT, systemic therapy and hormone therapy. Selection of therapy depends on the tumour burden (size and location of primary tumour, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression), as well as the age, menopausal status, general health status and preferences of the patient [4].

In early BC, RT is the standard of care after breast-conserving surgery (BCS) and it is sometimes also indicated after mastectomy [4]. Studies have shown that RT helps to decrease the risk of local recurrence or death in BC patients after breast conserving surgery [5]–[7]. Patients with locally advanced disease may receive RT in combination with surgery and systemic therapy or if surgery is declined or impractical after systemic treatment [8]. In patients with metastatic disease, RT may be considered to treat the symptoms of the primary tumour or distant metastases and improve quality of life [8].

RT in Estonia is done at two specialist cancer centres, located in Tallinn (the capital of Estonia) and in Tartu (a university town in Southern Estonia). During 2007–2011, three megavoltage (MV) units were in use; one was added in 2011, and two more in 2016, which currently totals 4.6 MV units per million population [9]. The machines are of linear accelerator type which can deliver high precision conformal treatments including intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT).

Although overall BC incidence has increased in Estonia [10], mortality from BC has decreased steadily since 2000 [11]. However, there's still a survival gap between Estonia and more developed countries [12], despite rapid increase observed since 1990s, particularly for locally/regionally spread cancers [13]. BC five-year relative survival ratio in Estonia was 81% in 2012–2016 [14], whereas the survival of BC patients in the Nordic countries was approximately 90% for the same period according to NORDCAN [15].

Cancer survival is affected by both early detection and the effectiveness of treatment. As the proportion of BC cases diagnosed at early stage is lower in Estonia than in many other European countries [16], this is probably the main reason for inferior survival. A nationwide BC screening program was launched in Estonia in 2004 and women aged 50–59 years were initially invited for mammography screening. The upper age limit was raised to 62 years in 2007, and only since 2018, target age group has been extended to 50–69 years which is the recommended age group for regular screening [17]. Although nationwide screening can contribute to improving BC survival through earlier diagnosis of cancer and quick initiation of treatment [18], low participation rate is one of the problems of organized screening in Estonia. For instance, participation rates in BC nationwide screening in 2017, 2018 and 2019 were 55%, 52%, 55%, respectively [19]. As organized screening has been only available to women with valid health insurance,

the actual rate of women in target group who were screened is even lower [20]. However, the role of treatment in inferior BC survival should be considered as well.

Social and geographic variations in receipt of BC treatments have been widely documented in different settings and populations [21]–[31]. In Estonia, there have been reports demonstrating regional and sociodemographic disparities in overall health status, cancer mortality, and BC early detection [20], [33]–[35]. The use of RT in women with BC in Estonia has previously been studied only within the framework of international high-resolution studies [16], [36]. Although the population-based Estonian Cancer Registry (ECR) collects limited data on treatment, there have been concerns about the completeness of these data. Also, no data are available on the association of RT utilization with individual sociodemographic factors.

The aim of the study was to examine the utilization of RT among BC patients in Estonia over time, by sociodemographic factors and stage at diagnosis, combining data from the cancer registry and other population-based databases. An additional aim was to assess the completeness of RT data at the ECR. The research questions were addressed as follows:

1. What is the proportion of BC patients receiving RT in Estonia and has it changed over time?
2. Do sociodemographic factors such as age at diagnosis, region of residence, nationality, educational level, and marital status affect receipt of RT among BC patients in Estonia? And to what extent?
3. Is RT utilization associated with BC stage at diagnosis in Estonia?
4. Is RT data recorded at the ECR complete? What proportion of RT data of BC patients is missing from the ECR?

Understanding the reasons for disparities in receipt of RT for different geographic locations and subpopulations may allow the improvement of access to RT for BC patients by attempting to modify the causes that contribute to inequalities.

Subjects and methods

Information on BC cases diagnosed in 2007–2018 was retrieved from the ECR, a population-based registry with nation-wide coverage (population 1.3 million). The ECR was founded in 1978, and reliable incidence data are available from 1968 [37]. It is

compulsory for all physicians and pathologists working in Estonia to report cancer cases to cancer registry. Additionally, the ECR uses multiple sources to ascertain cancer cases including regular comparisons on new cases with two cancer centres and trace-back of cases identified via death certificates. The ECR uses the 3rd edition of International Classification of Diseases for Oncology (ICD-O-3) for coding topography and morphology of the tumours.

The ECR provided data on all invasive BC cases (ICD-O-3 topography codes C50.0–C50.9) diagnosed in Estonia between 2007 and 2018, regardless of cancer sequence (n=8804). Data were collected using the same notification form during the study period. Male patients (n=68) and those with stage 0 disease (n=10) were excluded from the analysis. Also, cancer cases that were not registered in life, i.e., cases that were registered based solely on information from death certificates (death certificate only (DCO) cases, n=69), and cases detected at autopsy (n=20) were excluded from the analysis. The data obtained from the ECR included personal data, and data on diagnosis (date of diagnosis, age, and stage at diagnosis). Age at diagnosis was collapsed into four categories: <50, 50–59, 60–69, ≥70 years. Stage at diagnosis was categorized according to the AJCC TNM classification version 7. Period of diagnosis was divided into four three-year categories to account for the changes in the availability of RT equipment: 2007–2009, 2010–2012, 2013–2015 and 2016–2018. Region of residence was collapsed into five categories: Northern, Western, Central, North-Eastern and Southern Estonia.

Additional data on treatment was retrieved from the Estonian Health Insurance Fund (EHIF) database. Central electronic database of EHIF is a reimbursement database which contains claims for all medical procedures performed in insured persons including dates of services and diagnostic codes according to International Statistical Classification of Diseases and Health Problems 10th Revision (ICD-10). Healthcare financing in Estonia is based on mandatory health insurance since 1992. Health insurance tax is paid by employers for their employees, and by the state for other categories of insured people (e.g., children, retired and unemployed persons, pregnant women). In general, 95% of the population is covered by health insurance [38]. Health insurance covers a broad range of curative and preventive services, including standard cancer care. For BC cancer cases included in the study, EHIF provided data on claims for RT (separately for RT planning and procedures), chemotherapy, and surgery for 2007–2019. The primary outcome was defined as receipt of RT, based on claims filed for at least one RT procedure performed

within 12 months of diagnosis. The time frame was set to account for radiation performed during initial course of therapy. Time between diagnosis and RT was calculated from the date of cancer diagnosis to the date of starting RT. RT was considered as not received for cases for whom EHIF database included claims only for RT planning. All patients with claims for breast surgery dated within 12 months of diagnosis were considered as having had primary surgery.

The validity of RT data from EHIF was checked against an existing high-resolution database collected for a previous study including diagnosis and treatment data for BC cases diagnosed in 2011 from the medical records of cancer centres and other hospitals [9].

As an additional analysis, the completeness of RT data at the ECR was evaluated by comparing RT data reported to the ECR on cancer notification form to RT data obtained from EHIF. All cases for whom RT was reported on cancer notification form were compared to data on EHIF bills in order to distinguish the cases who received RT but were not reported to the ECR and also cases who didn't receive RT but were reported mistakenly.

Data on sociodemographic variables (nationality, education, and marital status) for BC cases included in the study were obtained from the population registry. Population registry is a national database maintained and developed by Estonian government and contains main personal information on all Estonian citizens and residents. Nationality was grouped into Estonian, other nationalities, and unknown. Educational level was categorised as university and higher education, secondary studies plus vocational education, secondary studies, basic or primary studies and unknown. Marital status was classified as married, divorced/widowed, single, and unknown.

Statistical analysis was performed with statistical software Stata 16 [39]. Chi-square test was used to compare proportions between groups. Two-sided p-value <0.05 was considered statistically significant. Odds ratios or risk ratios can be useful methods for summarizing cross-sectional studies with binary outcome variable [40]. The prevalence rate ratio (PRR) for receipt of RT with 95% confidence intervals (CI) was calculated using Poisson regression models with robust variance. This method was selected because the odds ratio calculated with logistic regression tends to overestimate the association

between variables when the prevalence is moderate to high [40]. Univariate analysis and multivariate analysis were performed using Generalized Linear Models with Poisson family with log link function. In regression modelling, women with stage I–III cancer, age <70 at diagnosis who underwent primary surgery were included to account for treatment guidelines. Cases with 'unknown' educational level, marital status or nationality were excluded from the modelling.

This study involves only register-based data and data subjects were not approached directly. Data linkages were done using unique personal identification numbers, which have been in use in Estonia since 1992. One of the main ethical concerns in data linkage studies is privacy and data protection [41]. Strict privacy measures including encryption were undertaken during data collection and transport to avoid data breach. For the purpose of linking together individual data from different databases, it was necessary to enable identification. Identifiable data were only used for data collection and quality control purposes. Subsequently, personal identifiers were removed, and coded data were used for analysis. These data were used without informed consent according to the Estonian Personal Data Protection Act, as it was not feasible to obtain informed consent from all individuals and their right was not damaged and the study outcome was in interest of public.

The study was conducted as part of the team grant project "Optimizing cancer care and outcomes: a population-based real-world approach", funded by the Estonian Research Council (grant no PRG722). The study protocol was approved by the Tallinn Medical Research Ethics Committee (Decision no 2652, March 12, 2019) and by the Research Ethics Committee of the National Institute for Health Development (Decision no 438, September 23, 2020).

Results

Conducted research fulfilled the aims of the study and identified factors that affect the utilization of RT in Estonia.

This population-based record linkage study of over 8600 BC patients demonstrated that receipt of RT was significantly associated with patients' educational level and marital status and increased considerably over time.

All research questions were answered within study. Among the total of 8637 women who met the inclusion criteria for this study, 50% received RT (Table 1, Appendix 1). The utilization of RT increased considerably over time (Table 1, Appendix 1). A 40% increase in receipt of RT was observed over the study period (Table 2, Appendix 1). Among women aged <70 years who underwent primary surgery, a significant increase of RT use over time was seen for stages I to III (Figure 1, Appendix 1). The largest increase was seen for stage III, from 55% to 86%.

RT utilization was highest in age group 50–59 (Table 1, Appendix 1). Age showed a slight reverse U-shape association with RT use, which was borderline significant (Table 2, Appendix 1). Study found significant impact of the patients' educational level and marital status on receipt of RT (Table 2, Appendix 1). Women with the lowest level of education were significantly less likely to receive RT than other educational categories. Also, divorced/widowed women and single women had lower rates of RT utilization than married women. Study did not find significant associations between RT utilization and nationality or place of residence (Table 2, Appendix 1).

RT use was also associated with stage, with stage I patients having the highest rates and stage II patients the lowest (Table 2, Appendix 1).

Evaluation of the completeness of RT information at ECR showed that RT information was not complete at ECR and data was missing for 31.2% of cases for whom RT was performed within 12 months of diagnosis according to EHIF data. The proportion of missing RT information was 33%, 27%, 33%, 28% and 38% for stages I, II, III, IV and unknown, respectively.

The primary outcome variable, receipt of RT within 12 months of diagnosis, identified from insurance claims, was validated against data collected for a previous high-resolution study. There was a 99.4% agreement as two cases who were reported to have undergone RT according to medical records had no claims in the EHIF database.

Discussion

The study demonstrated that the availability of RT increased considerably over time for Estonian BC patients. While there were no regional differences, the results suggest some

social inequalities in receipt of RT. The study did not address adherence to clinical guidelines.

The main strength of the study was the identification of BC cases from a high-quality cancer registry, with additional data on cancer treatment and sociodemographic factors obtained from two large national databases through individual linkages. Insurance claims have not been previously used to identify cancer treatment in Estonia. The validation of the primary RT variable against data collected from medical records showed a 99.4% agreement between these databases. The likely explanation for the minor discrepancy (two cases with missing insurance claims) is that data from medical records were collected from multidisciplinary meeting notes, which recorded treatment that was planned, but not actually performed. There were 17 cases identified from EHIF that had claims for RT planning, but no procedures. The study demonstrated the ability to use insurance claims data to define variables of cancer treatment. This is particularly important, as the additional analysis showed inadequate completeness of RT data reported to ECR and using ECR data only can lead to underestimation of the use of RT.

The main limitations of this study are lack of data on comorbidities, performance status and molecular profile of tumours, which may seriously affect the choice of treatment and the administration of RT. Also, data of patient refusals was not available which may play a large role. However, the analysis was limited to surgically treated patients, as a proxy for overall health status or patient compliance, to account for factors that this study was not able to measure. The focus was on sociodemographic factors, so examining the utilization of RT according to mode of surgery (BCS versus mastectomy) was beyond the scope of this paper.

In 2007–2018, half of the study population received RT within 12 months from diagnosis, which is comparable to data from the United States (51% during 2009–2018) [42]. Overall RT utilization reached 58% for 2016–2018, which is somewhat lower than the 63% shown for England in 2013–2014 [43]. Stage-specific RT utilization in England was 70%, 65% and 80%, for stages I, II and III, respectively, compared to Estonian respective estimates of 68%, 59% and 68% during 2016–2018 (data not shown). The proportion of stage IV patients receiving RT was considerably lower in Estonia (11% in 2016–2018, data not shown) compared to both United States and England.

Lower RT utilization in Estonia is in line with lower availability of RT equipment – in 2012, the total number of MV units in Estonia was 3.0 per million population, while it was 5.1 in England [44]. The finding that RT utilization increased over time is consistent with the increasing number of MV units in Estonia, and with prior studies conducted in other countries including the United States and Canada [25], [27]. A recent study showed that the proportion of early BC (T1N0M0) patients in Estonia receiving breast-conserving surgery followed by RT increased drastically from 9% in 1997 to 75% in 2011 [16]. Nevertheless, the same study showed that the use of breast-conserving surgery followed by RT in Estonia in women with stage I/IIA BC diagnosed 2009–2013 was the second lowest after Portugal among nine European countries [16]. The increase in RT use has been gradual and does not seem to be directly related to new MV units. The number of MV units per million population achieved in 2016 is still lower than the median of 5.3 of 28 European countries in 2012 [44].

Consistent with previous studies showing association between age at diagnosis and receipt of RT [25], [26], [28], the oldest patients had the lowest rate of RT in this study. RT utilization was the highest among women aged 50–59. It has been reported previously that mortality from BC among patients aged 50–59 in Estonia has significantly declined since 2000, while it did not decrease among women aged ≥60 over the same time period [11]. Whereas these trends are consistent with screening activities, as women aged 50–59 have been the target age group for organized mammography screening since 2004 [20], the impact of RT in combination with other therapies can be considered as well. Overall, women aged 70 years and over received considerably less RT than younger women, which is in line with growing evidence over the time period under study suggesting no benefit for women in this age group in early disease [45], [46]. Women under 50 years of age were less likely to receive RT than women aged 50–59, which may be associated with higher proportion of genetically determined cancers in this age group and recommendations to use mastectomy rather than BCS and RT in breast cancer gene (BRCA) positive cases [47].

Previous studies have revealed that early-stage BC patients residing in locations with poor access to RT facilities are more likely to receive mastectomy instead of BCS due to required daily trips to RT centres [22], [32]. Thus, one of the hypotheses of the study was that geographical distance from cancer centres is associated with receipt of RT. The islands of Western Estonia and the North-Eastern part of the country could be considered

the most remote. Northern and Western Estonia are serviced by the cancer centre in Tallinn, while Southern Estonia is serviced by the centre in Tartu. The rest of the regions are partly covered by both centres. However, no differences were observed by region of residence in multivariate analysis, even though overall receipt of RT was highest among women living in Southern Estonia and lowest among those living in Western Estonia. As living in rural areas and geographically remote areas have been shown to be one of the barriers to receipt of RT [24], [28]–[30], equal access to RT regardless of geographic factors in Estonia can be partly attributed to the opportunity to stay at the hospital for the duration of treatment, but also to urban life style of majority of Estonian populations. According to Statistics Estonia, approximately two-thirds of population in Estonia live in urban regions. Among people living in rural areas, those living in the suburbs of Tallinn, Tartu and Pärnu have urban lifestyles [48]. The finding of no association with place of residence is encouraging and suggests equal access to RT in Estonia regardless of geographic factors.

However, findings of this study demonstrate a strong impact of education and marital status on the use of RT. Educational level as an indicator of socioeconomic status has been shown to be associated with poorer health outcomes in Estonia, partly mediated by lower access to health care [33]–[35], [49]. Factors influencing receipt of optimal cancer treatment can be divided into three main categories: structural factors, factors affecting physician recommendation and factors affecting patient's decision making [50]. Even though structural barriers such as lack of health insurance may affect timely presentation, all patients in Estonia who receive a cancer diagnosis obtain insurance coverage and consequently, access to standard treatment. Besides clinical factors, physicians' recommendations may be influenced by their perception of patient's ability to comply with treatments, while patient-related factors include socioeconomic status, access to transportation, ability to take time off from work, but also patients' attitudes towards treatments and their beliefs [50]. Finding that higher level of education was a considerable predictor of increased RT utilization is consistent with prior studies [26], [51] and may be related to both physician- and patient-related factors. Several studies have observed that patients with higher level of education were more likely to receive BCS in comparison to other types of surgeries [23], [52]–[54]. Patients with lower socioeconomic status may struggle to cope with healthcare systems, have misperceptions about treatment

benefits and may be more likely to have difficulties in overcoming adverse effects of treatment or psycho-social problems [50].

Previous studies have reported lower BC survival among women with lower education independent of screening mammography and cancer stage at diagnosis, which play an important role in BC mortality [55], [56]. Although there's not a single element in BC care that can explain mortality disparities, it is essential to identify the importance of educational variations in access to optimal treatment in BC patients to reduce the variation in health outcomes.

Similar to previous studies [24], [57], women who did not have a partner failed to receive RT as often as married women. Furthermore, previous studies have shown marital status is a predictor of cancer survival [58]–[62]. Longer survival of married individuals can be attributed to increased social support and improved economic status [63]. Studies have shown unmarried women are more concerned about insufficient care after their treatment, and seeking help and transportation in comparison to married women and are thus more prone to refuse intense treatments and decline therapies such as axillary dissection and RT [64]. Such concerns can also have an impact on physician recommendations and physicians may be less likely to offer intense treatments to unmarried older women [61]. It might be beneficial for healthcare providers to identify unmarried women and provide comprehensive case managements to reduce health disparities. Studies have shown implementing nurse case management has improved receipt of RT among older BC patients, particularly those with poor social support [65].

These findings may be useful to target interventions to reduce disparities. The results have important implications for policymaking and evidence-based decisions. To minimise disparities in BC outcomes and avoid inequitable delivery of RT in Estonia, the healthcare and social system need a stronger focus on patient-centred care, offering patients psychosocial support, helping them cope with the disease and treatment effects and overcome any barriers to treatment.

The key takeaways from the article are the following:

- Study showed the ability to use administrative databases as an additional source for identifying individual cancer treatment data if such data are not complete at a cancer registry.

- The study showed considerable increase in the use of RT in Estonia over the study period, which is in line with increases in available equipment.

- The lack of geographic variations suggests equal access to therapy for patients living in remote regions.

- Unmarried women and those with lower educational level received less RT compared to their counterparts.

Further studies are needed to identify the exact mechanisms behind these findings to clarify the underlying reasons for lower receipt of RT among unmarried woman and women with lower level of education, but some of the likely reasons are misperceptions about treatment benefits, loss of social support and economical disadvantages. Additional research into effect of these disparities on BC outcome is also warranted.

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This study was formed as a scientific research article and was submitted to International Journal for Equity in Health on 31/03/2021. Journal's 5-year impact factor is 3.020 and is ranked 29/239 in health policy in 2019. Focus of this journal is on examining the political, policy-related, economic, social, and health-related influences as well as identifying differences and inequalities in distributions of one or more aspects of health in different subpopulations.

Article was structured according to the requirements of journal and consists of 3838 words, 2 tables, 1 figure and 57 references.

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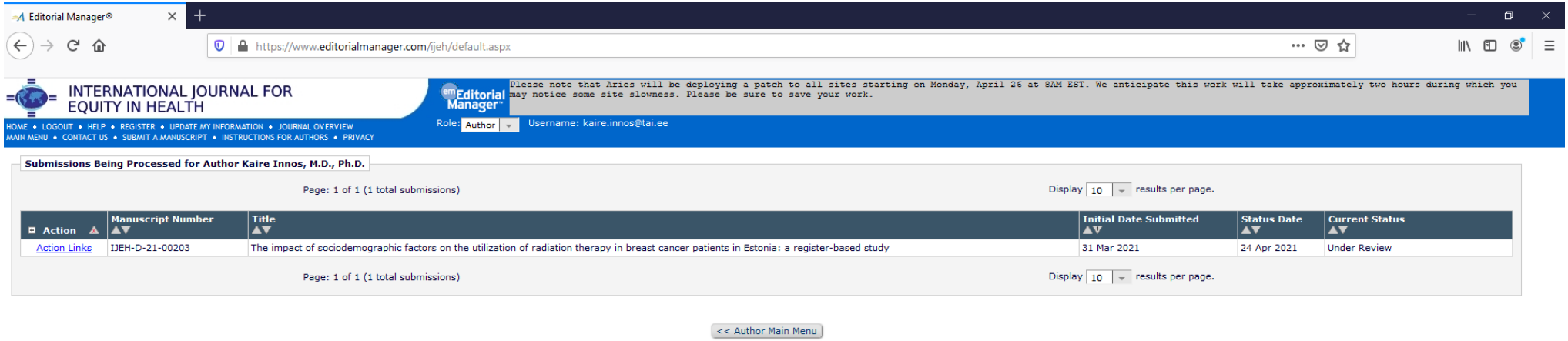
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The Impact of Sociodemographic Factors on the Utilization of Radiation Therapy in Breast Cancer Patients in Estonia: a register-based study

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Funding Information:	Eesti Teadusagentuur (PRG722) — Dr. Kaire Innos
Abstract:	Background Radiation therapy is an important part of multimodal breast cancer treatment. The aim was to examine the impact of sociodemographic factors on radiation therapy use in breast cancer patients in Estonia, linking cancer registry data to administrative databases. Methods Estonian Cancer Registry provided data on women diagnosed with breast cancer in Estonia in 2007–2018, including TNM stage at diagnosis. Use of radiation therapy within 12 months of diagnosis was determined from Estonian Health Insurance Funds claims, and sociodemographic characteristics from population registry. Receipt of radiation therapy was evaluated over time and by clinical and sociodemographic factors. Poisson regression with robust variance was used to calculate univariate and multivariate prevalence rate ratios (PRR) with 95% confidence intervals (CI) for receipt of radiation therapy among stage I–III breast cancer patients age <70 years who underwent primary surgery. Results Overall, of 8637 women included in the study, 4310 (50%) received radiation therapy within 12 months of diagnosis. This proportion increased from 39% to 58% from 2007–2009 to 2016–2018 ($p<0.001$). Multivariate regression analysis showed that compared to women with stage I breast cancer, those with more advanced stage were less likely to receive radiation therapy (for stage II, PRR 0.79, 95% CI 0.75–0.82; for stage III, PRR 0.93, 95% CI 0.88–0.97). Receipt of radiation therapy increased significantly over time and was nearly 40% higher in 2016–2018 than in 2007–2009. Use of radiation therapy was significantly lower for women with the lowest level of education compared to those with a university degree, and for divorced/widowed women compared to married women. Age at diagnosis, nationality and place of residence were not associated with receipt of radiation therapy. Conclusions The study showed considerable increase in the use of radiation therapy in Estonia over the study period, which is in line with increases in available equipment. The lack of geographic variations suggests equal access to therapy for patients living in remote regions. However, educational level and marital status were significantly associated with receipt of radiation therapy, highlighting the importance of psychosocial support in ensuring equal access to care.
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The Impact of Sociodemographic Factors on the Utilization of Radiation Therapy in Breast Cancer Patients in Estonia: a register-based study

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Abstract

Background Radiation therapy is an important part of multimodal breast cancer treatment. The aim was to examine the impact of sociodemographic factors on radiation therapy use in breast cancer patients in Estonia, linking cancer registry data to administrative databases.

Methods Estonian Cancer Registry provided data on women diagnosed with breast cancer in Estonia in 2007–2018, including TNM stage at diagnosis. Use of radiation therapy within 12 months of diagnosis was determined from Estonian Health Insurance Funds claims, and sociodemographic characteristics from population registry. Receipt of radiation therapy was evaluated over time and by clinical and sociodemographic factors. Poisson regression with robust variance was used to calculate univariate and multivariate prevalence rate ratios (PRR) with 95% confidence intervals (CI) for receipt of radiation therapy among stage I–III breast cancer patients age <70 years who underwent primary surgery.

Results Overall, of 8637 women included in the study, 4310 (50%) received radiation therapy within 12 months of diagnosis. This proportion increased from 39% to 58% from 2007–2009 to 2016–2018 ($p<0.001$). Multivariate regression analysis showed that compared to women with stage I breast cancer, those with more advanced stage were less likely to receive radiation therapy (for stage II, PRR 0.79, 95% CI 0.75–0.82; for stage III, PRR 0.93, 95% CI 0.88–0.97). Receipt of radiation therapy increased significantly over time and was nearly 40% higher in 2016–2018 than in 2007–2009. Use of radiation therapy was significantly lower for women with the lowest level of education compared to those with a university degree, and for divorced/widowed women compared to married women. Age at diagnosis, nationality and place of residence were not associated with receipt of radiation therapy.

Conclusions The study showed considerable increase in the use of radiation therapy in Estonia over the study period, which is in line with increases in available equipment. The lack of geographic variations suggests equal access to therapy for patients living in remote regions. However, educational level and marital status were significantly associated with receipt of radiation therapy, highlighting the importance of psychosocial support in ensuring equal access to care.

Keywords: breast cancer, radiation therapy, stage, sociodemographic factors, education, marital status, Estonia

Background

Breast cancer (BC) is a major health burden among women worldwide as well as in Estonia. Although overall BC incidence has increased in Estonia (1), mortality from BC has decreased steadily since 2000 (2). However, there's still a survival gap between Estonia and more developed countries (3), despite rapid increase observed since 1990s, particularly for locally/regionally spread cancers (4). BC five-year survival ratio in Estonia was 81% in 2012–2016 (5), whereas the survival of BC patients in the Nordic countries was approximately 90% for the same period according to NORDCAN (6).

Survival is affected by both early detection and the effectiveness of treatment. As the proportion of BC cases diagnosed at early stage is lower in Estonia than in many other European countries (7), this is probably the main reason for inferior survival. However, the role of treatment should be considered as well.

In early BC, radiation therapy (RT) is the standard of care after breast-conserving surgery (BCS) and it is sometimes also indicated after mastectomy (8). Studies have shown that RT helps to decrease the risk of local recurrence or death in BC patients after breast

conserving surgery (9–11). Patients with locally advanced disease may receive RT in combination with surgery and systemic therapy or if surgery is declined or impractical after systemic treatment (12). In patients with metastatic disease, RT may be considered to treat the symptoms of the primary tumour or distant metastases and improve quality of life (12).

Social and geographic variations in receipt of BC treatments have been widely documented in different settings and populations (13–24). In Estonia, there have been reports demonstrating regional and sociodemographic disparities in overall health status, cancer mortality, and BC early detection (25–28). The use of RT in women with BC in Estonia has previously been studied only within the framework of international high-resolution studies (7,29). Although the population-based Estonian Cancer Registry (ECR) collects limited data on treatment, there have been concerns about the completeness of these data. Also, no data are available on the association of RT use with individual sociodemographic factors.

The aim of the study was to examine the utilization of RT among BC patients in Estonia over time, by sociodemographic factors and stage at diagnosis, combining data from the cancer registry and other population-based databases. An additional aim was to assess the completeness of RT data at the ECR.

Materials and Methods

Information on BC cases diagnosed in 2007–2018 was retrieved from the ECR, a population-based registry with nation-wide coverage (population 1.3 million). ECR was founded in 1978, and reliable incidence data are available from 1968 (30). It is compulsory for all physicians and pathologists working in Estonia to report cancer cases to ECR. Additionally, ECR uses multiple sources to ascertain cancer cases including

regular comparisons on new cases with two cancer centres and trace-back of cases identified via death certificates. ECR uses the 3rd edition of International Classification of Diseases for Oncology (ICD-O-3) for coding topography and morphology of the tumours.

ECR provided data on all invasive BC cases (ICD-O-3 topography codes C50.0–C50.9) diagnosed in Estonia between 2007 and 2018, regardless of cancer sequence (n=8804). Data were collected using the same notification form during the study period. Male patients (n=68), those with stage 0 disease (n=10), death certificate only cases (n=69), and autopsy cases (n=20) were excluded from the analysis. The data obtained from the ECR included personal data, and data on diagnosis (date of diagnosis, age, and stage at diagnosis). Age at diagnosis was collapsed into four categories: <50, 50–59, 60–69, ≥70 years. Stage at diagnosis was categorized according to the Union for International Cancer Control TNM classification version 7. Period of diagnosis was divided into four three-year categories to account for the changes in the availability of RT equipment: 2007–2009, 2010–2012, 2013–2015 and 2016–2018. Region of residence was collapsed into five categories: Northern, Western, Central, North-Eastern and Southern Estonia.

Additional data on treatment was retrieved from the Estonian Health Insurance Funds (EHIF) database. Central electronic database of EHIF is a reimbursement database which contains claims for all medical procedures performed in insured persons including dates of services and diagnostic codes according to International Statistical Classification of Diseases and Health Problems 10th Revision (ICD-10). Healthcare financing in Estonia is based on mandatory health insurance since 1992. Health insurance tax is paid by employers for their employees, and by the state for other categories of insured people (e.g., children, retired and unemployed persons, pregnant women). In general, 95% of the population is covered by health insurance (31). Health insurance covers a broad range of

curative and preventive services, including standard cancer care. For BC cases included in the study, EHIF provided data on claims for RT (separately for RT planning and procedures), chemotherapy, and surgery for 2007–2019. The primary outcome was defined as receipt of RT, based on claims filed for at least one RT procedure performed within 12 months of diagnosis. The time frame was set to account for radiation performed during initial course of therapy. Time between diagnosis and RT was calculated from the date of cancer diagnosis to the date of starting RT. RT was considered as not received for cases for whom EHIF database included claims only for RT planning. All patients with claims for breast surgery dated within 12 months of diagnosis were considered as having had primary surgery.

The validity of EHIF RT data was checked against an existing high-resolution database collected for a previous study including diagnosis and treatment data for BC cases diagnosed in 2011 from the medical records of cancer centres and other hospitals (32).

As an additional analysis, we evaluated the completeness of RT data at the ECR, comparing RT data reported to the ECR on cancer notification form to RT data obtained from EHIF.

Data on sociodemographic variables for BC cases included in the study were obtained from the population registry. Population registry is a national database maintained and developed by Estonian government and contains main personal information on all Estonian citizens and residents. Nationality was grouped into Estonian, other nationalities, and unknown. Educational level was categorised as university and higher education, secondary studies plus vocational education, secondary studies, basic or primary studies and unknown. Marital status was classified as married, divorced/widowed, single, and unknown.

Data linkages were done using unique personal identification numbers, which have been in use in Estonia since 1992.

Statistical analysis was performed with statistical software Stata 16 (33). Chi-square test was used to compare proportions between groups. Two-sided p-value <0.05 was considered statistically significant. The prevalence rate ratio (PRR) for receipt of RT with 95% confidence intervals (CI) was calculated using univariate and multivariate Poisson regression models with robust variance, performed with generalized linear models with Poisson family and log link function in Stata. This method was selected because the odds ratio calculated with logistic regression tends to overestimate the association between variables when the prevalence is moderate to high (34). In regression modelling, we included women with stage I–III cancer, age <70 at diagnosis who underwent primary surgery, to account for treatment guidelines. Cases with 'unknown' educational level, marital status or nationality were also excluded from modelling.

The study protocol was approved by the Tallinn Medical Research Ethics Committee.

Results

In total, 8637 women met the inclusion criteria for this study. Patient demographics, stage distribution and receipt of treatment are shown in Table 1. Overall, half of the patients received RT. Receipt of RT increased considerably over time, was highest in age group 50–59 and at stage I. RT use was also associated with educational level, marital status, and region of residence. Patients who received primary surgical treatment or chemotherapy, were more likely to receive RT than those who did not receive these treatments.

Among women aged ≥70 years who underwent primary surgery, a significant increase of RT use over time was seen for stages I to III (Figure 1). The largest increase was seen for stage III, from 55% to 86%.

Table 2 presents the results of regression modelling for women with stage I–III cancer aged <70 years at diagnosis who underwent primary surgery. The associations observed in univariate analysis remained apparent after adjusting for other variables. A 40% increase in receipt of RT was observed over the study period. Women with the lowest level of education were significantly less likely to receive RT than other educational categories. Also, divorced/widowed women and single women had lower rates of RT utilization than married women. RT use varied by stage, with stage I patients having the highest rates and stage II patients the lowest. Age showed a slight reverse U-shape association with RT use, which was borderline significant. No associations were observed across regions of residence or by nationality.

The primary outcome variable, receipt of RT within 12 months of diagnosis, identified from insurance claims, was validated against data collected for a previous high-resolution study. There was a 99.4% agreement as two cases who were reported to have undergone RT according to medical records had no claims in the EHIF database.

Evaluation of the completeness of RT information at ECR showed that RT information was missing for 31.2% of cases for whom RT was performed within 12 months of diagnosis according to EHIF data. The proportion of missing RT information was 33%, 27%, 33%, 28% and 38% for stages I, II, III, IV and unknown, respectively. In addition, for 6.8% of cases with reported RT, there was no date at ECR, and the timing of RT could not be assessed. There was a 99.2% agreement between EHIF and ECR for not receiving RT. Among the 33 cases with discordant information, 11 cases did not have any claims

at EHIF, for 5 cases, there was a claim only for RT planning, and for 17 cases, RT was performed later that 12 months since diagnosis, but there was no date at ECR to assess the timing of RT.

Discussion

In this population-based record linkage study of over 8600 women with BC, we found a significant impact of the patients' educational level and marital status on receipt of RT. The utilization of RT increased considerably over time, particularly for stages II and III. We did not find significant associations between RT utilization and nationality or place of residence.

The main strength of the study was the identification of BC cases from a high-quality cancer registry, with additional data on cancer treatment and sociodemographic factors obtained from two large national databases through individual linkages. Insurance claims have not been previously used to identify cancer treatment in Estonia. The validation of the primary RT variable against data collected from medical records showed a 99.4% agreement between these databases. The likely explanation for the minor discrepancy (two cases with missing insurance claims) is that data from medical records were collected from multidisciplinary meeting notes, which recorded treatment that was planned, but not actually performed. There were 17 cases identified from EHIF that had claims for RT planning, but no procedures. The study demonstrated the ability to use insurance claims data to define variables of cancer treatment. This is particularly important, as the additional analysis showed inadequate completeness of RT data reported to ECR and using ECR data only could lead to underestimation of the use of RT.

The main limitations of this study are lack of data on comorbidities, performance status and molecular profile of tumours, which may seriously affect the choice of treatment and

the administration of RT. We did not have any data on patient preferences, which may play a large role. However, we limited the analysis to surgically treated patients, as a proxy for overall health status or patient compliance, to account for factors that we were not able to measure. The focus was on sociodemographic factors, so examining the utilization of RT according to mode of surgery (BCS versus mastectomy) was beyond the scope of this paper.

In 2007–2018, half of the study population received RT within 12 months from diagnosis, which is comparable to data from the United States (51% during 2009–2018) (35). Overall RT utilization reached 58% for 2016–2018, which is somewhat lower than the 63% shown for England in 2013–2014 (36). Stage-specific RT utilization in England was 70%, 65% and 80%, for stages I, II and III, respectively, compared to Estonian respective estimates of 68%, 59% and 68% during 2016–2018 (data not shown). The proportion of stage IV patients receiving RT was considerably lower in Estonia (11% in 2016–2018, data not shown) compared to both United States and England. Less frequent RT use in Estonia may be partly associated with higher prevalence of comorbidities. Among early BC patients, the proportion of women with no comorbidities was the lowest in Estonia among nine European countries (7).

However, lower RT utilization in Estonia is also in line with inferior availability of RT equipment – in 2012, the total number of megavoltage (MV) units in Estonia was 3.0, while it was 5.1 in England (37). RT in Estonia is done at two specialist cancer centres, located in Tallinn (the capital of Estonia) and in Tartu (a university town in Southern Estonia). During 2007–2011, three MV units were in use; one was added in 2011, and two more in 2016, which currently totals 4.6 MV units per million population (32). The machines are of linear accelerator type which can deliver high precision conformal treatments including intensity modulated radiotherapy (IMRT) and image-guided

radiotherapy (IGRT). Our finding that RT utilization increased over time is consistent with these developments, and with prior studies conducted in other countries including the United States and Canada (19,21). A recent study showed that the proportion of early BC (T1N0M0) patients in Estonia receiving breast-conserving surgery followed by RT increased drastically from 9% in 1997 to 75% in 2011 (7). Nevertheless, the same study showed that the use of breast-conserving surgery followed by RT in Estonia in women with stage I/IIA BC diagnosed 2009–2013 was the second lowest after Portugal among nine European countries (7). . The number of MV units per million population achieved in 2016 is still lower than the median of 5.3 of 28 European countries in 2012 (37).

Consistent with previous studies showing association between age at diagnosis and receipt of RT (19,20,22), the oldest patients had the lowest rate of RT in this study. RT utilization was the highest among women aged 50–59. It has been reported previously that mortality from BC among patients aged 50–59 in Estonia has significantly declined since 2000, while it did not decrease among women aged ≥60 over the same time period (2). Whereas these trends are consistent with screening activities, as women aged 50–59 have been the target age group for organized mammography screening since 2004 (28), the impact of RT in combination with other therapies can be considered as well. Overall, women aged 70 years and over received considerably less RT than younger women, which is in line with growing evidence over the time period under study suggesting no benefit for women in this age group in early disease (38,39). Women under 50 years of age were less likely to receive RT than women aged 50–59, which may be associated with higher proportion of genetically determined cancers in this age group and recommendations to use mastectomy rather than BCS and RT in cases with BC gene (BRCA) mutations (40).

Previous studies have revealed that early-stage BC patients residing in locations with poor access to RT facilities were more likely to receive mastectomy instead of BCS due to required daily trips to RT centres (14,16). Thus, one of the hypotheses of the study was that geographical distance from cancer centres is associated with receipt of RT. The islands of Western Estonia and the North-Eastern part of the country can be considered the most remote. Northern and Western Estonia are serviced by the cancer centre in Tallinn, while Southern Estonia is serviced by the centre in Tartu. The rest of the regions are partly covered by both centres. However, no differences were observed by region of residence in multivariate analysis, even though overall receipt of RT was highest among women living in Southern Estonia and lowest among those living in Western Estonia. As living in rural areas and geographically remote areas have been shown to be one of the barriers to receipt of RT (18,22–24), equal access to RT regardless of geographic factors in Estonia can be partly attributed to the opportunity to stay at the hospital for the duration of treatment, but also to urban life style of majority of Estonian populations. According to Statistics Estonia, approximately two-thirds of population in Estonia live in urban regions, and among people living in rural areas, those living in the suburbs of larger cities have urban lifestyles (41). The finding of no association with place of residence is encouraging and suggests equal access to RT in Estonia regardless of geographic factors.

However, our findings demonstrate a strong impact of education and marital status on the use of RT. Educational level as an indicator of socioeconomic status has been shown to be associated with poorer health outcomes in Estonia, partly mediated by lower access to health care (25–27,42). Factors influencing receipt of optimal cancer treatment can be divided into three main categories: structural factors, factors affecting physician recommendation and factors affecting patient's decision making (43). Even though structural barriers such as lack of health insurance may affect timely presentation, all

patients in Estonia who receive a cancer diagnosis obtain insurance coverage and consequently, access to standard treatment. Besides clinical factors, physicians' recommendations may be influenced by their perception of patient's ability to comply with treatments, while patient-related factors include socioeconomic status, access to transportation, ability to take time off from work, but also patients' attitudes towards treatments and their beliefs (43). Our finding that higher level of education was a considerable predictor of increased RT utilization is consistent with prior studies (20,44) and may be related to both physician- and patient-related factors. Several studies have observed that patients with higher level of education were more likely to receive BCS in comparison to other types of surgeries (17,45–47). Patients with lower socioeconomic status level may struggle to cope with healthcare systems, have misperceptions about treatment benefits and may be more likely to have difficulties in overcoming adverse effects of treatment or psycho-social problems (43).

Previous studies have reported BC survival is lower among women with lower education independent of screening mammography and cancer stage at diagnosis, which play an important role in BC mortality (48,49). Although there's not a single element in BC care that can explain mortality disparities, it is essential to identify the importance of educational variations in access to optimal treatment in BC patients to reduce the variation in health outcomes.

Similar to previous studies (18,50), women who did not have a partner failed to receive RT as often as married women. Furthermore, previous studies have shown marital status is a predictor of cancer survival (51–55). Longer survival of married individuals can be attributed to increased social support and improved economic status (56). Studies have shown unmarried women are more concerned about insufficient care after their treatment, and seeking help and transportation in comparison to married women and are thus more

prone to refuse intense treatments and decline therapies such as axillary dissection and RT (43). Such concerns can also have an impact on physician recommendations and physicians may be less likely to offer intense treatments to unmarried older women (54). It might be beneficial for healthcare providers to identify unmarried women and provide comprehensive case managements to reduce health disparities. Studies have shown implementing nurse case management has improved receipt of RT among older BC patients, particularly those with poor social support (57).

Conclusions

In conclusion, this study demonstrated the ability to use administrative databases as an additional source for identifying individual cancer treatment data if such data are not complete at a cancer registry. The study showed considerable increase in the use of RT in Estonia over the study period, which is in line with increases in available equipment. The lack of geographic variations suggests equal access to therapy for patients living in remote regions. However, unmarried women and those with lower educational level received less RT compared to their counterparts. Further studies are needed to identify the exact mechanisms behind these findings, but some of the likely reasons are misperceptions about treatment benefits, loss of social support and economical disadvantages. The results have important implications for policymaking and evidence-based decisions. To minimise disparities in BC outcomes and avoid inequitable delivery of RT in Estonia, the healthcare and social system need a stronger focus on patient-centred care, offering patients psychosocial support, helping them cope with the disease and treatment effects and overcome any barriers to treatment.

List of Abbreviations

BC	Breast cancer
RT	Radiation therapy
BCS	Breast conserving surgery
ECR	Estonian Cancer Registry
EHIF	Estonian Health Insurance Funds
ICD-O-3	3rd Edition of International Classification of Disease for Oncology
ICD-10	International Statistical Classification of Diseases and Health Problems 10th Revision
PRR	Prevalence rate ratio
CI	Confidence intervals
MV	Megavoltage
IMRT	Intensity modulated radiation therapy
IGRT	Image-guided radiation therapy

Declarations

Ethics approval

The study protocol was approved by Tallinn Medical Research Ethics Committee (Decision no 2652, March 12, 2019).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FSF and KI designed the study, KI obtained the data, FSF and KI performed data analysis, FSF wrote the first draft, KP and KI revised the manuscript critically, all authors read and approved the final manuscript.

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Figure title

Figure 1. Radiation therapy use over time among breast cancer patients, Estonia 2007–2018.

Figure legend

Includes women with stage I–III breast cancer, age <70 years who underwent primary surgery

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Table 1. Characteristics of women with breast cancer and receipt of radiation therapy, Estonia 2007–2018

			Receipt of radiation therapy				
			Yes		No		
Variable	No.	%	No.	row%	No.	row%	p-value[a]
Total	8637	100	4310	49.9	4327	50.1	
Microscopically verified	8387	97.1	4305	51.3	4082	48.7	<0.001
Age at diagnosis (years)							
<50	1523	17.6	943	61.9	580	38.1	<0.001
50–59	1993	23.1	1297	65.1	696	34.9	
60–69	2057	23.8	1230	59.8	827	40.2	
≥70	3064	35.5	840	27.4	2224	72.6	
TNM (7th edition) stage							
I	2483	28.8	1642	66.1	841	33.9	<0.001
II	3238	37.5	1531	47.3	1707	52.7	
III	1574	18.2	839	53.3	735	46.7	
IV	718	8.3	82	11.4	636	88.6	
Unknown	624	7.2	216	34.6	408	65.4	
Period of diagnosis							
2007–2009	1939	22.5	758	39.1	1181	60.9	<0.001
2010–2012	2144	24.8	1041	48.6	1103	51.5	
2013–2015	2218	25.7	1158	52.2	1060	47.8	
2016–2018	2336	27.1	1353	57.9	983	42.1	
Nationality							
Estonian	5490	63.6	2753	50.2	2737	49.9	0.163
Other nationalities	3112	36.0	1545	49.7	1567	50.4	
Unknown	35	0.4	12	34.3	23	65.7	
Region of residence							
North	4010	46.4	1991	49.7	2019	50.4	<0.001
West	927	10.7	420	45.3	507	54.7	
Central	704	8.2	347	49.3	357	50.7	
North-East	1077	12.5	518	48.1	559	51.9	
South	1919	22.2	1034	53.9	885	46.1	
Educational level							
University degree	1964	22.7	1139	58.0	825	42.0	<0.001
Secondary plus vocational studies	1860	21.5	1079	58.0	781	42.0	
Secondary studies	2593	30.0	1345	51.8	1248	48.1	
Basic and primary studies	1410	16.3	406	28.8	1004	71.2	
Unknown	810	9.4	341	42.1	469	57.9	
Marital Status							
Married	3035	35.1	1818	59.9	1217	40.1	<0.001
Divorced/widow	4389	50.8	1898	43.2	2491	56.8	
Single	976	11.3	488	50.0	488	50.0	
Unknown	237	2.7	106	44.7	131	55.3	
Primary surgical treatment							
Yes	7016	81.2	4208	60.0	2808	40.0	<0.001
No	1621	18.8	102	6.3	1519	93.7	
Chemotherapy							
Yes	5518	63.9	3147	57.0	2371	43.0	<0.001
No	3119	36.1	1163	37.3	1965	62.7	

[a] Chi-square test

Due to rounding, percentages may not total 100

Table 2. Prevalence rate ratio of radiation therapy use among women with breast cancer, Estonia 2007–2018

	Radiation therapy use (n=4273) [a]		Univariate PRR (95% CI)	Multivariate PRR (95% CI)
	No.	%		
Total	2937	68.7		
Age at diagnosis (years)				
<50	789	66.9	**0.94 (0.89, 0.99)**	0.96 (0.91, 1.01)
50–59	1124	71.1	Ref	Ref
60–69	1024	67.7	0.95 (0.91, 1.00)	0.95 (0.91, 1.00)
Period of diagnosis				
2007–2009	569	56.6	Ref	Ref
2010–2012	727	66.7	**1.18 (1.10, 1.26)**	**1.18 (1.10, 1.26)**
2013–2015	749	72.4	**1.28 (1.20, 1.37)**	**1.27 (1.19, 1.36)**
2016–2018	892	78.0	**1.38 (1.30, 1.47)**	**1.37 (1.28, 1.45)**
Nationality				
Estonian	1795	69.2	Ref	Ref
Other nationalities	1142	68.0	0.98 (0.94, 1.02)	0.97 (0.93, 1.02)
Region of residence				
North	1333	67.8	Ref	Ref
West	296	66.1	0.97 (0.91, 1.05)	1.00 (0.93, 1.07)
Central	247	68.4	1.01 (0.93, 1.09)	1.01 (0.94, 1.09)
North-East	394	69.4	1.02 (0.96, 1.09)	1.05 (0.98, 1.12)
South	667	71.6	1.06 (1.00, 1.11)	1.05 (0.99, 1.10)
Educational level				
University degree	870	69.6	Ref	Ref
Secondary plus vocational studies	840	70.8	1.02 (0.97, 1.07)	1.02 (0.97, 1.08)
Secondary studies	1030	68.6	0.99 (0.94, 1.04)	1.01 (0.96, 1.06)
Basic and primary studies	197	58.8	**0.84 (0.77, 0.93)**	**0.88 (0.80, 0.97)**
Marital status				
Married	1387	71.5	Ref	Ref
Divorced/widowed	1188	66.6	**0.93 (0.89, 0.97)**	**0.95 (0.91, 0.99)**
Single	362	66.1	**0.92 (0.86, 0.99)**	0.93 (0.87, 1.00)
TNM (7^{th} edition) stage				
I	1236	78.1	Ref	Ref
II	1133	60.4	**0.77 (0.74, 0.81)**	**0.79 (0.75, 0.82)**
III	568	69.7	**0.89 (0.85, 0.94)**	**0.93 (0.88, 0.97)**

Abbreviations: PRR – prevalence rate ratio; ref – reference category

Statistically significant results in bold.

[a] Women with stage I–III breast cancer, age <70 years who underwent primary surgery included in the analysis

Figure 1

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