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EVALUATION OF BREAST CANCER DIAGNOSIS WAITING TIMES BASED ON PATIENT PATHWAYS IN ESTONIA – DESCRIPTIVE REGISTRY-BASED STUDY

Master’s thesis

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PATSIENDI TEEKONDADEL PÕHINEV RINNAVÄHI DIAGNOOSI OOTEAEGADE HINDAMINE EESTIS – KIRJELDAV REGISTRIPÕHINE UURIMUS

Magistritöö

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

Background: Breast cancer incidence rates are high in Estonia and 16,6% of all cancer deaths are caused by breast cancer. Defining and measuring waiting times differ significantly in the world. In Estonia, the time period before the visit of breast cancer specialist is not measured, but rather the waiting times for treatment and there is no evidence-based information of diagnostic phase. *Aim*: The aim of this thesis is to describe the diagnostic waiting times for breast cancer through measuring the time from the first entrance to healthcare system to confirmed breast cancer diagnosis in Estonia. *Methods*: A retrospective registry-based study was conducted including women with primary breast cancer diagnosed in 2016. Data from medical bills from Estonian Health Insurance Fund was used to evaluate breast cancer diagnostic waiting time. Multivariate linear regression analysis was used to identify waiting times relationships with age and place of residence. *Results*: From 5366 women with primary breast cancer 290 were included. The median waiting time for breast cancer diagnosis was 8 days (mean 14,01 days) and the shortest via gynaecologist pathway with 5 days (mean 11,43 days). The longest median times were in South and North East Estonia. West Estonian women experience the longest median waiting time via family physician pathway (43 days). North Estonian women had shortest median waiting time (1 day) via gynaecologist appointment. North East and West Estonia are related to longer waiting times compared to North region of Estonia. *Conclusions*: There is large variation on individual level of breast cancer diagnostic waiting times. The median waiting time 8 days for breast cancer diagnosis is relatively low compared to the results of previous research. The place of residence in North East and West Estonia is related to longer waiting times compared to women living in North region of Estonia.

This thesis is written in English and is 64 pages long, including 6 chapters, 7 figures and 4 tables.

Annotatsioon

Patsiendi teekondadel põhinev rinnavähi diagnoosi ooteaegade hindamine Eestis – kirjeldav registripõhine uurimus

Taust: Rinnavähi esinemissagedus on Eestis kõrge ja 16,6% kõigist vähisurmadest põhjustab rinnavähk. Ooteaegade määratlemine ja mõõtmine erineb palju maailmas. Eestis ei mõõdeta ajaperioodi enne vähiravispetsialisti visiiti, vaid pigem ravi ooteaegasid ning puudub tõenduspõhine info diagnoosimise perioodist. *Eesmärk*: Töö eesmärk on kirjeldada rinnavähi diagnoosi ooteaegu mõõtes aega alates esimesest sisenemisest tervishoiusüsteemi kuni kinnitatud rinnavähi diagnoosini. *Metoodika*: Teostati retrospektiivne registripõhine uurimus, mis hõlmas 2016. aastal diagnoositud esmase rinnavähiga naisi. Eesti Haigekassa raviarvete andmeid kasutati rinnavähi diagnoosi ooteaegade hindamiseks. Ooteaegade seostamiseks vanuse ja elukohaga kasutati mitmemõõtelist lineaarset regressioonanalüüsi. *Tulemused*: 5366-st esmase rinnavähiga naisest kaasati 290. Rinnavähi diagnoosi mediaan ooteaeg oli 8 päeva (keskmine 10,4 päeva) ja lühim oli günekoloogia teekond 5 päeva (keskmine 11,4 päeva). Pikimad mediaan ajad olid Lõuna ja Kirde-Eestis. Lääne-Eesti naised kogevad kõige pikemat mediaan ooteaega perearsti teekonnal (43 päeva). Põhja-Eesti naistel oli günekoloogia teekonnal lühim mediaan ooteaeg (1 päev) Kirde ja Lääne-Eesti on seotud pikemate ooteaegadega võrreldes Eesti põhjaosaga. *Järeldused*: Rinnavähi diagnoosi ooteaegadel esines individuaalsel tasemel suur erinevus. Mediaan ooteaeg 8 päeva rinnavähi diagnoosimiseks on võrreldes varasemate tulemusega suhteliselt väike. Kirde ja Lääne Eesti elukoht on seotud pikemate ooteaegadega võrreldes Eesti põhjapiirkonnas elavate naistega.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 64 leheküljel, 6 peatükki, 7 joonist, 4 tabelit.

List of abbreviations and terms

EHIF	Estonian Health Insurance Fund
EHIS	Estonian Health Information System
ICD-10	International Classification of Diseases, 10th version
MRI	Magnetic resonance imaging
NEMC	The North Estonian Medical Centre
NHS	National Health Service
NICE	The National Institute of Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
TUH	Tartu University Hospital
WHO	World Health Organisation
NUTS	Nomenclature of Territorial Units for Statistics

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1 Introduction

The World Health Organisation (WHO) has stated that breast cancer is the most common form of cancer among women in the world. WHO emphases the importance of early detection of breast cancer which is achieved through diagnosing early including medical breast examination and screening. [1] Breast cancer incidence and death rates among women of all cancer types are the highest in Estonia. 16,6% of all cancer deaths are caused by breast cancer [2]. Among Organisation for Economic Co-operation (OECD) countries the five-year net survival of breast cancer patients in Estonia is in the lower end (age standardized survival 76,6% measured in 2010-2014) just before Poland, Chile, Slovak Republic and Lithuania [3]. Early detection improves outcomes and survival of breast cancer [4] thus focusing on minimizing delays in detection, diagnosis, and treatment is essential. [5], [6]

Waiting time guarantees are becoming more popular among OECD countries to tackle long waiting times, but these are effective only when enforced. Main options used for enforcement are waiting time targets that healthcare providers are accountable for and letting patients choose alternative providers when maximum limits are exceeded. [7] The NHS England new standard for faster diagnosis starting from 2020 sets the 28 days maximum limit for the time from receiving the family physician referral for suspected cancer, breast symptomatic referral and urgent screening referral to when patients are told if they have cancer or the diagnosis is excluded. The novelty part of the standard is using the waiting time limit to improve patient experience. [8]

The measurement of waiting times differ significantly among OECD countries – based on definition of time period seen as waiting time, which parameters are used and what is considered the starting point of patient journey for waiting time. The national comparison of waiting times is limited because of different measurements and data collection. [9] In Estonia the time from the first visit at healthcare provider to the start of an oncological treatment for breast cancer patients is measured as part of clinical quality indicators. [10] There is currently no measurement of time period before the breast cancer specialist visits in Estonia. The study focuses on women who contact the

healthcare system on a regular basis which also includes breast cancer screening program. Although, women with symptoms can also participate in the national breast cancer screening program it is aimed to age related risk group women with no breast symptoms to detect the breast cancer in asymptomatic period [11]. Outside of screening target group women with breast symptoms are expected to turn to family physician or specialist appointments.

The fields under research in this thesis are diagnostic waiting times and breast cancer pathways. The aim of this thesis is to describe the diagnostic waiting times for breast cancer through measuring the time from the first entrance to healthcare system to confirmed breast cancer diagnosis in Estonia. To achieve the aim four research objectives are established:

1. Identify the relevant data sources to map patient pathways from the first entrance to healthcare system to breast cancer diagnosis.

2. Identify and describe breast cancer patient pathways in Estonian healthcare system from the first entrance to healthcare system to breast cancer diagnosis.

3. Calculate average time periods between the first contact with healthcare system (early detection) to the first specialist visit (diagnosis) and compare the results with international standards/guidelines.

4. Describe to relationships between pathways and waiting times and possible associations with patient demographic data.

The thesis consists of six chapters. The first chapter is introduction to the topic and research objectives. The second chapter gives overview of breast cancer prevalence, diagnostic methods and research of measuring waiting times. Methodology and methods are described in the third chapter and results in fourth. The fifth chapter discusses the results of the study comparing them with previous literature. The final chapter six presents the conclusions of the study.

2 Background

2.1 Breast cancer

The incidence of breast cancer among women is much higher than any other cancer type according to World Cancer Report published in 2012 [12]. Women in Europe have a probability of developing breast cancer during their lifetime approximately 1 in 8. There are number of individual factors that may affect that probability like age, family history, reproductive history of woman, race, and other factors. [13] Higher incidence of breast cancer and other cancers not related by infectious causes is characteristic to industrialised countries [12].

Based on data from Health Statistics and Health Research Database 767 new cases of breast cancer were diagnosed in 2016 in Estonia and 756 of them were women. The number of deaths caused by breast cancer in the same year were 238 and among them 235 were women. [14] The mortality from breast cancer in Estonia has been in decline since 2000 but is still relatively high, especially among elderly women. There has been a change in breast cancer burden in Estonia with the incidence rate increasing. According to Baburin *et al* this change is characteristic to Western, Northern and Southern Europe where incidence rates are higher and mortality rates lower. [15]

According to WHO the early detection is necessary to improve outcomes and survival of breast cancer among women. Main strategies for early detection include diagnosing early and screening for breast cancer. [4] Diagnosing early may be affected by patient delay with seeking help after first symptoms have appeared. This risk has been identified among Estonian women in 2012. [16] According to the Estonian breast cancer patient handling guideline (unapproved) the criteria of symptoms for referring women include: changes in the tissues of breast – lumps or thickenings, the changes in breast gland's skin and shape, the instigation of nipple or skin, bloody discharge from the nipple, the swelling and redness of breast, enlargement of the lymph nodes. Also, important to mention that early stage breast cancer is asymptomatic. [17]

2.2 Diagnosing breast cancer

2.2.1 Diagnostic tests and guidelines

Breast cancer in early stages is asymptomatic which means that patients without any symptoms usually enter the healthcare system through the national breast cancer screening programme [18]. There are over 20 subtypes of breast cancers identified by WHO Classification of Tumours of the Breast. Carcinomas are most common cancers types. [12] Diagnostic tests and procedures available to diagnose breast cancer include mammography, breast ultrasound, magnetic resonance imaging. For more specific purposes some of newer and experimental imaging tests are used. Additionally, other types of tests are done to evaluate the spreading of breast cancer. [19]

Diagnostic mammography is a special imaging method for breasts. During the procedure x-ray images of breast are created to evaluate or diagnose changes in breast tissue. This procedure uses ionizing radiation in low doses that should not have negative effect. Mammography is the main suggested screening method for asymptomatic breast cancer. Usually any abnormal finding needs to be evaluated with additional methods. [20] **Ultrasound of breast** is used for masses or asymmetries in breast tissue. There is no ionizing radiation used during the procedure. Ultrasound procedure helps to distinguish between solid and liquid-filled masses. Ultrasound is used for screening method in case the breast tissue is dense, there are breast implants, for women who are pregnant, and for women with high breast cancer risk due to genetics. [21] **Magnetic resonance imaging** (MRI) is indicated to use for women with genetic predisposition. MRI is not suitable for daily use because of its low specificity. Although, it is mainly used for preoperative staging. [22] MRI uses magnetic field which means no ionizing radiation is used. [23]

Biopsy is used to evaluate any suspicious findings during imaging tests or physical examination of breast. [19] **Fine needle aspiration** is considered minimally invasive and can reduce pain related to biopsy because smaller needle with a 20-25 gauge is used. This procedure can provide fast results. A significant downside is not being able to distinguish in situ from invasive carcinoma due to the reason that the architectural pattern of tissues cannot be preserved. **Needle core biopsy** is done with bigger needles with sizes 8-11 and 12-18 gauge depending on if vacuums assisted or other types of biopsies are needed. There are some risks with using larger needles including the risk of

infection and haematoma. Both fine needle and core biopsy methods have different strengths and the choice should be made by the purpose of taking the biopsy. There are no definite suggestions made by European Commission so far. **Open biopsy** is used as a diagnostic surgical procedure which can frequently be part of a therapeutic measure. Being the most invasive of diagnostic methods it should only be used when other methods have not provided cancer diagnosis. [13] All of before mentioned methods are used in Estonia for diagnosing breast cancer. [24] Vacuum assisted biopsy was not added to the list of healthcare services covered by the EHIF before 2018 [25].

For early diagnosing of cancers in United Kingdom (UK) the National Institute for Health and Care Excellence (NICE) in 2015 has developed suspected cancer guidelines by cancer types and the goal is to recognise and refer early. For referring, a suspected cancer pathway referral (for an appointment within 2 weeks) is used. [26] There is a separate quality standard document for breast cancer for a specialist team to follow after patient has been referred to. This document includes six areas of improvement to achieve timely diagnosis, reduce unnecessary preoperative MRI scans, defines the need for gene analysis, describes the work of a multidisciplinary team and assigning a key worker for patients with complex breast cancer cases. [27]

In Estonia there are no country specific breast cancer diagnostic and treatment guidelines. There is an agreement among physicians to follow the American guidelines published in the National Comprehensive Cancer Network (NCCN Clinical Practice Guidelines in OncologyTM). [17] For quality improvement the Estonian Health Insurance Fund (EHIF) publishes clinical audits which goal is to improve overall quality of healthcare and patient outcomes that are systematically evaluated and suggested changes for implementation. There are certain criteria set for a topic to be chosen for clinical audit – differences in healthcare service provider medical treatment, increased costs, raised issues with quality or to evaluate the implementing of recommendations made in guidelines or follow-up audit. There has not been an audit published about breast cancer so far. [28] To improve the quality of healthcare services for patients in Estonia the EHIF supports the work of the Council of treatment guidelines. The goal of patient handling guideline is to provide the best evidence-based knowledge to help diagnose early and to define the patient pathway which also includes timeframe. The content of the guidelines has been agreed by family doctors and oncologists. The patient handling guideline for breast cancer was published in 2016 but the status of the

guideline is unapproved - Appendix 1 – Guideline for breast cancer patient handling. [17]

The unapproved patient handling guideline has set time limits for three specific stages of breast cancer patient pathway: "Within the 1st to 2nd week a symptomatic person to get to the first appointment in the healthcare system and be directed to investigations and/or to the appointment of a surgeon or gynaecologist specializing in breast pathology. Within the 3rd to 5th week from the appointment of a surgeon or gynaecologist specializing in breast pathology to a multidisciplinary oncological council for starting or changing a treatment plan. From the 6th week the planning and starting the treatment should begin." [17]

According to consultations with experts in the field family physicians are often left to choose between many options when handling a patient with breast problems – directly referring the patient to a specialist or referring the patient to diagnostic tests first and then if needed to the specialist. The e-consultation is also used which is a combination of referring patient to the specialist but sometimes doing the initial diagnostic test beforehand.

2.2.2 Breast cancer screening program

The screening programs are designed for healthy people without symptoms for early detection of cancerous diseases [29]. Breast cancer can be asymptomatic, and treatment started in later stages can negatively affect the outcome. Population-based screenings have been effective in high-income countries to reduce mortality from cancers. Sometimes a so-called opportunistic screening is used to screen women on a healthcare provider initiative, but this has not been a cost-effective solution so far. [12] Mammography is the preferred first investigation method for asymptomatic breast cancer screening. [30] Breast ultrasound is chosen in case of dense breast tissue and women under 30 years of age. It is used to assess changes of breast tissue which are not seen on mammograms and as a guidance for taking biopsy. [19]

There are many examples of coordinated referral systems in case of abnormal screening mammogram results. Breast Assessment Centres (BACs) in Ontario, Canada provide organised screening system with referral to additional tests, diagnostic procedures and consultations with surgeons. Women seen through BACs compared with usual care

proved to have shorter wait times. There was a significant improvement in timeliness to diagnosis meaning the patients with abnormal mammogram results should receive organised assessment. The results also indicated that BACs had important benefit on social disparities. One of the results was that women assessed through a BAC got their diagnoses faster and with less procedures. [31]

Estonia has established the population wide breast cancer screening already in 2002 [32]. 55636 women were invited to breast cancer screening in 2016 in Estonia and 56% of them participated. As the result 129 women received breast cancer diagnosis and 17 had precancerous changes identified through screening program. [12] The age group invited to the national breast cancer screening programme in 2016 was 50-62-year old women. [33] 6799 persons did not receive invitation for breast cancer screening program due to different reasons – 2686 had already had the diagnostic test done before the planned send out of invitation, 3212 did not have health insurance coverage, for 622 their home address was missing and 239 had left Estonia permanently or died. [34] Women who do not have health insurance can still participate in screening programs but have to pay for it themselves [29].

2.3 Waiting time

2.3.1 Factors influencing waiting time

Waiting times can be measured depending on the interest of the evaluator – waiting time to treatment, diagnosis or procedures [35]. In the case for cancers the diagnostic waiting time has been associated with the outcome [8]. According to the Aarhus statement both time points and time intervals need to be defined to measure any part of early cancer diagnosis [36]. The categorization of timepoints and intervals for delay were already described by Olesen et al in 2009. At that time Denmark had poor 5-year survival rates among cancer patients and the results of the nationwide experiment reduced delays for cancer patients. It also seemed to positively affect general public satisfaction with healthcare system. The suggestion was made that more research on the reasons for different type of delays would improve the clinical pathways. [37]

The factors influencing waiting times can roughly be divided in two based on literature – coming from patient and healthcare system. Baena-Cañada *et al* evaluated waiting times for breast cancer diagnosis and surgical treatment and noted that if the date of first

visit to health system cannot be identified the delay due to the patient cannot be determined. They also concluded that no delays were reported when patients entered the health system through screening program for breast cancer which was considered as the first contact. [38]

Early diagnosis of breast cancer is also dependent on the waiting times to get to the specialist appointments. The most common approach to organize waiting times among OECD countries is establishing the maximum waiting times guarantee which can be used with special targets for healthcare providers. The maximum waiting times targets differ among countries depending mainly what is possible and affordable in the specific country. [7] Estonia uses referrals for many specialist appointments and has set the quality indicators for breast cancer starting from the first visit at the specialist [39].

Waiting time may be affected by the diagnostic methods. Plotogea et al found that symptomatic breast cancer patients had shorter diagnostic wait time. The results also showed that diagnosis was reached at higher stages of disease compared to those who got their diagnosis through screening detection. [40] Implementing a systematic coordination of radiology and clinical care reduces diagnostic and surgical wait times and helps to achieve recommended targets. [41]

The delay of diagnosis is caused by different factors which are related to patient or practitioner. Often the delay is experienced by patients who had presented atypical or vague symptoms, but this also affects negatively the practitioner delay. [42] Vseviov (2012) defined the delay for breast cancer diagnosis as moderate (31-60 days) and long (over 60 days). Based on their data optimal time for waiting for breast cancer diagnosis is up to 30 days from the first contact with healthcare system. [43] This is the reason why the general practitioners need to have referral guidelines with access to diagnostic services. [42]

Redaniel *et al* concluded in their study about waiting times from diagnosis to surgery associated with survival that the shorter waiting time had little effect on survival from localised breast cancer in England. The evidence for an increase in mortality with longer waiting times with more than 62 days was not strong. Age and deprivation were found associated with the excess mortality, but it was not possible to explain the differences with waiting times. [44]

National Health Service (NHS) England is currently working on a new target where people are not supposed to wait more than 28 days after family physician referral to get cancer diagnosis confirmed or excluded. All hospitals in England will be obliged to collect information about waiting times and meet the target from April 2020. Right now, there are two types of pathways for patients needing urgent specialist appointment in England. Family physicians can use the two-week urgent referral for symptomatic patients and the urgent screening programme pathway is meant for individuals having abnormal screening results from national screening programmes for breast cancer, bowel cancer and cervical cancer. [45] The new standard for faster diagnosis sets the four-week maximum time interval from receiving the family physician referral for suspected cancer, breast symptomatic referral and urgent screening referral to when patients are told if they have cancer or it is excluded. [46] The unapproved Estonian breast cancer patient handling guideline suggests optimal time from the first contact with healthcare system to a multidisciplinary oncological council should be reached within five weeks [17]. There is no specification or criteria for the time to breast cancer diagnosis known to the author.

2.4 Measuring waiting times

Measuring and reporting waiting times is focused mainly on the treatment waiting times and there is a lack of evidence of the earlier phase [47]. There are statistics about waiting times which cannot be compared because the measurement and data collection varies greatly. The use of national care guarantees indicates that there may be problems with healthcare availability. The study of 23 OECD countries identified three different types of waiting times: retrospective look at so-called “complete waits”, “on-going waits” that measure time using waiting lists and “expected waiting time” which is estimation of new patients. [35] Although, the measurement of waiting times varies across OECD, the “inpatient waiting time” using lists or “referral-to-treatment” using referral letters are mainly used. Most countries seem to be measuring inpatient wait time, but there is a shift towards the wait from family physician referral to treatment. DRG-type administrative database can be used to measure inpatient waiting time from one event to the other. [39]

There is some criticism and confusion towards defining the first event of waiting time [38], [47], [35]. If the first visit cannot be identified, there is no accurate way to

distinguish the delay due to the patient from the one coming from the healthcare system [38]. Viberg *et al* collected information about all the services for which the waiting times are measured, information about which types of waiting times are measured and which parameters are used for measurement. The last information collected was the starting point of waiting time measurement. The main parameters used to measure elective surgeries waiting times were mean and median and starting points of measurement were decision to treat, referral received, and patient listed. [35]

The research mapping diagnostic waiting time measurement in Ontario, Canada found out that the variability of waiting times is high but setting targets for diagnostic part is low. Other problematic issues included lacking patient handling guidance for family physicians and the lack of agreement on the starting and ending points of measurement (especially suspicion on cancer). The main goal of developing a framework for diagnostic waiting times is to reduce the variation of care process and ensure access to patients who need it. [47]

Clinical indicators are used as part of ensuring healthcare services' quality in Estonia and are continuously monitored and evaluated by the EHIF. [48] For breast cancer there are four clinical indicators and one of them measures the time from the first visit at healthcare provider to the start of an oncological treatment for breast cancer patients. [49] There is no indicator to measure the time from the first visit in the healthcare system with breast cancer suspicion to breast cancer diagnosis.

2.4.1 Diagnosis waiting times in Estonia

Two studies published in 2012 studied the risk factors of delay of breast cancer diagnosing caused by patient and physician/healthcare system. The pathway from the first visit in healthcare system to the first visit at breast cancer specialist (oncologist-mammologist) was measured. Data was collected with questionnaires and included women who had breast cancer diagnosed during 2008-2010. Two treating centres were included in the study – The North Estonian Medical Centre (NEMC) and Tartu University Hospital (TUH). The median time period from the first visit to oncologist-mammologist visit was 16 days. The results showed that women living in other regions than in southern Estonia have higher risk for moderate delay meaning the delay between 31 to 60 days. The risk for long time delay with more than 60 days was higher in western and in north-eastern Estonia compared with women living in southern Estonia.

The conclusion in the study was that the main risk factor for the delay due to doctor/healthcare system is the onset of the disease as a symptom other than a lump in the breast tissue. [43], [16]

The report evaluating mammography in breast cancer screening in Estonia was published in 2013 and presented measurement of time from breast cancer suspicion to diagnosis and the beginning of treatment. The study included data from cancer registry and EHIF medical invoices which could definitely exclude breast cancer based on diagnostic tests and also medical invoices that presented the onset of breast cancer treatment. The dates from medical bills and time of diagnosis from cancer registry were used to calculate how long it will take from the first suspicion to confirming breast cancer diagnosis. The dates of either mammography or breast ultrasound were considered as the beginning of a suspicion of breast cancer. The results showed that 56% of studied women received breast cancer diagnosis within one month and 88% received their diagnosis within three months from the first suspicion. [50]

3 Methodology and methods

3.1 Choice of method

This is a descriptive, observational, retrospective registry-based study. Descriptive analysis of collected data includes calculating mean, median and mode. Also, interquartile range is used to describe waiting times [39]. Baena-Cañada *et al* used similar statistic to analyse the delay for surgery among women. [38] Other researchers have used multivariate logistic regression analysis [31] and simple regression together with multivariate linear regression analyses [43] for evaluating associations between waiting times and different other variables. Regression analysis can be used to estimate the associations between variables. The descriptive model and the prognosis are more accurate when the independent variables have stronger association with the dependent variable. [51] To identify possible waiting times associations with pathways and demographic data multivariate linear regression analysis is used.

Data from medical bills from EHIF allows retrospective evaluation of the diagnostic waiting times of breast cancer patients in 2016. Retrospective approach is suitable when the start of the investigation is the disease itself [52] – breast cancer diagnosis and the reason why this study design was chosen. Retrospective approach has been used to analyze waiting times based on medical records [38]. The median is less sensitive to extreme values compared to the mean and therefore is preferred measure for the average waiting time [53].

Since it is a retrospective study based on the data from EHIF database and there was no intervention or risks to patients, their informed consent was not necessary. The linking of data of different activities for pathways was done by the EHIF analyst and the approval of ethics committee was not necessary because data subjects were coded. To identify the study population the inclusion criteria were applied, and exclusion criteria was used to weigh the suitability of characteristics of data for the study.

The demographic variables of women with primary breast cancer diagnosis are presented with using summary statistics. To achieve the first objective of this thesis the entry to the healthcare system and the diagnosis of breast cancer are described with summary statistics presented in days. To achieve the second objective study subjects are divided in groups according to the pathways identified and described with summary statistics. To achieve the third objective the waiting times per pathways are compared with NHS England new standard for faster diagnosis of breast cancer. To achieve the fourth objective the multiple linear regression analysis is used to assess the associations between pathways and waiting times with patient demographic data.

The diagnoses of diseases in Estonia are coded using ICD-10 (International Classification of Diseases, version 10) classification adapted to Estonian language. The Estonian version RHK-10 (*Rahvusvaheline Haiguste Klassifikatsioon, versioon 10*) was issued in 1996 but has been updated six times since then. [54] The Estonian Cancer Registry uses additionally ICD-Oncology 3rd Edition (*RHK-O-3 in Estonian*) which includes two different coding systems for marking tumours topography and morphology. [55] The diagnoses in the EHIF databases for breast cancer are classified with ICD-10. [56] All diagnoses codes for referring and diagnosing breast cancer were included. Healthcare services are coded according to the regulation of the Estonian Health Insurance Fund healthcare services list of 2016 [57] and all services related to diagnosing breast cancer (imaging and histology tests) were included.

The diagnostic imaging tests included mammography, breast ultrasound and magnetic resonance imaging. The histological tests included fine needle and core needle biopsy and open biopsy done during surgery. Due to the complexity of healthcare system organization in Estonia data from medical bills need systematic approach in defining the starting point and the end point of diagnostic waiting times. According to the Aarhus statement [36] both time points and time intervals need to be defined to measure any part of early cancer diagnosis. The date of primary cancer diagnosis from EHIF medical bills does not always equal to the date of the confirmation of breast cancer diagnosis, so the date of breast cancer diagnosis was defined according to the hierarchy composed by European Network of Cancer Registries as seen on Figure 1. European Network of Cancer Registries: Hierarchy for Defining the Date of Diagnosis.

European Network of Cancer Registries: Hierarchy for Defining the Date of Diagnosis (http://www.encr.com.fr/incideng.pdf)

In the order of declining priority:

1. Date of first histological or cytological confirmation of this malignancy (with the exception of histology or cytology at autopsy). This date should be, in the following order:

   (a) date when the specimen was taken (biopsy)

   (b) date of receipt by the pathologist

   (c) date of the pathology report

2. Date of admission to the hospital because of this malignancy.

3. When evaluated at an outpatient clinic only: date of first consultation at the outpatient clinic because of this malignancy.

4. Date of diagnosis, other than 1, 2 or 3.

5. Date of death, if no information is available other than the fact that the patient has died because of a malignancy.

6. Date of death, if the malignancy is discovered at autopsy.

Figure 1. European Network of Cancer Registries: Hierarchy for Defining the Date of Diagnosis. [36]

The **diagnostic waiting time** is defined as the number of days between the date of the first visit in healthcare system related to breast problem where a referral to a diagnostic imaging test or to a breast cancer specialist appointment was issued to the date of breast cancer diagnosis or the date of the first histological test of breast tissue. Breast cancer treatment specialist is according to the EHIF quality standard for the first treatment a mammologist, gynaecologist, general surgeon or oncologist [58], but **breast cancer specialist** in the field on breast pathologies is defined in this thesis according to the breast cancer patient handling guideline as general surgeon or gynaecologist - Appendix 1 – Guideline for breast cancer patient handling.

3.2 Identified patient pathways

The construction and later the validation of patient pathways was done by the help of experts in the field – two family physicians and oncologist. Descriptions of patient pathways are used to identify all activities in healthcare system in order to diagnose breast cancer among women in Estonia. Gilbert et al identified the timepoints to

measure in diagnostic pathways as suspicion, referral, diagnosis and treatment in the creation process of the diagnostic wait times measurement framework. As the creators of the framework concluded that the suspicion is very difficult to define or measure, it was left out the framework. [47]

The pathway starts with the first visit to healthcare service provider with breast problem and ends with confirmed breast cancer diagnosis. The first visit is identified as patient being referred to a breast cancer specialist or a diagnostic test for breast cancer and the date of the visit when referral was issued was obtained from EHIF medical bills. The confirmed diagnosis includes the presence of an imaging test(s) of breast(s) and a histological analysis of breast tissue. In some cases, only the presence of a mammogram and a breast cancer diagnosis is considered valid in this thesis. This is based on the new NHS criteria for faster cancer diagnosis that the dismissal of cancer diagnosis is part of diagnostic waiting time [46]. Also, patients who receive the diagnosis only based on mammography results may have decided not to take any other tests or start the treatment, but they still participate in the breast cancer diagnostic pathway. The structure of data collection points for pathways can be seen on Figure 2. Timepoints between breast cancer diagnosis and first entrance to healthcare system.

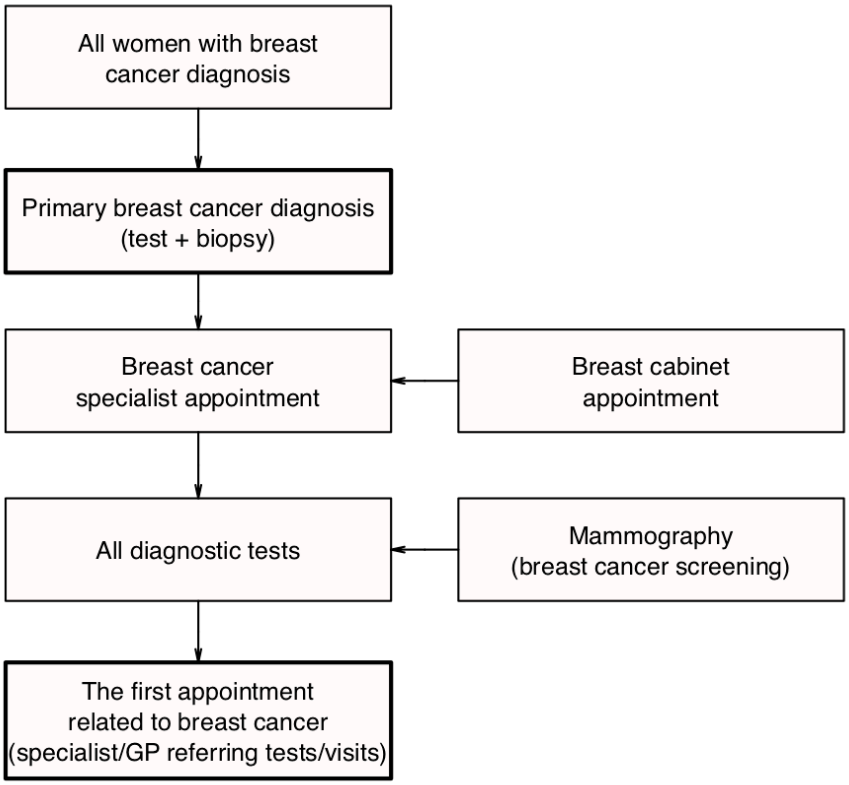

Figure 2. Timepoints between breast cancer diagnosis and first entrance to healthcare system.

Although, the emergency department is also one of the pathways identified it was not considered as a standard use of healthcare services for diagnosing breast cancer and is not considered relevant in this study. There are differences in accessing some services based on whether the referral letter from family physician is mandatory or not. Most of the specialist appointments in Estonia need the referral from family physicians, no referral letter is needed for ophthalmologist, dermatovenerologist, psychiatrist and gynaecologist appointment. [59] There were four main pathways identified for women with breast problems to reach breast cancer diagnosis in Estonia:

- Family physician pathway (Shown Appendix 2.1 Family physician pathway)
- Gynaecologist and other specialists pathway (Shown in Appendix 2.2 Gynaecologist and other specialists' pathway)
- Breast cabinet pathway (Shown in Appendix 2.3 Breast cabinet pathway)

- Breast cancer screening pathway (Shown in Appendix 2.4 Breast cancer screening pathway)

The starting point of the data collection is the primary breast cancer diagnosis. Although, it is required from physicians to state the primary diagnosis on medical bills, there are a lot of confusion whether it is the first-time diagnosis or first time in a certain hospital. The primary diagnosis was defined so that there was no previous breast cancer diagnosis within 10 years (2006-2016). The confirmed breast cancer diagnosis needs to be a combination of imaging tests and a histological test. The end point of the data collection includes visits at family physician, gynaecologist or other specialist, breast cabinet or breast cancer screening program.

3.3 Description of data

3.3.1 Study population

All female breast cancer patients of any age who had primary breast cancer diagnosed between 1 January 2016 to 31 December 2016 were eligible. Information was collected from medical bills available in the EHIF database about patients' diagnoses, diagnostic tests, information about referring specialties and demographic data (age, place of residence and health insurance status).

Diagnoses codes on medical bills are documented as primary diagnoses which represent the primary condition for treatment, or the costliest condition needed more resources and secondary conditions [60]. The primary diagnosis definition used on medical bills is not uniformly used or understood by physicians. This issue has been described also in the EHIF quality report in 2016 [61].

There are three centres in Estonia that provide oncological treatment for breast cancer – North Estonian Regional Hospital, East Tallinn Hospital and Tartu University Hospital [62], the cases chosen could be distributed between them to get the best representation of study subjects. Based on information given by the expert in the field the breast cancer screenings and diagnostic procedures which include biopsies are also done at Pärnu Hospital. Thus, some patients from Pärnu may have already confirmed the breast cancer diagnosis and come for treatment in any of two Tallinn's hospitals.

Some of the demographic characteristics are grouped for better readability and representation. The age groups are formed in 20-year interval to better represent the study population. For the regression analysis the place of residence based on counties is grouped based on the classification used by Statistics Estonia. The NUTS 3 classification (The Nomenclature of Territorial Units for Statistics) is used for the level of 150 000-800 000 inhabitants. According to NUTS 3 level counties are grouped as follows: North Estonia (Harju county), West Estonia (Hiiu, Lääne, Pärnu and Saare county), Middle Estonia (Järva, Lääne-Viru and Rapla county), North East Estonia (Ida-Viru county) and South Estonia (Jõgeva, Põlva, Tartu, Valga, Viljandi and Võru county). [63]

The inclusion criteria included: diagnoses codes based on ICD-10 C50 with sub codes and D05 (in situ) with sub codes, healthcare services codes mammography 6074, breast ultrasound 7952, magnetic resonance imaging 79250, 79251, 79252, 79253, fine-needle biopsy 7890, core needle biopsy 7891, open biopsy 66801, 66817, Her2 FISH analysis from breast or stomach tissue 66635. Also, diagnoses codes for referral: R92, Z12.3, Z80.3, Z01.4, N63. The detailed information about diagnoses codes and healthcare services codes is shown in Appendix 3 – The description of data selection process and in Appendix 4 – The explanation of included ICD-10 codes.

The exclusion criteria included: men were excluded from this study due to Estonia's small size to have only few cases of men with breast cancer diagnosis therefore the anonymity cannot be guaranteed. Also, women with previous breast cancer diagnoses during 2006-2016 were excluded because they are already monitored regularly and waiting times may be shorter than average. The selection process of study subjects is shown on Figure 3. Selection of study subjects based on selected pathways who had their first visit with specific diagnoses codes and received breast cancer diagnosis in 2016 in Estonia.

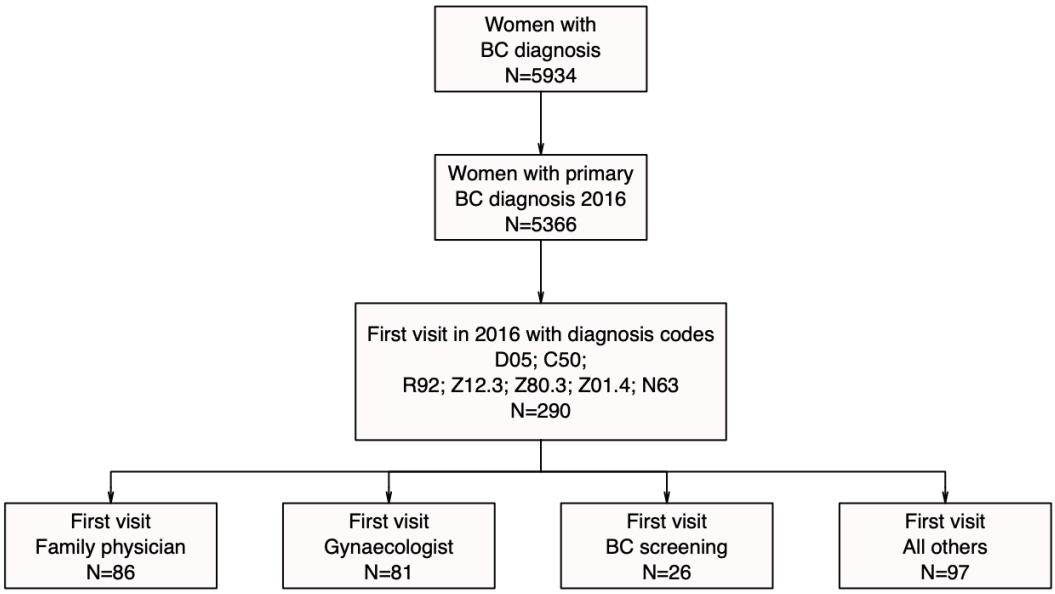

Figure 3. Selection of study subjects based on selected pathways who had their first visit with specific diagnoses codes and received breast cancer diagnosis in 2016 in Estonia.

3.3.2 Data collection

Anonymised data was collected from medical bills from the EHIF database which included diagnoses codes, health services codes, dates of visits and tests. The linking of data of different activities for pathways was done by the EHIF analyst and data subjects were coded for the author. The collected variables related to patients were age, place of residence (on a county level), health insurance status. Variables related to diagnosis were the breast cancer diagnosis (diagnostic or breast cancer screening program), type of imaging test performed (mammography, ultrasound, MRI), type of histological tests (fine needle or core needle biopsy, open biopsy). Variables related to waiting times were the dates of the first visit with breast problem (a referral for diagnostic tests or a specialist appointment), of mammography (diagnostic or breast cancer screening program), ultrasound, MRI, and of confirmed breast cancer diagnosis (presence of a combination of imaging test together with histological test). Variables related to pathways were the speciality of referring physician or nurse/midwife (referring to diagnostic test or specialist appointment), the speciality of diagnosing physician and the diagnosing institution.

The most recent and complete data from medical bills in the EHIF database is from the year 2016. Therefore, patients receiving their breast cancer diagnosis in 2016 were chosen for data subjects. Data about breast cancer diagnostic tests is traced back in time for time period of ten years (2006-2016). Finding any previous diagnostic procedures long before breast cancer diagnosis might be important factor influencing diagnostic waiting times. Individuals who have had previous experience with testing procedures already know how to approach healthcare system to get appropriate help. Longer time period was also suggested by the analyst at the EHIF. Ten-year period was chosen to differentiate between primary and not primary breast cancer diagnosis. Although, medical bills in EHIS contain the field which requires physicians to state if the cancer diagnosis is primary or not the misuse is common according to data analysts at EHIF. Longer period allowed the author to exclude all these patients who met the inclusion criteria but did have previous breast cancer diagnosis. And wise versa, medical bills which did not contain information about the cancer diagnosis being primary and did not have any previous diagnosis could be included in the study.

3.4 Data analysis

Descriptive analysis of collected data about waiting times includes calculating mean, median, mode and interquartile range. Other researchers have used multivariate logistic regression analysis [31] and simple regression together with multivariate linear regression analyses [43] for evaluating associations between waiting times and different other variables. Regression analysis can be used to estimate the associations between variables. The descriptive model and the prognosis are more accurate when the independent variables have stronger association with the dependent variable. [51] The multiple linear regression analysis was chosen to see if different patient characteristics and pathways variables are related to the waiting times and to understand the size of their effect. There is no series of simple regression analyses done as it is suggested to give possibly erroneous results because the simultaneous interaction of all variables is not included in the analysis. [64]

The regression analysis needs to be simple and explain well the dependant variable through independent variables. Sometimes it is needed that some of the independent variables are not included due to before mentioned reason. [65] The categorical data like

pathways and place of residence is dummy coded for the analysis. It is advisable to plot the data which helps to choose the right model [51]. First the data is visualized in scatter plots to get the overview of data distribution. Any data subject with missing data is eliminated from the data set before doing the regression analysis. Data management and statistical analysis are performed with program MS Excel.

3.5 Method quality control

3.5.1 Validity and reliability

The consent of patients was not asked because the data was used in an anonymised form. There was no need for ethics committee approval because all data was anonymised by the EHIF before handing over to researcher. Also, no identifiable personal information was collected. The anonymity was ensured with using any identifiable information in generalised form. For example, the information about diagnosis was person-based but place of residence within a county accuracy. There is no possibility to identify anyone according to collected and analysis of data.

3.5.2 Biases

Misclassification bias may occur due to differences in diagnoses codes entered by physicians on the medical bills presented to the EHIF. According to consultations with analytics from the EHIF there are issues with indicating whether the cancer diagnosis is primary or not. To overcome this bias, data from previous ten years was included for background information to exclude patients who had previous cancer diagnosis. Misclassification may arise also among healthcare services entered to medical bills.

3.5.3 Ethical considerations

Data was collected anonymously from medical bills and the linking of data of different activities for pathways was done by the EHIF analyst and data subjects were coded for the author. All collected data will be deleted within one week from the defence of this thesis. There is no conflict of interest to report.

4 Results

4.1 Descriptive results

4.1.1 Demographics

There were 5934 medical bills identified for 2016 in EHIF database with breast cancer diagnoses codes and healthcare service codes for imaging tests in combination with breast tissue biopsies. 5366 of them had primary breast cancer diagnosis reported on medical bills in 2016 in Estonia. Data subjects were excluded if they did not have any date of first visits related to breast problems. The final sample included 290 women, of whom 26 (9%) entered the healthcare system through breast cancer screening program. 86 (29,7%) of women had their first visit at family physician, 81 (27,9%) gynaecologist and 97 (33,4%) women had first visits at different specialists.

The mean age of women at breast cancer diagnosis was 64,8 years (median 73,5 years), with largest difference of 44,1% of study subjects were in the age group of 60-79 years. The least women were diagnosed with breast cancer aged 20-39 (3,4%). The vast majority of the study subjects 128 (44,1%) live in Harju county. Two of the next largest groups were Ida-Viru county with 42 (14,5%) and Tartu county with 32 (11%) women. The place of residence was not recorded for one woman. The date of death was recorded for 8 of study subjects and 6 (2,1%) women died due to breast cancer in 2016. The detailed overview of the results is shown in Table 1. Demographic characteristics and overall diagnostic waiting time of women diagnosed with breast cancer.

Table 1. Demographic characteristics and overall diagnostic waiting time of women diagnosed with breast cancer.

Category	N	%
Age		
20-39	10	3,4
40-59	77	26,6
60-79	128	44,1
80-100	75	25,9
Place of residence		
North Estonia	128	44,1
West Estonia	26	9
North East Estonia	42	14,5
Middel Estonia	31	10,7
South Estonia Jõgeva county	62	21,4
Not known	1	0,3
Waiting time		
Mean	14,01	
Median	8	
Mode	0	
IQR *	14	
Min value	0	
Max vaule	112	
First visit (based on pathway)		
Breast cancer screening	26	9
Family physician	86	29,7
Gynaecologist	81	27,9
Other specialists	97	33,4
Died (due to breast cancer)	8 (6)	2,8
Total	290	100

**IQR – interquartile range*

4.1.2 Waiting time for breast cancer diagnosis

The mean waiting time for breast cancer diagnosis was 14,01 days and median was 8 days. The minimum of days to wait for diagnosis was zero days and the overall maximum time 112 days. The most frequently occurring number of days to have to wait for breast cancer diagnosis was zero days. The results of waiting time were compared with NHS new faster diagnosis guideline which states 28 days for the maximum diagnostic waiting time for breast cancer [8]. The overall waiting time for breast cancer diagnosis in studied women is less than 28 days and is likewise with all waiting times based on pathways.

4.2 Diagnostic waiting times based on pathways

The initially defined pathways were reorganised based on the usability of available data. The breast cabinet pathway was not clearly identifiable and was excluded from the pathway list. There was not enough midwife (or nurse) appointments (2 appointments met the inclusion criteria) that could represent the breast cabinet appointments. Therefore, these results were included in the gynaecologist pathway because for both appointments there is no need for referral letter.

Additionally, the other specialists' visits were separated from gynaecologist pathway due to the difference in access – most of other specialist appointments in Estonia need a referral letter. The pathways were divided as follows: family physician, gynaecologist, all other specialists and breast cancer screening pathway. All other specialists' pathway (97 subjects) included specialities like anaesthesiologist, dermatovenerologist, emergency medicine, gastroenterologist, nephrologist, oncologist, pulmonologist, radiologist, internal medicine, general medicine (residents) and general surgery was documented in 44 cases which constitutes a 45,3% of other specialists' pathway.

The mean waiting time was shortest for gynaecologist pathway – 11,43 days and the median waiting time was also shortest for the same pathway with 5 days. The minimum and maximum values of waiting time differed greatly - zero and 93. The detailed overview of the results is shown in Table 2. Diagnostic waiting time statistics according to patient pathways. Waiting times comparison according to the four pathways showed that breast cancer screening program has the longest median waiting time – 13 days. The shortest mean diagnostic waiting time was 5 days in gynaecologist pathway. The visualisation of waiting times based on patient pathways is shown on Figure 4. Comparison of median diagnostic waiting times based on patient pathways.

Table 2. Diagnostic waiting time statistics according to patient pathways.

	Total	Family physician	Gynaecologist	Screening	All others
Mean	14,01	17,45	11,43	17,77	12,1
Median	8	10,5	5	13	7
Mode	0	7	0	10	0
IQR	14	16,5	14	11,75	13
Min value	0	0	0	0	0
Max value	112	112	93	103	92

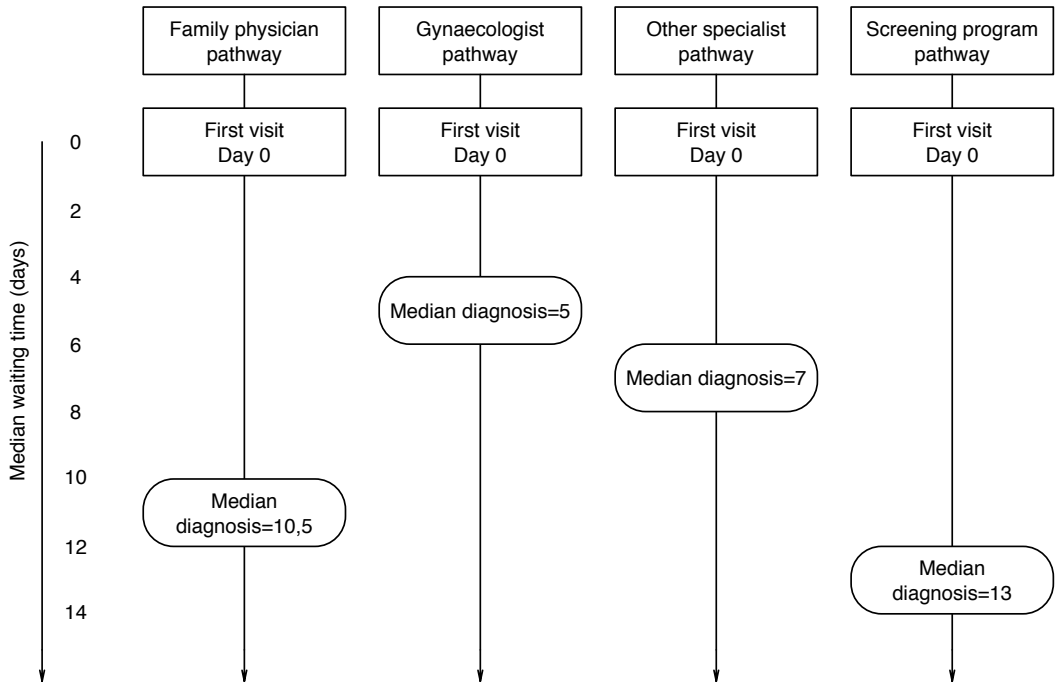

Figure 4. Comparison of median diagnostic waiting times based on patient pathways.

The distribution of diagnostic waiting times for breast cancer revealed differences in the place of residence of study subjects. Women living in North East Estonia had mean waiting time 21 days (median 12 days), in West Estonia 19,8 days (median 9,5 days) and in South Estonia 16,5 days (median 13 days). The distribution also showed the possible outlier results for all groups but with higher results in three groups – West, North East and North Estonia. The rest of the results are visualised on Figure 5. Breast cancer diagnostic waiting times distribution according to place of residence.

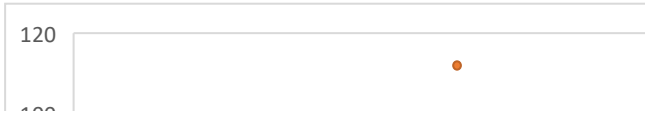

Figure 5. Breast cancer diagnostic waiting times distribution according to place of residence.

4.3 Demographic differences in breast cancer diagnostic waiting times based on pathways

The total median diagnosis waiting time was shortest in the age group of 20-39 years (5,5 days). The longest waiting time between 74-83 days was among the oldest study subjects aged in the age groups of 60-79 years and 80-100 years with slightly longer for the oldest age group. The longest median waiting times were measured in South (13 days) and North East Estonia (12 days) and the lowest median waiting times were in Middle (6 days) and North Estonia (6 days).

Women who enter the healthcare system through family physician pathway have the median diagnostic wait time 43 days if they are living in West Estonia. The shortest median waiting time (1 day) is among North Estonian women who start their path at gynaecologist appointment. The longest median waiting times for screening and other specialist pathway were measured among North East Estonian female residents (40 days and 12 days respectively). The detailed overview of median diagnostic waiting times is

shown in Table 3. The median diagnostic waiting time based on pathways and demographic data.

Table 3. The median diagnostic waiting time based on pathways and demographic data.

	Family physician N=86 (29,7%)	Gynaecologist N=81 (27,9%)	Screening N=26 (9%)	Other N=97 (33,4%)	Total time N=290 (100%)
Age at diagnosis					
20-39	35	-	-	2	5,5
40-59	15	6,5	13	8	11,5
60-79	8,5	5	64	6	74
80-100	9	3	-	11	83
Place of residence					
North Estonia	8	1	10	7	6
South Estonia	14	13	14	6	13
West Estonia	43	7	18,5	6	9,5
Middle Estonia	6	4	19	8	6
North East Estonia	11,5	7	40	12	12
Total time	10,5	5	13	7	8

One of the data subjects with missing data about place of residence was eliminated from the data set before doing the multivariate linear regression analysis. Insurance status was excluded from data due to not being significant because there were no uninsured women in the study sample. North Estonia region was chosen for the reference group for the regression analysis because of the large number of inhabitants in the area and one of the two regional medical competence centres NEMC is located there. Breast cancer screening pathway was chosen for the reference group for pathways because of its organized approach for assessment and diagnosing breast cancer.

The result of the first scatter plot analysis showed that there was positive relationship between diagnostic waiting time with place of residence and age among women living in South Estonia (R^2=0,003) and Middle Estonia (R^2=0,0015). The detailed overview of a scatterplot summarized results on Figure 6. Breast cancer diagnostic waiting times based on age and place of residence.

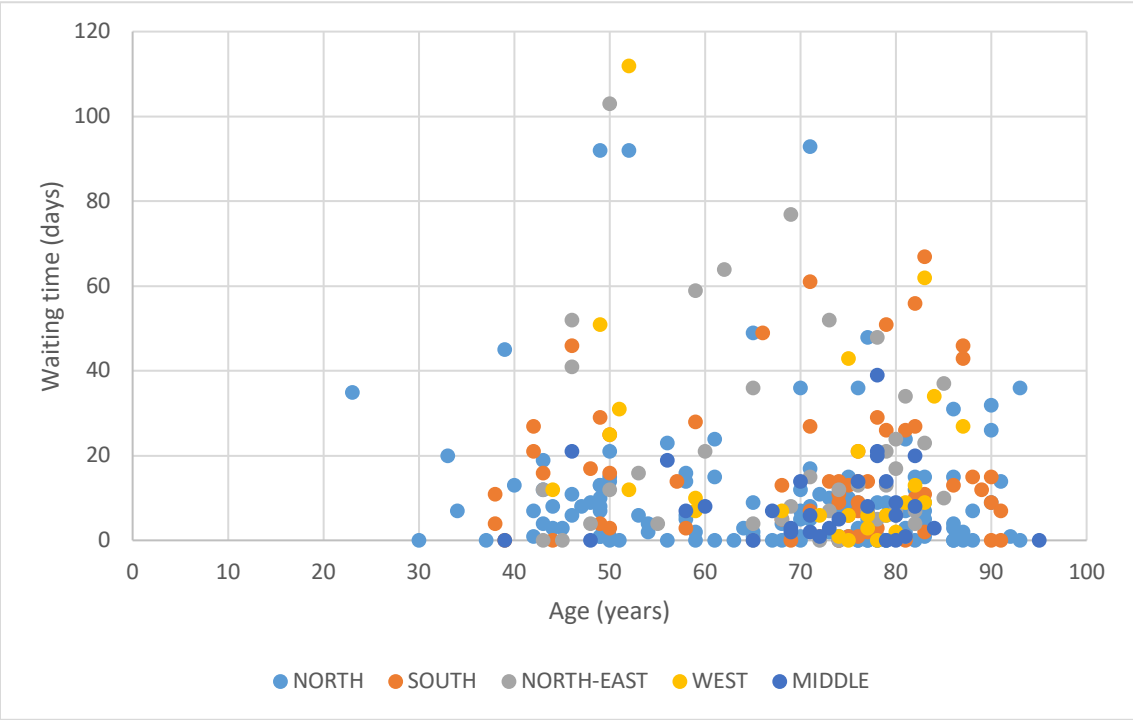

Figure 6. Breast cancer diagnostic waiting times based on age and place of residence.

The results of the second scatter plot analysis showed that there was positive relationship between diagnostic waiting time with pathway and age among women starting their patient journey through other specialists' pathway (R^2=0,0087), family physician pathway (R^2=0,0432), gynaecologist pathway (R^2=0,0166) and through breast cancer screening program (R^2=0,0044). The detailed overview of a scatterplot summarized results on Figure 7. Breast cancer diagnostic waiting times based on age and patient pathway.

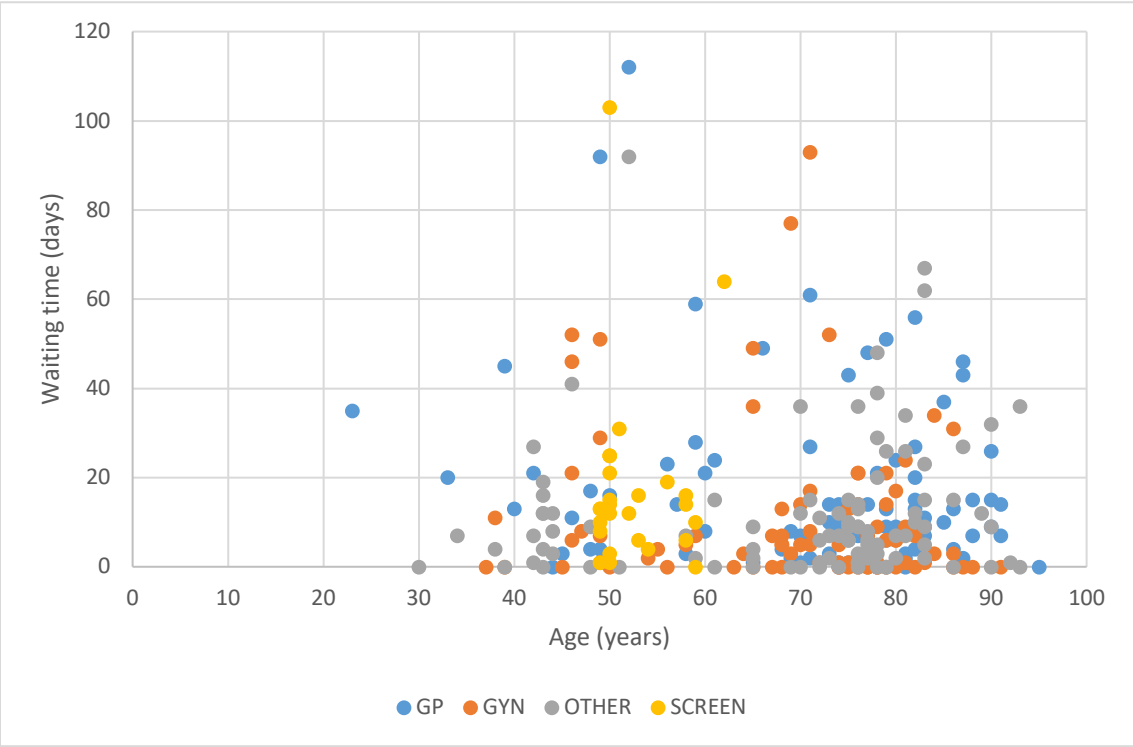

Figure 7. Breast cancer diagnostic waiting times based on age and patient pathway.

The significant relationship between waiting times and place of residence appeared from the results of multivariate linear regression analysis. The place of residence in North East Estonia (p=0,00092504) and West Estonia (p=0,00888271) are related to longer waiting times compared to women living in North region of Estonia. The p-value for South Estonia was slightly over the recommended threshold, but the result could still be included. Based on the results none of the pathways nor age had any relationship with breast cancer diagnostic waiting times in Estonia. The detailed report of regression analysis is shown in Table 4. The analysis report of multivariate linear regression.

Table 4. The analysis report of multivariate linear regression.

Regression Statistics	
Multiple R	0,29880026
R Square	0,089281596
Adjusted R Square	0,06326107
Standard Error	17,80496876
Observations	289

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	8701,984256	1087,748032	3,43119875	0,00087461
Residual	280	88764,73547	317,0169124		
Total	288	97466,71972			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95,0%*	*Upper 95,0%*
Intercept	19,77475373	5,266749556	3,754640984	0,00021111	9,40730207	30,1422054	9,40730207	30,1422054
PW 1	2,042316626	4,313279893	0,473495038	0,63622899	-6,4482562	10,5328895	-6,44825623	10,5328895
PW2	-4,311098731	4,213246496	-1,023224902	0,30708473	-12,604759	3,98256113	-12,6047586	3,98256113
PW3	-3,923807805	4,155551858	-0,944232665	0,34586481	-12,103897	4,25628175	-12,1038974	4,25628175
Place1	5,178757778	2,828390512	1,830991073	0,06816447	-0,3888512	10,7463667	-0,38885116	10,7463667
Place2	-2,018412043	3,602169735	-0,560332297	0,57570085	-9,1091841	5,07236002	-9,10918411	5,07236002
Place3	10,60868043	3,168531127	3,348138304	0,00092504	4,37151405	16,8458468	4,37151405	16,8458468
Place4	10,16941965	3,859381032	2,634987207	0,00888271	2,57233422	17,7665051	2,57233422	17,7665051
Age	-0,104967179	0,074052661	-1,417466678	0,15745833	-0,2507378	0,04080345	-0,25073781	0,04080345

5 Discussion

5.1 Summary of the results and theory

5.1.1 Data sources for mapping and describing patient pathways

The definition of time interval that is measured as waiting time ought to emphasise on defining the starting timepoint to avoid the confusion [38], [47], [35]. If the starting point is clearly defined the measurement of waiting time gives reliable and comparable results which can be used for quality improvement purposes in the healthcare system. During the data collection preparation phase all activities in Estonian healthcare system were identified in order to diagnose breast cancer among women. Still, during data collection phase some difficulties appeared with defining the patient's first entrance to healthcare system. If the first date of the visit was not available these data subjects were removed. The final study sample of 290 women is rather small compared to the national statistics in Health Statistics and Health Research Database about new breast cancer cases in 2016 in Estonia which was 767 [14]. Waiting times due to the patient choice to deliberately delay can influence the statistical number [35] and should be excluded from the data set or handled separately. Since based on available data from the EHIF this was not possible, this could possibly influence the total results of measured waiting times for breast cancer diagnosis. Therefore, this could be due to the weakness of chosen method, but it could also mean that measuring diagnostic waiting times for breast cancer based on data from EHIF database is not suggested. The data on medical bills serves the main purpose of paying for indicated healthcare services and the data may not be comprehensive enough for evaluating other purposes like waiting times.

Viberg *et al* pointed out that for some OECD countries the measurement of waiting times starts before the actual first appointment and this could possibly influence the total length of waiting time for breast cancer diagnosis [35]. According to before mentioned if the first contact with healthcare system is not defined as the first visit, the actual first contact by the patient is when the appointment due to the problems related to breasts is booked. The data from EHIF database did not provide this type of information to possibly identify the first contact when patient is booking an appointment due to breast problems. Although, it is questionable but some of this kind of data might be found in medical records in EHIS.

The NHS uses the suspected cancer referral targets to ensure that patients with suspected cancer can get to the cancer specialist with maximum of two weeks. The suspicion is defined as the first visit with the cancer related problem at family physician appointment. [53] Gilbert et al identified the suspicion as one of the timepoints in measuring the diagnostic pathway but was later dismissed as being too difficult to define or measure correctly [47]. During the data collection preparation phase, it became evident that not always is the suspicious finding recorded accordingly with diagnoses codes on medical bills. There were a lot of data subjects with the same date on the first visit and the breast cancer diagnosis. Although, the reasons behind this phenomenon were not analysed one of the reasons may be the inconsistent use of diagnoses codes for primary diagnosis which is also mentioned in the EHIF quality report in 2016 [62].

The construction and later the validation of identified patient pathways was done by the help of experts in the field – two family physicians and oncologist. Descriptions of patient pathways were used to identify all activities in healthcare system in order to diagnose breast cancer among women in Estonia. During the data analysis phase, it occurred that the initial pathways are not all suitable to measure waiting times. There were only two midwife appointments in the study sample and those were then included to the gynaecologist pathway. Additionally, the other specialists' visits were separated from gynaecologist pathway due to the difference in access in healthcare system – most of other specialist appointments in Estonia need a referral letter. The new pathways were divided as follows: family physician, gynaecologist, all other specialists and breast cancer screening pathway. Although, 45,3% of other specialists' pathway constitutes for general surgery specialty which may influence the representativeness of that pathway. Since the surgeon appointments need referral letter these results are more than surprising. More research is needed on the reasons why the first visits of general surgeon's patients are not recorded in anywhere else (primary level or gynaecologist for example).

The results showed that the others specialists' pathway with 33,4% was the most preferred when entering the healthcare system with breast problems. The breast cancer screening program pathway with 9% was the least preferred pathway but the total number of women who chose this pathway was smaller compared to all other pathways. This is because this pathway has the age limitation which is the set age group

representing women with highest risk of developing breast cancer. All pathways besides breast cancer screening program had similar numbers of study subjects (gynaecologist 27,9% and family physician 29,7%) in the final sample. This shows that the distribution of subjects is more similar in all pathways but not in the breast cancer screening program.

The mean age of women at breast cancer diagnosis was 64,8 years (median 73,5 years), with largest difference of 44,1% of study subjects were in the age group of 60-79 years. These results demonstrate well that the probability of receiving breast cancer diagnosis is at older age. The two second largest groups with similar number of study subjects were from 40-59 years and 80-100 years with 26,6% and 25,9% respectively. Based on the results it is seen that the number of breast cancer diagnoses is almost double in the group of 60-79 years compared with the before mentioned age groups. The suggested age for screening programs is 50-69 [4] is based on the risk for developing breast cancer increases at the age 50. The negative correlation (r=–0,081899056) between the age and waiting time suggest that increase in women's age is related with decreased diagnostic waiting time in Estonia. This could be due to increased access to healthcare services in the form of breast cancer screening program. The majority of study subjects of 128 (44,1%) lived in Harju county and two of the next largest groups were Ida-Viru county with 42 (14,5%) and Tartu county with 32 (11%) women. These results are explained with the higher number of inhabitants in these regions.

5.1.2 Measuring diagnostic waiting time

In Estonia there are no country specific breast cancer diagnostic and treatment guidelines and the agreement among physicians is to follow American guidelines. The Estonian breast cancer patient handling guideline was published in 2016 but is currently in an unapproved state [17]. The need for this kind of guideline has been also reported in Ontario, Canada where the lack of agreement caused variation in care process and possibly missing patients who needed access to healthcare system but could not get that. Another issue mentioned was the need of setting targets for diagnostic part of patient pathway. [47] EHIF has set a criterium where the time from the first visit at healthcare provider to the start of an oncological treatment needs to be measured for breast cancer patients. [49] There is no indicator to measure the time from the first visit in the healthcare system with breast cancer suspicion to breast cancer diagnosis. If there are no

specific instructions to follow the data collection process may also suffer and the lack of incentives will not support the need for change.

There is growing interest in reducing cancer related waiting times which can be the sources of anxiety and distress for patients [66]. This means that for the evaluation of diagnostic waiting times needs good quality data sources. According to the Aarhus statement both the time points and the time intervals need to be defined to measure any part of early cancer diagnosis [36]. The date of primary cancer diagnosis from EHIF medical bills does not always equal to the date of the confirmation of breast cancer diagnosis. In this study the date of breast cancer diagnosis was defined according to the hierarchy composed by European Network of Cancer Registries. The date of the first appointment related to breast problem was traced by referral letter information or referral to diagnostic tests showing the first time woman visited healthcare provider and started the breast cancer diagnosis pathway. The diagnostic tests that were required for breast cancer diagnosis are mammography and breast tissue biopsy, but only the biopsy date and breast cancer diagnosis were considered valid. This is based on the new NHS criteria for faster cancer diagnosis that the dismissal of cancer diagnosis is part of diagnostic waiting time [46]. Also, patients who receive the diagnosis only based on mammography results still participate in the breast cancer diagnostic pathway.

Baena-Cañada *et al* concluded that no delays were reported when patients entered the health system through screening program for breast cancer [38]. Although the duration of delay can be defined differently in other countries, based on the results of this study women who entered the healthcare system through the gynaecologist pathway had the highest number of waiting time with zero days. Also, the overall results for gynaecologist waiting time were lower than compared with other pathways. This could be explained with the fact that the gynaecologist appointments do not need referral letter. The longest of median waiting time of 13 days was in breast cancer screening pathway. Similar results were found by Vseviov in her study that women diagnosed with breast cancer during screening had significantly higher risk for moderate delay [43]. Although, women of the risk group who are invited to breast cancer screening can book appointment according to their own preference and they do not need to wait for the paper-based invitation.

The results of measuring diagnostic waiting time from medical bills data showed that the overall median time for breast cancer diagnosis is 8 days. The mean waiting times were measured higher than median in all pathways which indicates the distorted distribution of waiting times. Compared with NHS new faster diagnosis target [8] the maximum diagnostic waiting time mean and media for breast cancer in Estonia is less than 28 days. The mean waiting time is lower compared to the results of study by Vseviov in 2012 where the median time period from the first visit to oncologist-mammologist visit was 16 days [43]. The minimum and maximum number of days that women had to wait for their diagnosis were zero and 112 which means that for few cases waiting time is more than three months. The most frequently occurring number of days to have to wait for breast cancer diagnosis was zero days which could refer to good access to physician appointments and diagnostic tests. Also, on the negative side this could be the sign of misclassification problem among physicians who are not consistent with diagnoses codes. The reasons behind the large number of zero days waiting time were not researched in this study.

The results showed that the longest median waiting time was for breast cancer screening pathway with 13 days. The nationally organised screening programs have proved being the most effective way for early diagnosis of breast cancer among asymptomatic women [18], [29], [30], [31]. The breast cancer screening program in Estonia is organised based on the increased risk for age in developing breast cancer so that women of the risk group are invited at that year can book appointments according to their own preference and they do not need to wait for the paper-based invitation [11]. The well-organised system should be able to guarantee the high level of quality and accuracy of data that is recorded during the screening appointments. The reason for the longest median waiting time may be derived from the well documented status of breast cancer screening program appointments and diagnoses concluding that this pathway could be used as the good standard for measuring the breast cancer diagnosis waiting times in Estonia. More research is needed to identify the timepoints that are used for documenting the breast cancer screening process to evaluate the suitability for the same timepoints used for different pathways for waiting times measurement.

Similar research was done in 2012 by Vseviov who studied the risk factors of delay of breast cancer diagnosing caused by healthcare system [43]. The median time from the first visit in healthcare system to the first visit at breast cancer specialist (oncologist-

mammologist) was 16 days compared to 8 days from the first visit to breast cancer diagnosis according to the results of this study. The work of Vseviov had some differences with this thesis as using only patient reported and survivor data. The comparison of results from both works showed that women living in North-East and West Estonia have significant difference in waiting times compared other regions. Interestingly the comparison is made with different region – Vseviov compared them with South Estonia and the author of this thesis used the comparison using North Estonia region as a reference.

The outlying results were also detected in the measurement of diagnostic waiting times for breast cancer using both the scatter plots and the box chart. Based on the evaluation of available data related to the outlying results, it was concluded that these are valid datapoints and should not be excluded as outliers from the statistical analysis. This means that all necessary datapoints for measuring diagnostic waiting time (the dates of imaging tests with biopsy and the date of first visit with diagnoses codes related to breast problems) were present and the calculation of waiting time was possible. Also, all of the top five waiting time results represented all pathways.

5.1.3 Diagnostic waiting times differences based on demographic data

The results showed that younger women wait significantly less for breast cancer diagnosis compared with the older women. The total median diagnosis waiting time for younger women in the age group of 20-39 years was 5,5 days compared with 74 and 83 days among women in the age groups of 60-79 years and 80-100 years. The differences were also found in comparing median waiting times based on the place of residence of women. The longest wait for diagnosis was measured for women who lived in South and North East Estonia with median 13 and 12 days. Women living in both North and Middle Estonia had to wait for breast cancer diagnosis for median 6 days.

Significant difference was seen in diagnostic waiting times based on patient pathways. Women in West Estonia who enter the healthcare system through family physician pathway have the median diagnostic wait time 43 days. The shortest median waiting time at gynaecologist pathway was among women living in North Estonia with only 1 day. These results may differ whether woman lives in the capital Tallinn or in Harju county. Since the place of residence data was obtained on the county level there was no possibility for more precise analysis. Women living in the North East region had the

longest median waiting times for breast cancer screening and other specialists' pathways with 40 and 12 days respectively. More research is needed to analyse the reasons for long diagnostic waiting times in North East Estonia.

Multivariate linear regression was used to analyse multiple variables relationship with breast cancer diagnostic waiting time. This analysis was chosen to consider the interactions of variables as well as their relationship with waiting times simultaneously. As it is suggested that the descriptive model and the prognosis are more accurate when the independent variables have stronger association with the dependent variable [51], the scatterplots were used for summarizing the results before regression analysis. The removal of one subject due to missing place of residence data was needed to keep the model simple. The multiple linear regression analysis revealed the relationship between place of residence and breast cancer diagnostic waiting times.

The significant relationship between waiting times and place of residence appeared from the results. The place of residence in North East Estonia and West Estonia are related to longer waiting times compared to women living in North region of Estonia. The *p-value* for South Estonia was slightly over the recommended threshold, but the result could still be included. The results are very similar to the work of Vseviov which concluded that the highest moderate risk for delay is among women living in West Estonia and high risk for delay among women living in West and North East Estonia [43]. Based on the results none of the pathways nor age had any relationship with breast cancer diagnostic waiting times in Estonia.

5.2 Main contribution to the core audience

Measuring diagnostic waiting times is done less than measuring treatment or procedures waiting time. Therefore, there are few guidelines and special targets to tackle the long diagnostic waiting times problem. The measurement of diagnostic waiting times should be based on clearly identified timepoints in the process of diagnosis. The emphasize should also be on the good quality of recorded data to be able to use them for waiting times measurement. For improving healthcare processes quality special waiting times target could be used which should be based on the best practice and research.

The measurement of diagnostic waiting time can only be done in a retrospective way because of the starting point being the diagnosis received. Although, the retrospective analysis cannot predict the need to decrease the waiting time, it still gives valuable information about diagnostic waiting times for receiving cancer diagnosis or for dismissing it. Waiting for cancer diagnosis is burdensome for most patients and setting targets to keep the time period as short as possible is a sign of putting patient first.

The overall median breast cancer diagnostic waiting time was below NHS new criteria for breast cancer faster diagnosis. The longest median waiting time was measured among women who entered the healthcare system through breast cancer screening program. There was large variation on individual level seen in breast cancer diagnostic waiting times. The results showed that younger women wait significantly less for breast cancer diagnosis compared with older women. Women living in South and North East Estonia experience the longest median waiting times were measured. The family physician pathway had the median diagnostic wait time 43 days being the longest for women living in West Estonia. The results of multivariate linear regression analysis are similar with earlier results from 2012. Additionally, the results did demonstrate that none of the pathways nor age had any relationship with breast cancer diagnostic waiting times.

5.3 Limitations

The inconsistency of recording the date of the first visit related to breast problems caused the elimination of large amount of study subjects during the data selection process. This can limit the generalisation of the results to all women, though the reason is more related to available data quality. Since the results of diagnostic waiting times in relation with demographic data were similar with earlier study done in 2012 this could add some credibility to the results of this thesis.

Limitations are related to data availability and quality because the main purpose of medical bills is not related to measure waiting times. The data was collected according to inclusion and exclusion criteria to ensure the best quality to fulfil the thesis aim. There was no possibility to remove the results of data subjects whose waiting time length was influenced due to the personal choice of delaying. Therefore, it is impossible

to say how much person-based delay may affect the breast cancer diagnosis waiting time.

Although, the regression analysis revealed the significant relationship of waiting times and people living in West and North-East Estonia compared with women from North Estonia it is not correct to conclude that other variables do not account for waiting times. There may be other predictors that were not measured due to not being able to identify them based on available data. The other limitation with regression analysis is that even though the relationships were revealed the causality cannot be determined. [67]

5.4 Future Research

Analysing the theory and the results of this study some new areas of investigation were identified:

- Further research is needed to study on the diagnostic waiting times because of the limitations of this thesis. The methodology chosen together with data from medical bills of the EHIF database lead to large number of eliminated study subjects. Based on the first visit definition in this thesis other data sources are suggested for future research.

- Further research is needed to evaluate the reasons why the first visits of general surgeon's patients are not recorded in anywhere else (primary level or gynaecologist for example).

- Further research is needed to identify the timepoints that are used for documenting the breast cancer screening process to evaluate the suitability for the same timepoints used for different pathways for waiting times measurement.

- The data quality and integrity assessment because of the measured breast cancer waiting times having large number of zero days visits.

- Research is needed to identify and analyse the reasons behind longer waiting times and especially in the North East region of Estonia.

- Research is needed to identify the reasons for large variation of diagnostic waiting times for breast cancer on individual level.

5.5 Final conclusions

Medical bills from EHIF database may not be comprehensive enough to cover all the steps from breast problems to breast cancer diagnosis and therefore not suggested for measuring the breast cancer diagnostic waiting time. The inconsistency of using diagnoses codes for the first visit is seen as there was a large number of visits to general surgeon speciality where referral letter is mandatory.

The first steps of measuring diagnostic waiting time include clear definition of the timepoints and intervals of breast cancer diagnostic process and agreement on the consistency of recording data related to waiting time.

There is large variation on individual level of breast cancer diagnostic waiting times.

The most frequently occurring number of days to have to wait for breast cancer diagnosis was zero days.

The median waiting time 8 days for breast cancer diagnosis is relatively low compared to the results of previous research done in Estonia and other countries.

The breast cancer diagnostic waiting times differ significantly based on the place of residence and patient pathway with longest waiting time 43 days among women living in West Estonia and starting their path in healthcare from family physician.

The place of residence in North East Estonia and West Estonia is related to longer waiting times compared to women living in North region of Estonia.

6 Summary

The aim of this thesis was to describe the diagnostic waiting times for breast cancer through measuring the time from the first entrance to healthcare system to confirmed breast cancer diagnosis in Estonia.

The results of this thesis provide information about diagnostic waiting times for breast cancer. Firstly, the relevant data sources to map patient pathways were identified as the date of first visit with diagnosis codes related to breast problems and the date of breast cancer diagnosis was identified in the order of importance as the date of imaging test and breast tissue biopsy if available.

Secondly, the identified patient pathways are as follows: family physician, gynaecologist, other specialists' and breast cancer screening program. 33,4% of women with breast problems preferred the other specialists' pathway to enter the healthcare system.

Thirdly, the overall median breast cancer diagnostic waiting time is below NHS new criteria for breast cancer faster diagnosis since no available target for diagnostic waiting time in Estonia is available. The longest median waiting time is among women who enter the healthcare system through breast cancer screening program. Large variation on individual level is seen in breast cancer diagnostic waiting times.

Fourthly, the longest median waiting times are experienced by women living in South and North East Estonia. Women in West Estonia have the longest median diagnostic waiting time via family physician pathway. The place of residence in North East and West Estonia are related to longer waiting times compared to women living in North region of Estonia. None of the patient pathways nor age has any relationship with breast cancer diagnostic waiting times.

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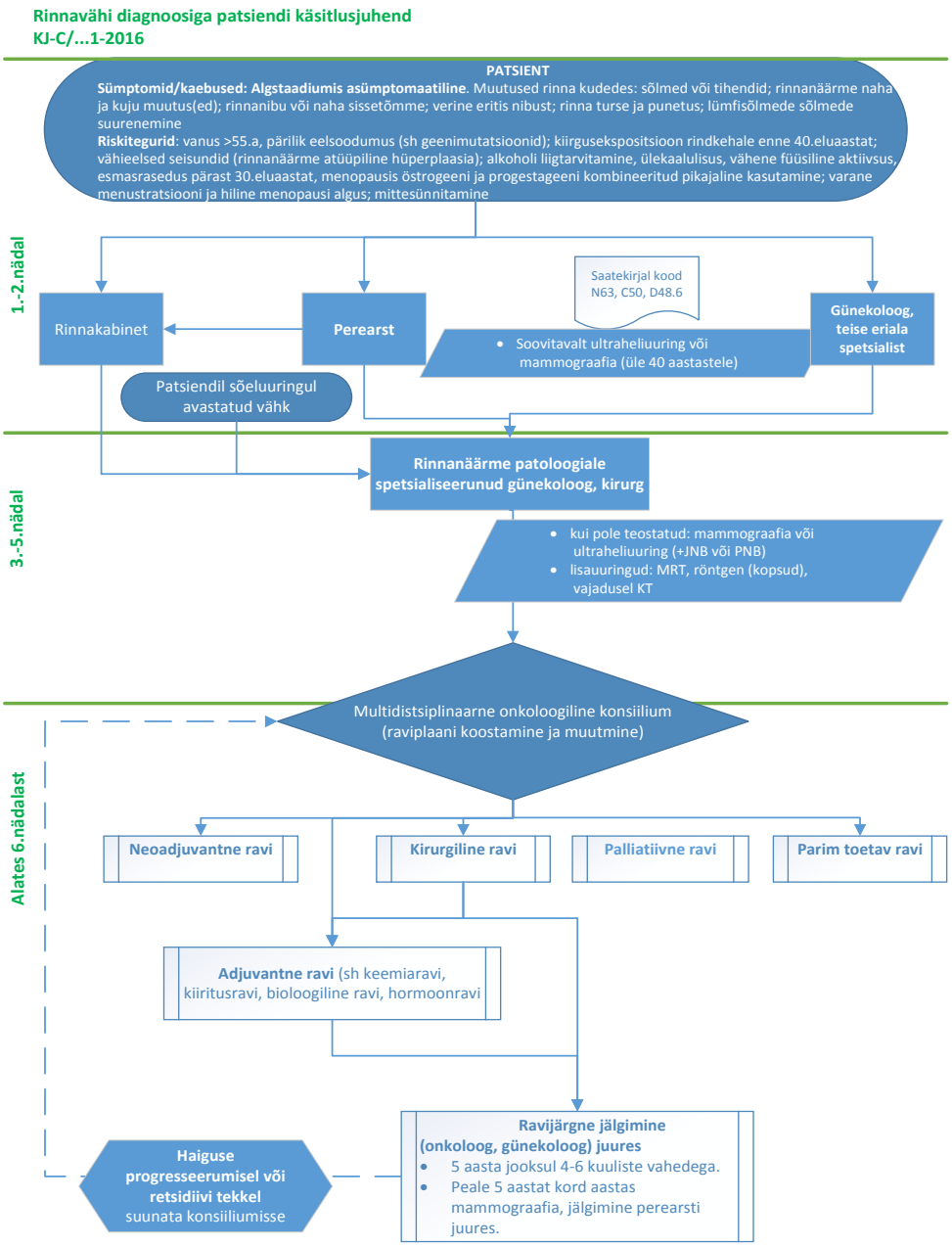
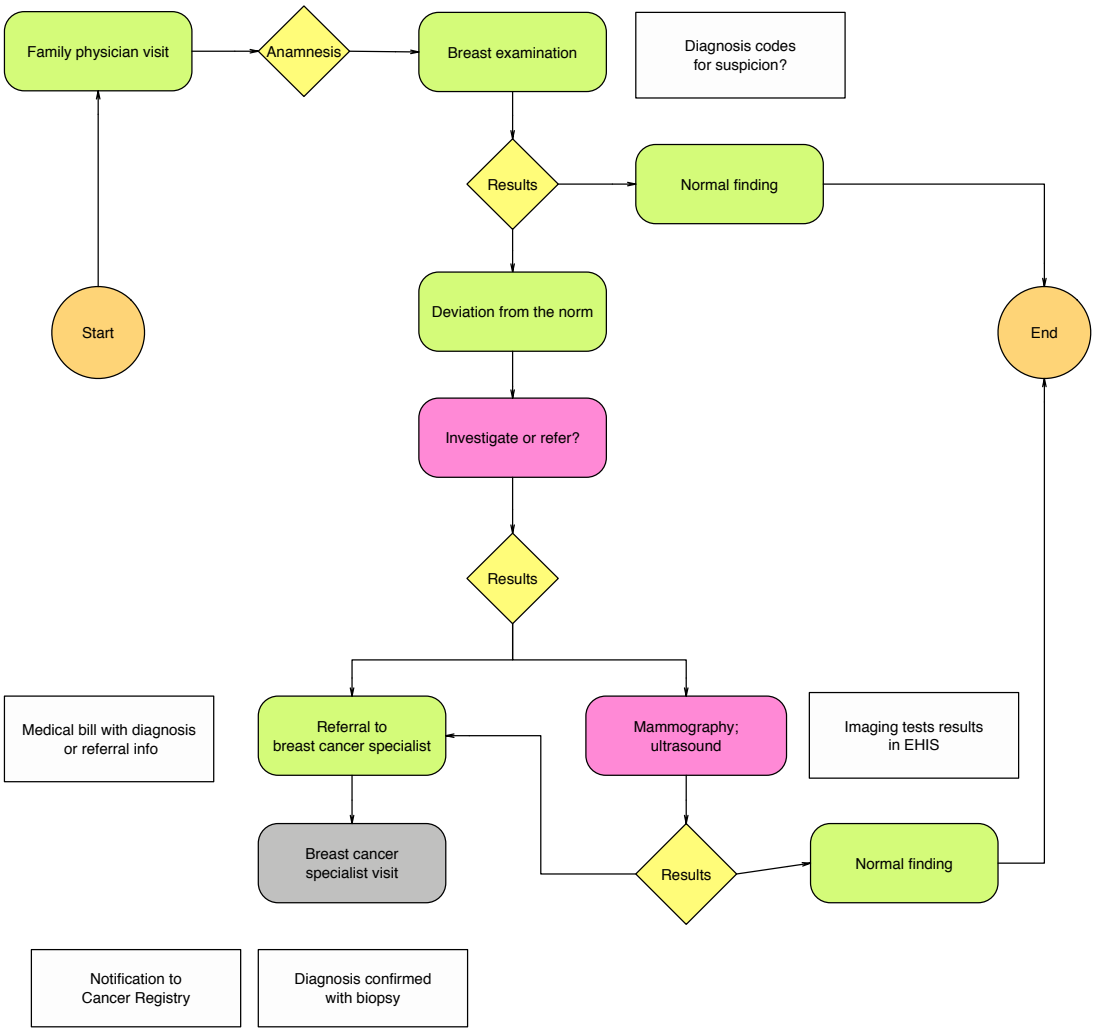
Appendix 1 – Guideline for breast cancer patient handling



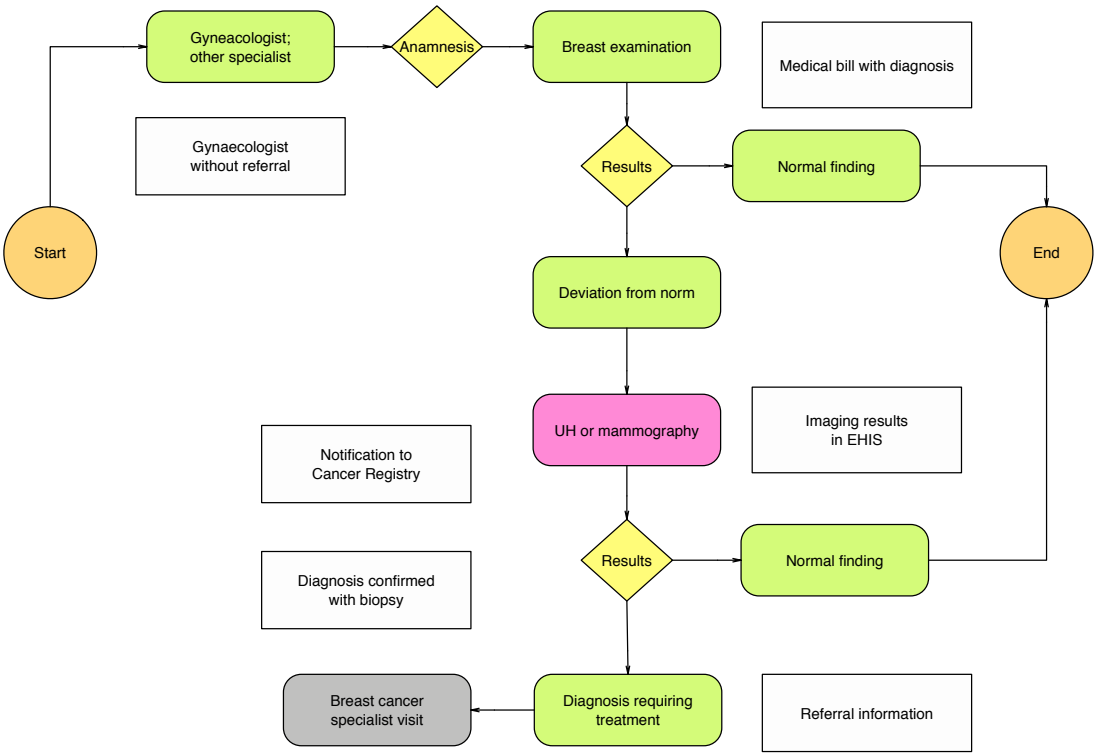
Source: Ravijuhend.ee https://www.ravijuhend.ee/tervishoiuvarav/juhendid/62/rinnavahiga-patsiendi-kasitlusjuhend [17] (10.12.2018)

Appendix 2 – Patient pathways

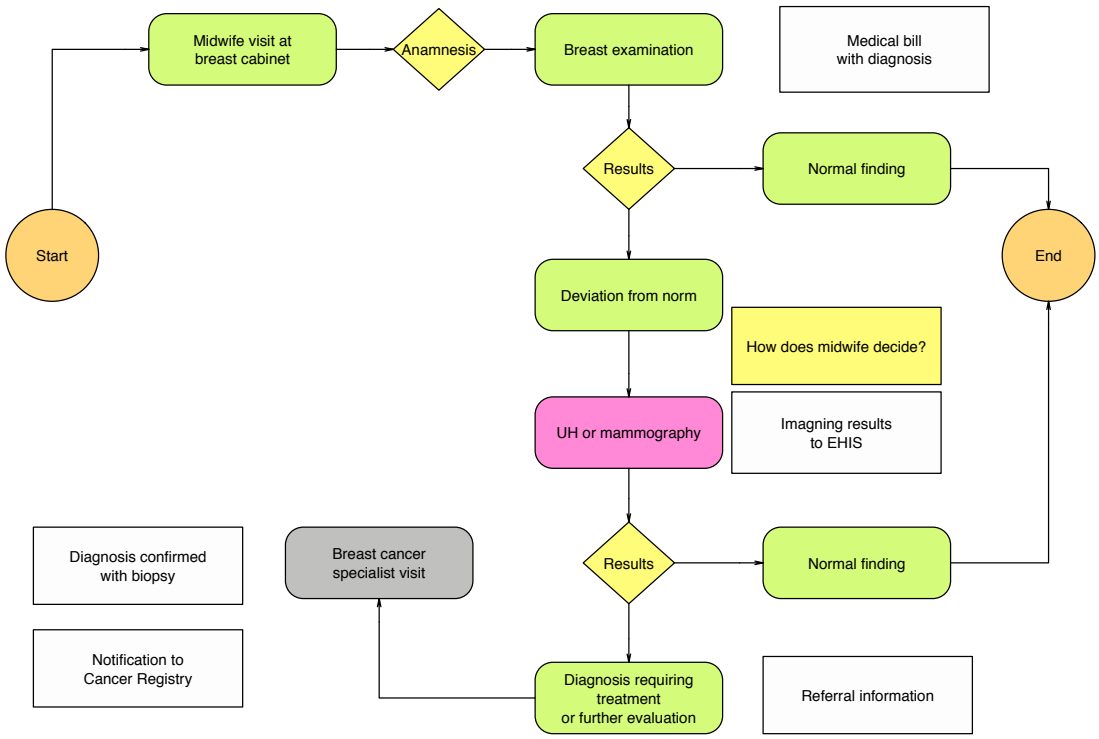
Appendix 2.1 Family physician pathway



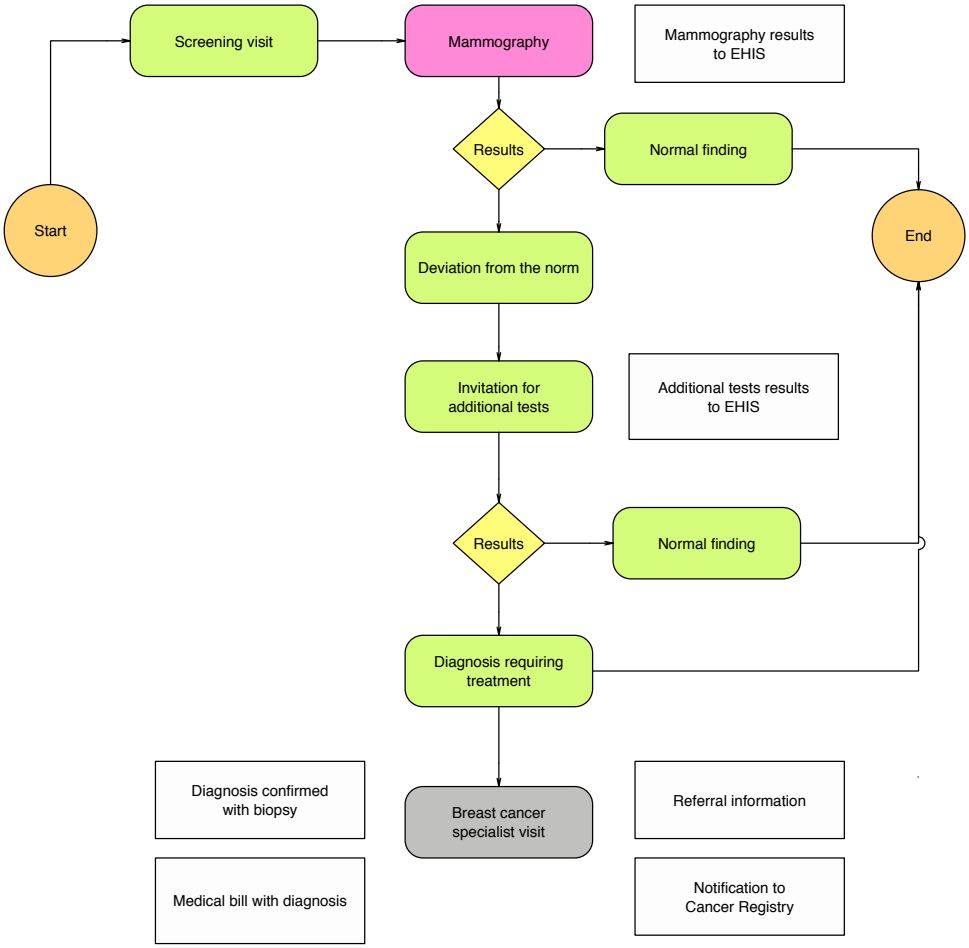
Appendix 2.2 Gynaecologist and other specialists' pathway



Appendix 2.3 Breast cabinet pathway



Appendix 2.4 Breast cancer screening pathway



Appendix 3 – The description of data selection process

<table>
<tr><td>Starting point</td><td colspan="3"></td><td>Presumable first visit</td><td>Patient info</td></tr>
<tr><td>Diagnosis codes</td><td>Healthcare service codes</td><td>Additional service codes for diagnosis confirmation</td><td>Referrals information</td><td>Healthcare service provider specialty</td><td>Patient code</td></tr>
<tr><td rowspan="3">C50 sub codes:
C50.0
C50.1
C50.2
C50.3
C50.4
C50.5
C50.6
C50.8
C50.9</td><td rowspan="2">6074 (mammography)</td><td rowspan="2">66803 (histological test)</td><td>Family physician</td><td>Date of service provision</td><td>Age group</td></tr>
<tr><td>Specialist physician</td><td>The beginning and the end of invoice</td><td>Only females</td></tr>
<tr><td>7952 (breast ultrasound)</td><td>7890 (fine needle biopsy)
7891 (needle core biopsy)
7895 (localization done under mammography control)
Open biopsy: 66801
66817</td><td>e-consultation</td><td></td><td>Place of residence (county)</td></tr>
<tr><td>D05 (in situ) + sub codes:
D05.0
D05.1
D05.7
D05.9</td><td>MRI codes:
79250
79251
79252
79253</td><td>66635 (Her2 FISH analysis from breast or stomach tissue)</td><td rowspan="2">Possible diagnoses codes for referral:
R92
Z12.3
Z01.4
N63</td><td></td><td>Health insurance status (yes/no)</td></tr>
<tr><td>Information about the diagnosing institute</td><td></td><td></td><td></td><td></td></tr>
</table>

Appendix 4 – The explanation of included ICD-10 codes

C50 Malignant neoplasm of breast *Incl.:* connective tissue of breast *Excl.:* skin of breast (C43.5, C44.5)	D05 Carcinoma in situ of breast *Excl.:* carcinoma in situ of skin of breast (D04.5) melanoma in situ of breast (skin) (D03.5)
C50.0 Nipple and areola	D05.0 Lobular carcinoma in situ
C50.1 Central portion of breast	D05.1 Intraductal carcinoma in situ
C50.2 Upper-inner quadrant of breast	D05.7 Other carcinoma in situ of breast
C50.3 Lower-inner quadrant of breast	D05.9 Carcinoma in situ of breast, unspecified
C50.4 Upper-outer quadrant of breast	
C50.5 Lower-outer quadrant of breast	
C50.6 Axillary tail of breast	
C50.8 Overlapping lesion of breast	Other codes:
C50.9 Breast, unspecified	N63 Unspecified lump in breast
	R92 Abnormal findings on diagnostic imaging of breast
	Z12.3 Special screening for detection of breast tumour
	Z01.4 Gynaecological examination

Source: Sotsiaalministeerium: Diagnoosikoodid. http://rhk.sm.ee (10.12.2018)