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Mammography Screening in Lithuania: The Program's Course and its Influence on the Epidemiological Situation of Breast Cancer

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VILNIAUS UNIVERSITETAS

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Atrankinė mamografinė patikra Lietuvoje: programos eiga ir jos įtaka krūties vėžio epidemiologinės situacijos pokyčiams

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CONTENT

1. ABBREVIATIONS

APC – Anual percentage change

BIRADS – Breast Imaging Reporting and Data System

BRCA1 – oncogene Breast Cancer Type 1

BRCA2 – oncogene Breast Cancer Type 2

BSE – Breast self-exam

CBE – Clinical breast examination

EU – European Union

ME – Mammography exam

MH – Ministry of Health

MRI – Magnetic resonance imaging

MS – Mammography screening

MSP – Mammography screening program

NCI – National Cancer Institute

NHIF – National Health Insurance Fund under the Ministry of Health

WHO – World Health Organization

1. INTRODUCTION

1.1 Revalence of the Study

The number of achievements of contemporary medicine in the development of various means meant to avoid cancer, its treatment, and cure are growing steadily; however, oncological diseases remain a critical problem of public health. On a global scale, oncological diseases are one of the leading causes of mortality and disability.

Breast cancer is among the most relevant problems of female health in the world as well as in Lithuania. It is the second most common malignant disease after lung cancer and the most common malignant disease of women in the entire world. Each year, more than 1.5 million new cases of breast cancer are diagnosed. In 2012, there were approximately 1.7 million (25% of all cancer cases) new cases (http://globocan.iarc.fr). In Lithuania, like in the rest of the world, breast cancer is the most common malignant disease that women suffer from. According to the latest data of the Cancer Registry of Lithuania, 1526 breast cancer cases were identified in Lithuania (18% of all were malignant tumors) (http://www.nvi.lt/index.php?1014526156). Compared to other states of the European Union (EU), the rate of the standardized incidence of breast cancer among women in Lithuania is smaller by a half (65.2 cases/100 000 residents) than in France (118 cases/100 000 residents), Holland (131 cases/100 000 residents), and Finland (121 cases/100 000 residents), but the mortality from breast cancer in Lithuania and the said countries is nearly the same (23.4; 23.7; 26.0; 19.7 cases/100 000 residents correspondingly) (http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=46&Gender=2).

The incidence of breast cancer can be reduced through the application of the primary measures of cancer prophylaxis. The objective of primary prophylaxis is to reduce the incidence by affecting the factors that determine it. In pursuit of the objective to

reduce the economic and social burden due to mortality from breast cancer, methods to reduce the mortality are sought systematically. Mortality from breast cancer can be reduced by applying the measures of secondary prophylaxis. Screenings of large groups of residents, comprised of individuals who do not feel any symptoms of the disease and consider themselves healthy, to detect cancer or precancerous alterations, are called *screenings*. A screening examination for breast cancer does not protect the individual from the development of breast cancer but allows to identify it earlier, when effective treatment is possible and less aggressive treatment methods can be applied. Thus, the survival duration of the disease-stricken individuals is prolonged, and a better life quality assured. For the currently performed women's screenings for breast cancer, it is recommended to use an X-ray examination of breasts – a mammography – distinguished as the most sensitivite and specific type of screening (Greif 2010).

The effectiveness of mammography screening was evaluated in randomized clinical trials. The first trial started in the USA in 1963 (Shapiro 1997). Later, similar trials were conducted in other countries. The obtained results allowed to determine how effective mammography screening (MS) is in the reduction of mortality from breast cancer. According to data from different authors, the performance of MS can reduce mortality by 20–35% (Marmot et al. 2013; Gotzsche et al. 2011). Results of randomized clinical trials had demonstrated that mammography screenings could significantly reduce mortality from breast cancer; therefore, mammographies began to be conducted in many European countries on a national or regional level. In 2012, after reviewing 20 trials, Njor and co-authors had established that MS has influence on reduced mortality in European countries and that the mortality of women summoned to take part in MS had dropped by 26% (Njor 2012). Broeders and co-authors conducted a comprehensive review of all observational studies in which an influence of MS in reduced mortality from breast cancer was assessed and established that mammography screenings conducted in

Europe reduce mortality among women summoned to take part in the screening by 25–31%, and by 38–48% among women who took part in the screening (Broeders et al. 2012).

The efficiency of MS when conducted in the general population may differ from the efficiency established during clinical trials [10]. Differences may occur due to the varying professionalism of staff taking part in MS, due to the different characteristics of women taking part in MS, due to a different technique of mammography, etc. (Gabe et al. 2005; van Schoor et al. 2011). It is noteworthy that mammography is just one element of the whole sequence of events which allows diagnosing cancer or rules out the presence of cancer altogether. When the performance of MS began in the general population, and upon realization that it is an integrated and complicated process with undesirable effects (hyperdiagnostics, X-ray radiation, pain experienced during the procedure, additional diagnostic procedures, and the effect of the psychological stress), as well as upon realizing how important it is to ensure the appropriate quality of screening, efforts were made to develop standards for quality assurance. Back in 1989, Day with co-authors announced the most significant efficiency measurement indicators for a correctly organized MS, which are mandatory to ensure reduced mortality from breast cancer (Day et al. 1989). Therefore, already in the eighties, the medical community realized the need for a mammography screening program (MSP) that would allow to perform mammography screenings in an organized manner, by following specific standards of quality. In 2006, upon summarizing data from numerous clinical trials and the experience of various countries in the performance of MS, based on guidelines previously published and reviewed in the European Union, fourth version of comprehensive multidisciplinary recommendations was published, in which measures assuring the quality of the performed MSP were indicated (Perry et al. 2006). In this document, the course of MSP and the necessary conditions for its efficient performance are discussed at length. In each part of the

recommendations, indicators (their minimum and desirable values) are pointed out, the monitoring of which guarantees a smooth course of the program and good quality and allows to expect that such a program will be effective, i.e., that a reduced mortality rate from breast cancer will be achieved. The performance of MSP is assessed according to numerous criteria, which could be distributed into 2 main groups: program performance indicators necessary to assess and ensure that the program is executed correctly and according to the existing recommendations, and influence indicators of the program, reflecting the influence of MSP implementation on changes of the epidemiologic indicators of cancer. In Lithuania, the implementation of MSP began back in 2005; however, neither the course of the program nor its effectiveness were thus far put under study.

1.2 Aim of the Study

To assess the course of the mammography screening program in Lithuania and its influence on changes in the epidemiologic situation of breast cancer in Lithuania.

1.3 Tasks of the Study

1. To assess the performance indicators of the mammography screening program in Lithuania.
2. To assess incidence and mortality, as well as changes in early and advanced stages of breast cancer, before the start of the mammography screening program and during its implementation.
3. To establish the differences of pathological characteristics of breast cancer in groups of women who did and did not participate in the mammography screening program.
4. To assess the ratio of interval cancers.
5. To establish the sensitivity of the mammography screening program.

1.4 Statements to be Defended

1. The mammography screening program, when implemented in an organized manner, can reduce mortality from breast cancer. To achieve this objective, constant monitoring of the implementation of the mammography screening program is necessary.

2. Its implementation (participation rate, rate of repeated mammographies due to technical reasons, rate of additional summonings) and effect (reduced mortality, interval cancer rate, stages of cancers) are critically important for monitoring the mammography screening program.

3. Aiming to assess the efficiency and sensitivity of the mammography screening program, the monitoring of interval cancers is a necessary process.

1.5 Scientific Novelty of the Study

In Lithuania, MSP is being implemented since 2005; however, a comprehensive and consistent assessment of the program's implementation and its influence on the epidemiological situation of breast cancer has not been conducted thus far.

In works performed in Lithuania, only the quality of radiologists of the MSP and the survival rate of women diagnosed with breast cancer, as well as the ethical aspects of MS or the costs due to breast cancer, were analyzed in then again only in the Kaunas city region. Assessment research encompassing both the MSP's implementention process nationwide in Lithuania and the MSP's influence indicators assessment research in which contemporary cancer epidemiology methods are employed has not been performed until now.

For the first time since the start of the MSP for cancer detection, the relative interval cancer rate and the sensitivity of MSP implemented in Lithuania were assessed. For the first time, the

influence of MSP on the incidence of breast cancer, the distribution of diagnosed disease stages, and changes in mortality in Lithuania have been assessed. Differences of pathological characteristics of breast tumors in groups of women who did and did not participate in the MSP were assessed for the first time.

2. MATERIAL AND METHODS

The research was conducted from 2015 to 2019 at the National Cancer Institute (NCI). The research protocol was assessed and approved by the council of the National Cancer Institute (September 28, 2016, protocol No. A37-5). A permission to carry out the biomedical research titled "Analysis of the Course of Programs of Mammographic Screening and Early Prostate Diagnostics and Impact on the Oncological Situation in the Country" was approved by Vilnius Regional Biomedical Research Ethics Committee (December 13, 2016, Protocol No. 158200-16-879-388). Permission for the processing of data and database creation was received from the State Data Protection Inspectorate (April 05, 2017, protocol No. 2R-2129).

2.1 Sources of Data

The primary sources of data were Cancer Registry data on newly diagnosed breast cancers and deaths caused by them in Lithuania, National Health Insurance Fund (NHIF) data about provided services within limits of the mammography screening program, and the MS information system of the NCI.

The Cancer Registry of Lithuania is a cancer registry of the population in which personal and demographic information (place of residence, gender, date of birth, and vital status), information about the respective diagnosis (cancer localization, histology, date of diagnosis, and cancer identification method), and the death of the patient (date of death and cause of death) are kept. Main information sources about cancer are primary, secondary, and tertiary healthcare institutions, responsible for the submission of reports when a malignant disease is newly diagnosed. All doctors, hospitals, and other institutions of the state must send a notification to the Cancer Registry of Lithuania on every case when cancer is diagnosed. In the formation of the database, other data sources are also used, based on which the

currently possessed data are specified, corrected, and the missing cases of oncological diseases are registered. Death certificates are one of the most critical data sources for the supplementation of the incidence database and control of the quality of registration of oncological diseases, as well as for identification of the cause of death, date, and face in case of an already registered oncological disease. This database contains information about cases of cancer that have been diagnosed in Lithuania since 1978. From 1988, the data of the register were included into *Cancer Incidence in Five Continents*, a central publication of the International Agency for Research on Cancer.

Data about participation in the MSP of Lithunia were obtained from the NHIF. This database was created in 1999, aiming to compensate from the Social Insurance Fund for healthcare services provided to healthcare institutions. The system is used to manage, accumulate, exchange, analyze, and provide reports on healthcare services provided by healthcare institutions. In the national database is kept any information regarding information provided to women on MS as well as mammographies performed and their assessment.

Data on organizing MS and its implementation were obtained from information system of the National Cancer Institute. At the Institute, all data of women who performed a prophylactic mammogram – the date of mammogram, assessment results, and the recommendations of two radiologists – are accumulated in the MSP information system. If a woman was summoned to perform additional tests, data about an additional visit time, the tests performed, and the established diagnosis are also accumulated in this system.

2.2 Fragments of the Study

Several phases of the study were distinguished. First of all, the MSP implementation indicators and changes were assessed since its beginning up to 2016. Later, an assessment of the MSP's influence was carried out by calculating the parameters of incidence, mortality,

and other surrogate indicators of MSP's influence. MSP implementation and fundamental indicators were separately examined in a specialized center of mammography screening. NCI, since it is one of the largest centers providing services according to the MSP and contains an MS information system, was selected as such center.

2.2.1 Assessment of the Organization and Implementation of the Mammography Screening Program

The organization and implementation data of MSP were obtained from the NHIF and are concerned with the provided services: informing about the prophylaxis of malignant breast tumors and referrals to perform mammographies, the service of the mammographies performed, the mammography assessment service (the BIRAD system – Breast Imaging Reporting and Data System), and the dates when these services were provided. The organizational aspects of the MSP were also assessed: what is the age of the women participating in the SM; where from do they get the information about SM; how is the response received. The dynamics of women's screening according to MSP during the period from 2006 to 2017 were assessed. The number and rate of tumors annually diagnosed with MSP in 10 000 screened women was calculated, including a portion from all diagnosed tumors in a group of women aged 50 to 69 years during the period from 2006 to 2012.

During the implementation of the MSP, the rate of screen-detected cancers was calculated according to the following formula:

$$\text{Rate of screen detected cancers} = \frac{\text{Number of cances diagnosed during MSP}}{\text{Number of women screened}} \times 10{,}000$$

Screen-detected cancers were considered tumors that were histologically confirmed after BIRADS 4, BIRADS 5, and BIRADS 0 assessment categories. Only invasive breast carcinoma cases were included in the analysis because data on carcinoma *in situ* are not systemically accumulated in the cancer register.

2.2.2 Assessment of the Influence of the Mammography Screening Program

Aiming to assess the influence of the MSP, a database was compiled by connecting data about services provided to the data of the Cancer Registry about malignant breast tumors diagnosed in the period from 2005 to 2012. During the assessment of the influence of the MSP, the distribution of screen-detected cancers according to the stages of the disease has been calculated; trends in the incidence of breast cancer, changes in stages and mortality before the start of the MSP and during its implementation were also assessed. An analysis of the pathological characteristics of breast tumors in the groups of women who have and have not participated in the MSP was performed. The interval cancer rate was established, and program sensitivity was assessed. Also, differences in interval cancers from screen-detected cancers were scrutinized. Only cases of invasive breast carcinomas were included in the analysis, because data on carcinoma *in situ* are not systemically accumulated in the cancer register.

The analysis of incidence and changes in stages included the period from 1998 to 2012, aiming to assess the trends in changes before the start of the MS implementation and during its course. The period until 2012 was selected for analysis because the data of later years are not complete in the Cancer Registry. Primary data accumulated in the Cancer Registry's database on diagnosed breast tumors during the assessed period – the dissemination of the disease, its stage, histological form, and the demographic characteristics of those sick with the disease – were used. Women were divided into 3 age groups: 0 to 49, 50 to 69 (target population summoned to take part in MS), and 70 and older, aiming to assess the influence of the MS within the target population. The research period was divided into 2 periods: the period before MS (from 1998 to 2005) and the period of the MS being implemented (from 2006 to 2012). Breast tumors less

than 20 mm in size with no identified metastases in the lymph nodes were considered as stage I cancer. Tumors of advanced stages (II+) included tumors T2, T2, and T4 tumors, and all those with metastases in the lymph nodes. Tumors the stage of which is not indicated in the Cancer Registry are separated into a different category. To assess changes, an age standardized incidence was calculated (the direct standardization method was applied). A standardized incidence (mortality) rate (IR) was calculated from the age-specific incidence (mortality) rate (wi), and a coefficient indicating which standard part of the population is comprised of that age group (wi) was derived:

$$\text{Standardized rate} = \Sigma(ri\ wi)/\Sigma(wi) \times 10{,}000$$

ri – incidence (mortality) rate in a specific age group i,

wi – part of standard population in a specific age group i.

The analysis of changes in mortality included the period from 1998 to 2017. The aim was to assess the trends of changes before the start of MS implementation and during its course. Just as in the case of calculating the changes in incidence, women were divided into 3 age groups: from 0 to 49, from 50 to 69 (target population summoned to take part in MS), and 70 and older, aiming to assess the influence of the MS on mortality in the target population. The period of research was divided into 2 periods: the period before MS (1998 to 2005) and the period of the MS being implemented (from 2006 to 2017). Age standardized mortality rates were calculated for the assessment of changes (the direct standardization method was applied).

The analysis on breast cancer incidence, changes in the division of stages of the disease, and mortality was performed using the segmented regression model, in which a trend is explained by a specific number of linear segments and joinpoints in which the change is established. This regression model was also used for the identification of the number and location of joinpoints and the calculation of annual average changes. The largest number of joinpoints was three in every age category. The location of the best joinpoint of each model (i.e., the year and its 95% of confidence

intervals) was identified using the grid search method algorithm. The directions of changes were assessed by presuming that data are approximated using the Poisson distribution (which is used in cancer epidemiology, since its considered that the cancer is a rare, random event and no presumption about normality is being made) and using the log-linear regression equation of (y) = b + xb + a, where *x* is an independent variable year, *y* is the incidence or mortality rate, *b* is a coefficient of regression, and *a* is an error (assessed by making a presumption about equality of dispersions). The logarithm of incidence or mortality in the model is a linear function of time (year), which shows the internal annual percentage change (APC) of the rate in percentage when antilogarithmized.

Aiming to compare the main characteristics of tumors diagnosed in women who have ever participated and have not participated in the MSP, two groups of women were compiled: women who were diagnosed with breast cancer after 2006 and who participated in the MSP (the cancer was diagnosed not necessarily during their MSs), women for whom breast cancer was identified after 2006, and those who had never participated in the MSP. Differences were assessed according to age at diagnosis, histologic type, stage of the disease, size of the tumor, presence of metastases in the lymph nodes, presence of distant metastases, and the degree of differentiation of a tumor. The same parameters were also analyzed when comparing screen-detected cancers with interval breast cancers.

The interval cancer rate was calculated according to the formula:

$$\text{Interval cancer rate} = \frac{\text{Number of interval cancers}}{\text{Number of women screened}} \times 10{,}000$$

Interval cancers were considered malignant breast tumors, identified in the period of 90–730 days (period of one screening cycle) after a performed mammography and if no changes were seen in the mammography, or if the changes were assessed as non-malignant (BIRADS 1, 2, and 3).

The ratio of interval cancers was calculated according to the methodology proposed by Andersen and co-authors:

$$\text{Interval cancers ratio} = \frac{\text{Interval cancers}}{\text{Interval cancers} + \text{ screen} - \text{detected cancers}}$$

The sensitivity of the program was calculated according to the following formula:

$$\text{MSP sensitivity} = \frac{\text{Screen-detected cancers}}{\text{"Screen-detected cancers"} + \text{all interval cancers}}$$

The sensitivity of the program was calculated dependingly on age and the histological variant of breast cancer. Women were divided into 5 age groups: 50 to 54 years, 55 to 59, 60 to 64, 65 to 69, 70 years and older. For the assessment of the program's sensitivity according to the histological variant of cancer, 2 groups were separated: a lobular carcinoma of the breast and a ductal and carcinoma of the breast.

2.3 Statistical Data Analysis

For the assesment of qualitative attributes, rates (n) of values and percentages of relative rates (%) were calculated. The sensitivity of the program is presented in percentages by providing 95% confidence intervals. A comparison between groups was performed using the t criterion for the significance of the difference of averages and using the Chi-square criterion for the difference of proportions. Differences between groups were considered statistically significant if the p value was less than 0.05.

Statistical analysis was performed with the computer statistical software package SPSS 17.0 and Microsoft Excel software. The analysis of breast cancer incidence, changes in the distribution of disease stages, and mortality was carried out using JOINPOINT software (version 4.3.1.0), the APC considered significant if the p value was less than 0.05.

The graphic depiction was implemented using Microsoft Excel software.

3. RESULTS

3.1 Organization of the Mammography Screening Program in Lithuania

Services of the elective screening mammography program are being implemented in Lithuania since October 2005. According to the order of the Minister of Health of the Republic of Lithuania No. V-729, issued on September 23, 2005, "Regarding Funding Approval of the Mammography Screening Program For Breast Cancer," preventive services of three types are provided: informing about the prophylaxis of malignant breast tumors, performing mammograms, performing assesments of mammograms. The methodology of the implementation of program services is regulated based on the order of the Minister of Health of the Republic of Lithuania No. V-901, issued on December 10, 2004, "Regarding Approval of Methodology of Mammography Screening for Women." According to the approved methodology, the patient receives information about the screening and a referral for examination from the family doctor. After receiving the referral, women go to a certified center where mammography is performed and assessed. Mammograms are done in two directions (craniocaudal and mediolateral). Mammography can be both film-screen and digital or fully digital. Two independent radiologists evaluate the performed mammograms under the BIRAD (Breast Imaging-Reporting and Data System) system; the ACR (American College of Radiologists) system is used to assess breast tissue density. The reply is sent within two weeks to the family doctor who had issued the referral. In Lithuania, mammograms according to MS are performed every 2 years. The target population are women aged 50 to 69 years. Nineteen certified centers were registered at the beginning of the program; in 2016, 31 such centers were registered. Some centers provide only the mammography performance service, while others provide both performance and assessment services. Only 5 of these centers in

Lithuania perform further testing of the identified changes. Specialized treatment is also available in these centers. Additional summoning to specialized centers is usually performed when the opinions of two radiologists do not match or when suspicious changes are identified. Only in specialized centers such procedures like the magnification of suspicious trouble-spots, mammograms conducted using additional breast compression, breast tomosynthesis, an ultrasound examination, a core needle biopsy or vacuum-assisted biopsy, a breast MRI, or an excisional biopsy are performed.

According to the order on the program services implementation methodology, only a few indicators are assessed: the number of women invited to take part in the program, the number of perfomed and assessed mammograms, and the funding of a program.

3.2 Indicators of the Implementation of the Mammography Screening Program

According to the NHIF data, the number of screened women from the target population is continuously increasing. This number has increased from 47 440 women in 2006 to up to 106 403 women in 2017. In 2006, 14% of women from the target population were screened, and in 2017, this percentage rose to 24.3%. The number of the target population and women screened is presented in Table 1.

Table 1. **Participation in the MSP in Lithuania from 2006 to 2017.**

Year	Target population	Women screened	Part from the target population, %
2006	347487	48540	14.0
2007	351518	47396	13.5
2008	356621	52670	14.8
2009	365987	59150	16.2
2010	379063	61537	16.2
2011	399730	76902	19.2
2012	406323	83278	20.5
2013	405494	81227	20.0
2014	434969	93372	21.5
2015	438196	97072	22.2
2016	435580	100101	23.0
2017	437441	106403	24.3

The number of new cases of breast cancer in Lithuania is growing every year. Approximately 1500 new cases of breast cancer are diagnosed in Lithuania each year; however, breast tumors identified during the MS comprise just a small portion of all tumors diagnosed among women aged from 50 to 69 years (Table 2).

Table 2. **Breast cancer cases in Lithuania from 2006 to 2012.**

Year	All diagnosed breast tumors	Breast cancers in age group 50 to 69 years	Screen-detected cancers	Number of cancers diagnosed during MSP/10000 women screened	Part of the cases diagnosed in the age group 50 to 69 years, %
2006	1436	765	114	23.5	14.9
2007	1378	653	195	41.1	29.9
2008	1534	742	187	35.5	25.2
2009	1527	733	190	32.1	25.9
2010	1490	735	180	29.3	24.5
2011	1544	798	206	26.8	25.8
2012	1531	784	225	27.0	28.7

In 2006, 114 breast cancer cases were diagnosed during MS, while 2012 saw 225 new cases of breast cancer. During the implementation of MS in the analyzed period, 1297 breast tumors were identified in total. The most prominent frequency of tumors identified during MS was in 2007 – 41.1 case in 10 000 women screened. During the implementation of the MS, the frequency of identified tumors was 30.2 cases in 10 000 women screened (1297/429 473). The part of tumors identified during the MS is increasing; however, only approximately a quarter of the tumors diagnosed in the target population are identified during MS.

3.3 Indicators of the Mammography Screening Program's Impact

Distribution of Screen-Detected Cancers by Stage

During the period from 2006 to 2012 and in the course of MS procedures the following stages and number of tumors were identified: 632 I stage tumors (48.7%), 441 stage II tumors (34.0%), 163 stage III tumors (12.6%), and 35 stage IV tumors (2.7%). The majority of tumors identified during the implementation of the program were of the I stage (48.7%); however, up to 15% of tumors identified during the the program were of the advanced (III od IV) stages. The distribution of tumors identified during MS according to stage of the disease is presented in Figure 1.

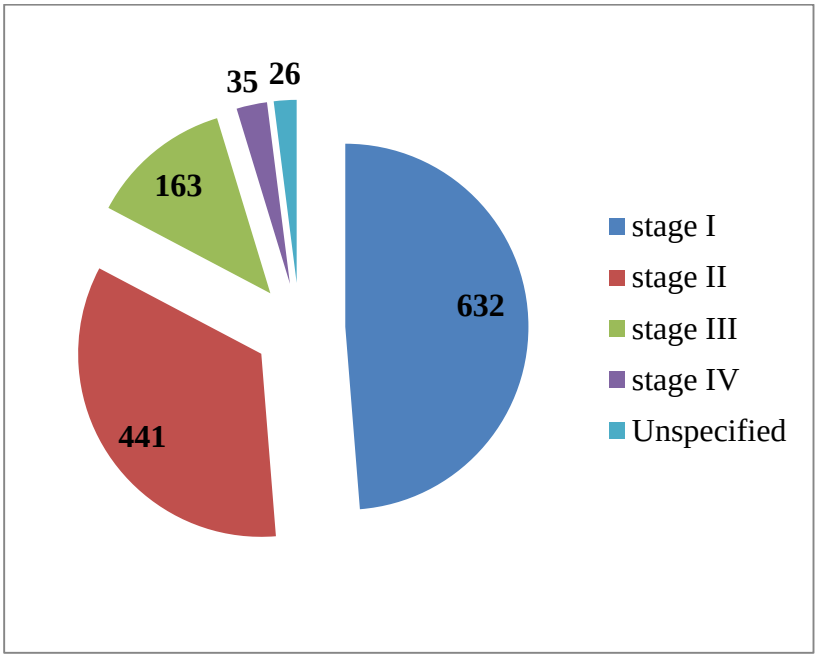

Figure 1. **Distribution of screen-detected cancers by stage, in Lithuania from 2006 to 2012.**

Changes in Breast Cancer Incidence before the Start of MSP Implementation and during Its Course

From 1998 to 2012, a total of 13 874 cases of invasive breast cancer were diagnosed in Lithuania. During the research, the standardized incidence rate increased from 56.8 cases/100 000 women to 71.7 cases/100 000 women. Breast cancer incidence increased by 1.6% each year (95 % CI= 1.1;2.1) (Figure 2). Breast cancer incidence rates and changes in separate age groups are presented in Table 3 and Figure 3.

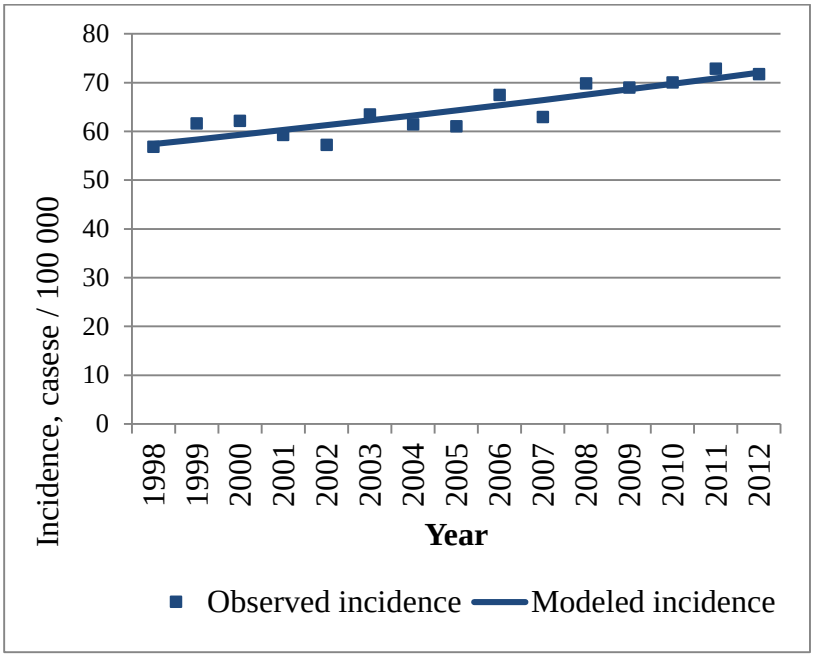

Figure 2. **Trends in breast cancer incidence in Lithuania from 1998 to 2012.**

Table 3. **Age-standartized breast cancer incidence rates and changes in age groups in Lithuania from 1998 to 2012.**

Age group	1998		2012		APC	95 % CI
	Newly diagnosed cases	Incidence rate	Newly diagnosed cases	Incidence rate		
< 50	310	17.5	285	18.5	0.4	[-0.4;1.1]
50–69	591	24.4	788	31.8	2.2	[1.3;3.1]
≥ 70	266	9.1	461	11.9	0.8	[-0.4;1.9]
In total	1167	56.8	1534	71.7	1.6	[1.1;2.1]

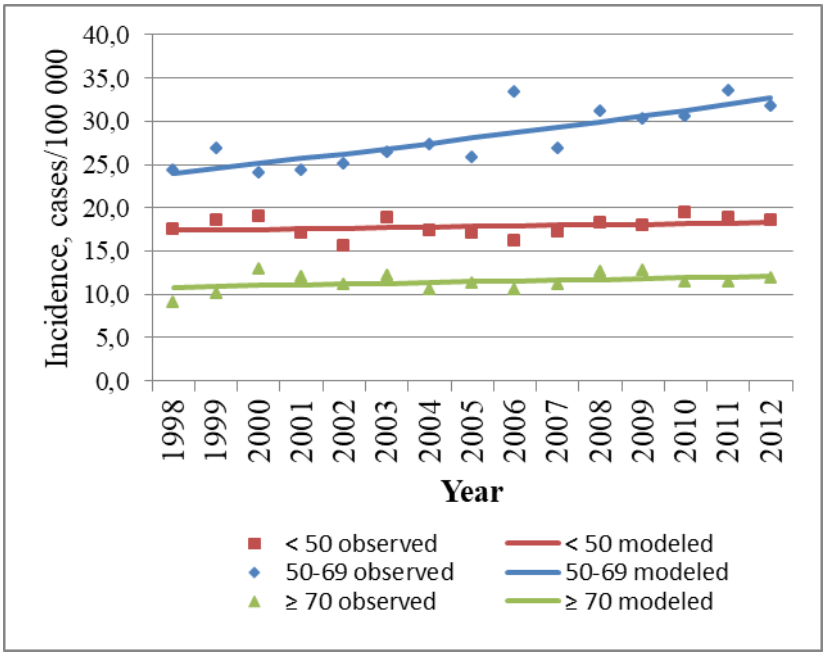

Figure 3. **Age-standardized incidence rates by age groups in Lithuania from 1998 to 2012.**

Changes of Incidence of the Early and Advanced Stages of Breast Cancer before the Start of the Program's Implementation and during Its Course

The main characteristics of malignant breast tumors are presented in Table 4. More tumors of early stages were identified during the MSP's implementation period (29.1%) than before MSP (18.7%), meanwhile the segment of advanced tumors decreased from 78.4% during the period before the start of MSP down to 63.7% during the MSP's implementation period.

Table 4. **Characteristics of the newly diagnosed breast cancer cases before MSP implementation (from 1998 to 2005) and during its course (from 2006 to 2012).**

	1998–2005		**2006–2012**		**P value**
	Newly diagnosed tumors		Newly diagnosed tumors		
	Cases	Percent	Cases	Percent	
Breast tumors	10252	100	10492	100	-
Age group					
< 50	2551	24.9	2214	21.1	<0.001
50–69	4828	47.1	5239	49.9	
≥ 70	2873	28.0	3039	29.0	
TNM Stage					
Stage I	1915	18.7	3054	29.1	<0.001
Stage II +	8033	78.4	6687	63.7	
Unspecified	304	3.0	751	7.2	

In all age groups, the incidence of stage I breast cancer constantly grew, while the incidence of advanced breast cancer decreased (Figure 4).

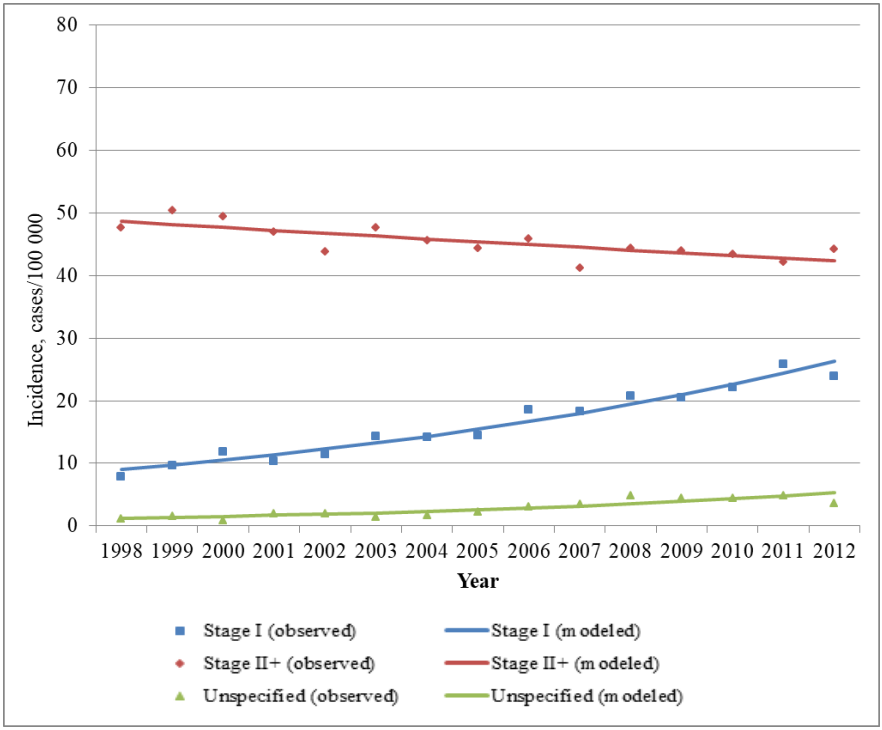

Figure 4. **Breast cancer incidence rates in Lithuania according to the stage of the disease from 1998 to 2012.**

It was established that the incidence of stage I breast cancer increased by 7.9% each year. From 1998 to 2012, the increasing incidence was observed in all age groups – in the age group under 50 years by 3.6%, in target population by 10.2%, and in the age group older than 70 years by 6.2%. The incidence of advanced breast cancer significantly decreased by 1.1%, 1.2%, 1.1%, and 1.6% in all age groups, in the group under 50 years, in the group of 50 to 69 years, and in the group of 70 years and older, respectively.

Changes of incidence rates based on stages of the disease and age groups are presented in Figure 5.

Changes of incidence rates based on the stages of the disease and period in age groups (before the start of MS and during its implementation) are presented in Table 5.

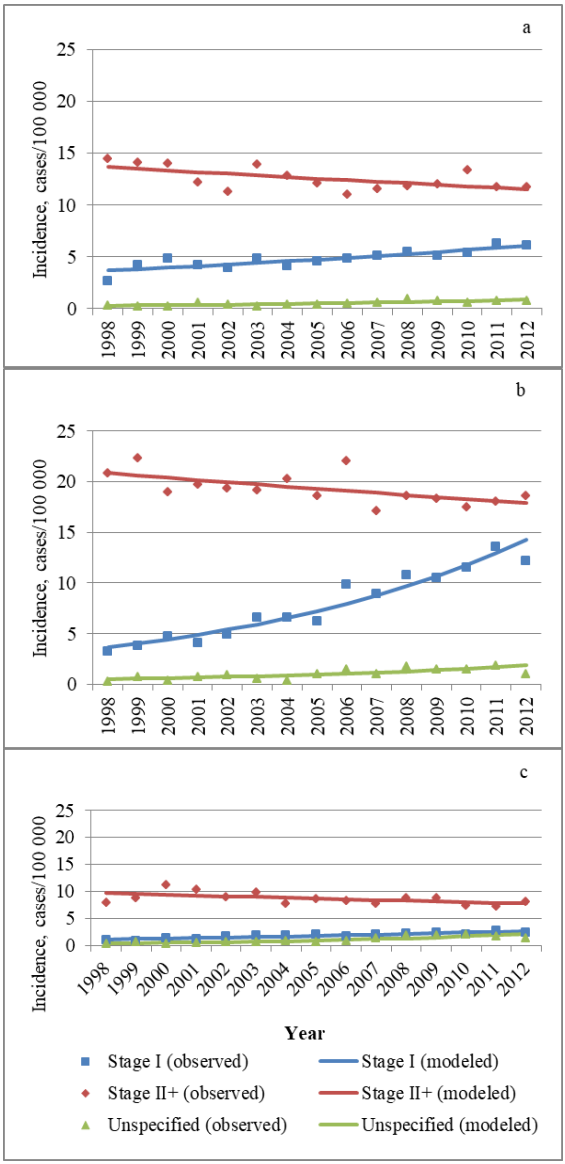

Figure 5. **Breast cancer incidence rates according to the disease stages in groups under 50 y.o. (a), 50 to 69 y.o. (b), and older than 70 y.o. (c) from 1998 to 2012 in Lithuania.**

Table 5. **Changes in breast cancer incidence before the start of MS (1998 to 2005) and during its implementation (2006 to 2012) according to age and cancer stage in Lithuania.**

Incidence based on age groups	**1998**		**2012**		AMP	95 % CI	**1998–2005**		**2006–2012**	
	Newly diagnosed cases	Incidence rate	Newly diagnosed cases	Incidence rate			APC	95 % CI	APC	95 % CI
All age groups	1167	56.8	1534	71.7	1.6	[1.1;2.1]	0.6	[-0.9;2.1]	1.7	[0.1;3.3]
Stage I	162	7.9	475	23.9	7.9	[6.8;9.0]	8.1	[4.4;11.9]	5.6	[2.8;8.5]
Stage II+	978	47.7	958	44.3	-1.0	[-1.5;-0.5]	-1.4	[-2.8;0.0]	-0.3	[-2.1;1.5]
Unspecified	27	1.2	101	3.6	11.0	[7.5;14.5]	7.6	[-0.9;16.8]	3.6	[-5.0;13.0]
< 50 y.o.	310	17.5	285	18.5	0.4	[-0.4;1.1]	-0.7	[-3.2;1.8]	2.2	[0.4;4.0]
Stage I	49	2.7	93	6.1	3.6	[2.2;5.0]	3.2	[-2.8;9.6]	4.1	[1.5;6.9]
Stage II+	256	14.5	180	11.7	-1.2	[-2.2;-0.3]	-2.2	[-4.9;0.6]	1.2	[-1.8;4.3]
Unspecified	5	0.3	12	0.8	8.5	[4.3;12.9]	4.6	[-11.3;23.3]	4.8	[-5.1;15.6]
50–69 y.o.	591	24.4	788	31.8	2.2	[1.3;3.1]	0.9	[-0.8;2.7]	0.8	[-2.8;4.6]
Stage I	86	3.3	297	12.2	10.2	[8.4;12.0]	10.3	[5.6;15.2]	5.7	[1.6;9.9]
Stage II+	493	20.8	465	18.6	-1.1	[-1.9;-0.3]	-1.5	[-3.4;0.4]	-1.9	[-5.7;2.0]
Unspecified	12	0.3	26	1.0	9.6	[4.7;14.8]	8.4	[-6.0;24.9]	0.4	[-12.0;14.6]
≥ 70 y.o.	266	9.1	461	11.9	0.8	[-0.4;1.9]	1.4	[-3.0;6.0]	1.0	[-2.3;4.5]
Stage I	27	0.9	85	2.3	6.2	[4.0;8.5]	13.4	[8.2;18.9]	4.7	[-0.8;10.6]
Stage II+	229	7.9	313	8.1	-1.6	[-3.0;-0.2]	-0.8	[-6.1;4.8]	-1.2	[-4.9;2.6]
Unspecified	10	0.3	63	1.4	13.1	[8.7;17.8]	10.6	[-0.1;22.5]	6.0	[-8.4;22.6]

During the study period, the incidence in the target population increased from 3.3/100 000 in 1998 up to 12.2/100 000 in 2012. The increasing incidence of stage I breast cancer was more substantial during the period before the start of MS than during its implementation period (from 2006 to 2012) (10.3% and 5.7%, respectively). Throughout the entire period, a small but statistically significant decrease of incidence of the advanced stages of breast cancer was monitored (-1.1% each year); however, in the implementation period of MS, no significant changes were found in the incidence of advanced stage breast cancers. Similar changes were observed in the age group older than 70 years. The incidence of stage I breast cancer significantly increased by 13.4% each year during the period before the MS start and increased statistically insignificantly by 4.7% during the period of the MS implementation. Meanwhile, in the age group up to 50 years, the incidence of stage I breast cancer significantly increased during the period of the MS implementation. No significant changes in the incidence of advanced breast cancer stages in groups up to 50 and older than 70 years of age have been identified during the period of the MS implementation (the period from 2006 to 2012).

Changes in Breast Cancer Mortality before the Start of the Program and during Its Course

The age standardized mortality rate in 1998 was 25.1/100 000, and in 2017, it was 18.6/100 000. During the study period, mortality was statistically decreasing by -1.1% each year (95% CI=-1.3;-0.9). The decrease in mortality was also observed in all age groups, but it has not been statistically significant in the group older than 70 years of age. Mortality rates and their changes are presented in Table 6.

Table 6. **Breast cancer mortality rates and changes in age groups in Lithuania from 1998 to 2017.**

Age group	1998		2017		APC	95% CI
	Number of deaths due to breast cancer	Mortality rate	Number of deaths due to breast cancer	Mortality rate		
< 50	103	5.8	42	3.0	-2.1	[-2.5.;-18]
50–69	266	13.6	189	9.4	-1.4	[-1.6;-1.2]
≥ 70	166	5.7	258	6.2	0.2	[-0.2;0.5]
In total	535	25.1	489	18.6	-1.1	[-1.3;-0.9]

Changes in mortality in all age groups and according to age groups are presented in Figures 6 and 7.

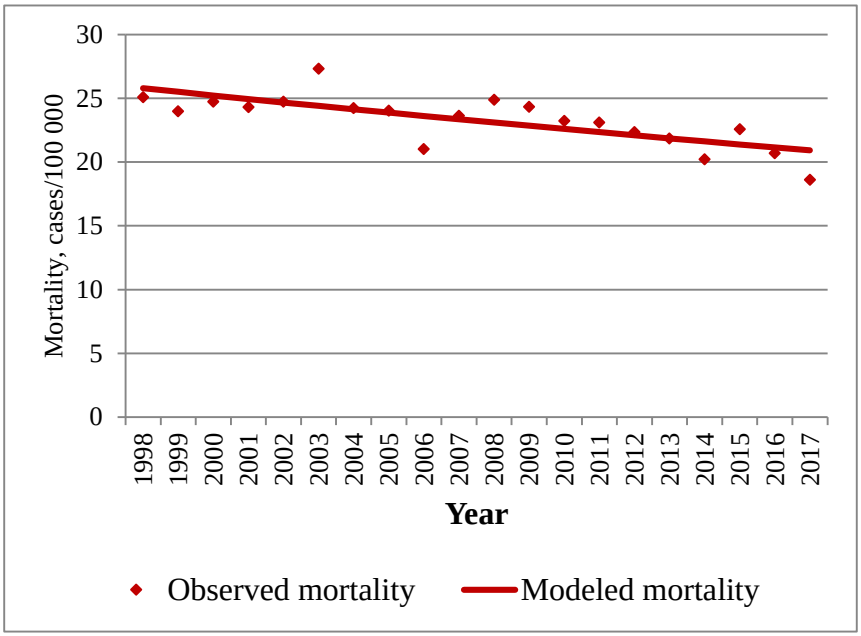

Figure 6. **Age-standardized mortality rates in Lithuania in the period from 1998 to 2017.**

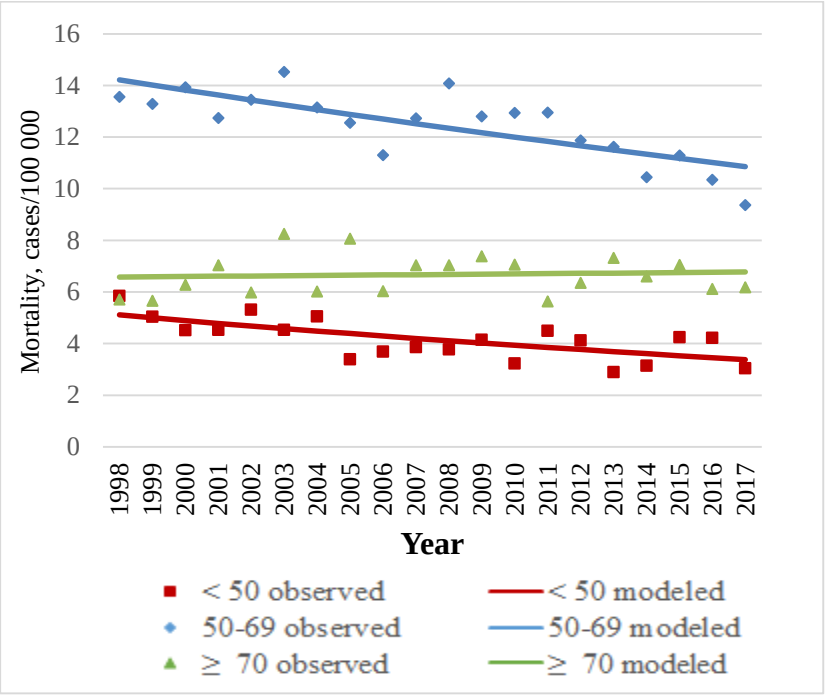

Figure 7. **Age-standardized mortality rates by age groups in Lithuania during the period from 1998 to 2017.**

Differences in Pathological Characteristics of Breast Tumors in Groups of Women Who Have and Have Not Participated in Mammography Screening

After comparing the main characteristics of tumors diagnosed in women who have ever participated in MSP and women who have not, it was established that tumors of smaller size were diagnosed in women who took part in MSP. T1 tumors (<2 cm) in the group of women who participated in MSP comprised 60.8% of all diagnosed tumors, meanwhile in the group of women who have not participated in MSP, these tumors comprised only 31.4%. In the group of women who have not participated in MSP, a much larger number of T4 tumors (with skin lesions) was identified: 13.7%, in comparison to 3.0% in

the group of women who took part in MSP. In the group of women who took part in MSP, well-differentiated tumors (13.8%) were far more often diagnosed than in the group of women who were never screened (7.5%). Metastases in the regional lymph nodes were more often identified in the group of women who never took part in MSP (46.0%, in comparison to 35%). Women who took part in the MSP were twice more often diagnosed with stage I tumors (46.3%) than women who have never participated in MSP (21.4%). The main characteristics of tumors diagnosed from 2006 to 2012 to women who have ever participated in MSP and to those who have not are presented in Table 7.

Table 7. **Pathological characteristics of breast tumors diagnosed to women who have and have not participated in MS.**

Characteristic	Have participated in MSP		Have not participated in MSP		P value
	Cases	%	Cases	%	
Overall number of tumors	2053	44.2	2592	55.8	-
Histological type					
Ductal carcinoma	1495	72.8	1676	64.7	<0.001
Lobular carcinoma	208	10.1	181	7.0	
Other	280	13.6	465	17.9	
Unspecified	70	3.4	270	10.4	
Size of a tumor (according to TNM)					
T1	1249	60.8	813	31.4	<0.001
T2	594	28.9	897	34.6	
T3	45	2.2	137	5.3	
T4	61	3.0	356	13.7	
Unspecified	104	5.1	389	15.0	
Metastases in lymph nodes					
Present	718	35.0	1193	46.0	<0.001
None	1156	56.3	872	33.6	
Unspecified	179	8.7	527	20.3	
Distant mestastases					
Present	56	2.7	309	11.9	<0.001
None	1736	84.6	1605	61.9	
Unspecified	261	12.7	678	26.2	
Stage					
I	951	46.3	555	21.4	<0.001
II	702	34.2	953	36.8	
III	289	14.1	555	21.4	
IV	61	3.0	348	13.4	
Unspecified	50	2.4	181	7.0	
Degree of differentiation					
G1	284	13.8	194	7.5	<0.001
G2	681	33.2	823	31.8	
G3	386	18.8	437	16.9	
G4	0	0.0	0	0.0	
Unspecified	702	34.2	1138	43.9	

Interval Cancers and the Sensitivity of the Mammography Screening Program

Throughout the entire period of the study, 431 cases of interval cancers were diagnosed among women to whom mammographies were performed according to MS and no signs of tumor were visible (assessment according to the BIRAD system: BIRADS1, BIRADS2, BIRADS3). The unterval cancer rate is presented in Table 8.

Table 8. **Interval breast cancer rate in Lithuania from 2006 to 2012.**

Year	Interval cancers	Interval cancer rate /10 000 women screened	Interval cancer ratio
2006	40	8.24	0.26
2007	64	13.50	0.25
2008	74	14.05	0.28
2009	84	14.20	0.31
2010	89	14.46	0.33
2011	62	8.06	0.23
2012	18	2.16	0.07

The interval cancer ratio fluctuated from 0.23 to 0.33. The interval cancer rate for the year 2012 is low as these women were observed for only 1 year after their mammographies were performed. The overall relative interval tumor rate was 0.25 (431/431+1279).

The overall sensitivity of MSP in Lithuania reached 75.1% (95% CI =71.1;79.3). The sensitivity of a program according to age and histological type of the tumors is presented in Tables 9 and 10. The age and histological type of the tumors had impact on the sensitivity of the program. A lesser sensitivity of the program was observed in the age group of 50 to 54 years (69.0%; 95%

CI=54.5;87.4), especially among women diagnosed with lobular tumors (60.0%; 95%. CI =19.4;186.0).

Table 9. **MSP sensitivity in age groups in Lithuania from 2006 to 2012.**

Age group	Screen-detected cancers		Interval cancers		Sensitivity of the program, % [95% CI]
	Cases	%	Cases	%	
50–54	69	5.3	31	7.2	69.0 [54.5;87.4]
55–59	368	28.4	121	28.1	75.3 [67.9;83.4]
60–64	442	34.1	140	32.5	75.9 [69.2;83.4]
65–69	405	31.2	129	29.9	75.8 [68.8;83.6]
In total	1297	100.0	431	100.0	75.1 [71.1;79.3]

Table 10. **Sensitivity of MSP according to histological tumor type and age in Lithuania from 2006 to 2012.**

Age groups	Screen-detected cancers		Interval cancers		Sensitivity of a program, % [95% CI]
	Cases	%	Cases	%	
Lobular carcinoma					
50–54	3	2.4	2	3.7	60.0 [19.4;186.0]
55–59	41	33.3	11	20.4	78.8 [58.1;107.1]
60–64	42	34.1	23	42.6	64.6 [47.8;87.4]
65–69	37	30.1	18	33.3	67.3 [48.7;92.8]
Viso	123	100.0	54	100.0	69.5 [58.2;82.9]
Ductal carcinoma					
50–54	56	5.8	23	7.7	70.9 [54.6;92.1]
55–59	268	27.7	82	27.3	76.6 [67.9;86.3]
60–64	331	34.2	95	31.7	77.7 [69.8;86.5]
65–69	305	31.5	91	30.3	77.0 [68.8;86.2]
In total	969	100.0	300	100.0	76.4 [71.7;81.3]

Upon examining the main characteristics of tumors identified during MS and interval cancers, it was established during the study that interval cancers were larger, with more frequent metastases in the lymph nodes, and more often of the lobular type than the tumors identified during MSP; however, these differences were not statistically significant (Table 11).

Table 11. **Differences of the pathological characteristics of screen-detected cancers and interval cancers in Lithuania from 2006 to 2012.**

Characteristic	Screen-detected cancers		Interval cancers		P value
	Cases	%	Cases	%	
Total number of tumors	1297	75.1	431	24.9	-
Histological type					0.10
Ductal carcinoma	969	74.7	300	69.6	
Lobular carcinoma	123	9.5	54	12.5	
Other	161	12.4	65	15.1	
Unspecified	44	3.4	12	2.8	
Tumor size (according to TNM)					0.40
T1	823	63.5	257	59.6	
T2	350	27.0	132	30.6	
T3	24	1.9	11	2.6	
T4	35	2.7	8	1.9	
Unspecified	65	5.0	23	5.3	
Metastases in lymph nodes					0.48
Present	432	33.3	157	36.4	
None	747	57.6	235	54.5	
Unspecified	118	9.1	39	9.0	
Distant metastases					0.24
Present	31	2.4	14	3.2	
None	1083	83.5	368	85.4	
Unspecified	183	14.1	49	11.4	
Stage (according to TNM)					0.12
I	632	48.7	191	44.3	
II	441	34.0	142	32.9	
III	163	12.6	67	15.5	
IV	35	2.7	17	3.9	
Unspecified	26	2.0	14	3.2	

4. CONCLUSIONS

1. Only about half the number of women to whom it is recommended to take part in the mammography screening program in Lithuania do actually participate in it. Breast tumors, diagnosed during a mammography screening, comprise only 25% of all breast tumors diagnosed in women aged 50 to 69 years, and stage I breast tumors comprise only 49% of all diagnosed tumors.

2. In Lithuania, an increased breast cancer incidence and a small decrease in mortality due to this disease are observed. The number of breast tumors diagnosed in early stages is increasing, and the number of tumors diagnosed in the late stages is decreasing; however, the influence of the mammography screening program on these changes was not established. Changes established during the study period could reflect an increasing awareness about breast cancer, an improvement of diagnostics, and an increased influence of options for effective treatment.

3. Tumors diagnosed in women who have ever participated in mammography screening program were smaller in size, better differentiated, of earlier stages, and with less frequent metastases in the lymph nodes.

4. The interval cancer ratio in Lithuania from 2006 to 2012 was 0.25. This ratio does not fundamentally differ from data published by other countries.

5. The overall sensitivity of the mammography screening program implemented in Lithuania amounts to 75% and is similar to that of other countries. The most substantial sensitivity of the mammography screening program was monitored among the oldest participants of the program and in cases of a ductal histology of the tumor.

5. PRACTICAL RECOMMENDATIONS

1. It is necessary to develop a centralized system of invitations to take part in the mammography screening program, which would allow to significantly increase the number of women participating in the program – and that, in turn, would allow us to expect an increase in the incidence of early breast cancer stages and a decreased mortality due to breast cancer.

2. Continuous monitoring and evaluation of the implementation of the mammography screening program must be carried out. In order to accomplish this task, it is necessary to create an information system of the mammography screening program that collects data on the course and execution of the program and then analyzes the collected data.

3. Continuous monitoring and evaluation of the impact of the mammography screening program must be carried out. To achieve this goal, it is necessary to develop a monitoring system for the impact indicators of the mammography screening program to assess changes in incidence, stage distribution, mortality, interval tumors, and program sensitivity.

4. Continuous monitoring and assessment of the mammography screening program must be performed, and, depending on the results obtained, the program must be corrected and improved.

6. LIST OF SCIENTIFIC PUBLICATIONS AND PRESENTATIONS ON THE TOPIC OF THE DISSERTATION

Scientific publications

1. Steponaviciene L, Briediene R, Vanseviciute R, Smailyte G. Trends in Breast Cancer Incidence and Stage Distribution Before and During the Introduction of the Mammography Screening Program in Lithuania. *Cancer Control*. 2019;26:1–7.

2. Steponaviciene L, Vincerzevskiene I, Briediene R, Smailyte G. Breast cancer screening program in Lithuania: interval cancers and program sensitivity after seven years of mammography screening. *Submitted*

3. Gudavičienė D, Steponavičienė L, Lachej N. Breast cancer in Lithuania (in Lithuanian). *Acta Medica Lituanica* 2015; 3(22):150–60.

4. Steponavičienė L, Vansevičiūtė R. Breast cancer risk factors and diagnostics (in Lithuanian). *Lietuvos akušerija ir ginekologija*. 2017; 2(20):160–5.

5. Steponavičienė L, Briedienė R, Šenbergė S, Gudavičienė D, Smailytė G. Mammography screening program. Experience at the National Cancer Institute (in Lithuanian). *Sveikatos mokslai*. 2017;27(6):161–8.

6. Steponavičienė L, Gudavičienė D, Smailytė G. Interval cancers and their impact on breast cancer screening program sensitivity. Review of the literature (in Lithuanian). *Visuomenės sveikata*. 2018;1(80):11–21.

7. Steponavičienė L, Vincerževskienė I, Vansevičiūtė-Petkevičienė R, Smailytė G. Implementation of mammography screening program in 2006-2017 in Lithuania (in Lithuanian). *Visuomenės sveikata*. 2019; 1(84):39–46.

Scientific presentations

1. Steponaviciene L, Briediene R, Grigiene R, Cechanoviciene I. "Breast Cancer Services in Lithuania." Plenary of the European Commission Initiative on Breast Cancer (ECIBC). December 9–11, 2016. Baveno, Italy.

2. Steponaviciene L, Smailyte G, Briediene R, Gudaviciene D. "Opportunistic screening does not improve early breast cancer (BC) detection and does not reduce BC mortality." The 15th St. Gallen International Breast Cancer Conference, March 15–18, 2017. Vienna, Austria.

3. Steponaviciene L. "Breast cancer in Lithuania. Trends in incidence and mortality." Annual Conference of the Lithuanian Senology Society "Trends in Modern Breast Cancer Treatment." May 19, 2017. Vilnius, Lithuania.

4. Steponaviciene L, Smailyte G, Vincerzevskiene I, Gudaviciene D. "Breast cancer screening in Lithuania: trends in incidence and stage distribution." International Conference of the Cancer Registries "Ensuring quality and use of data from cancer registries in the 21th century." October 17–19, 2017. Utrecht, The Netherlands.

5. Steponaviciene L, Vanseviciute R, Zabuliene L, Jasilionis D, Smailyte G. "Reproductive factors and breast cancer risk in Lithuanian women: A population based cohort study." The 11th European Breast Cancer Conference. March 21–23, 2018. Barcelona, Spain.

6. Steponaviciene L. "Screening for breast cancer. Experience at the National Cancer Institute." The 1st International Doctoral Students' Conference "Science for Health 2018." April 13, 2018. Kaunas, Lithuania.

7. Steponaviciene L, Vincerzevskiene I, Gudaviciene D, Briediene R, Smailyte G. "Breast cancer screening in Lithuania: interval breast cancers and sensitivity of the programme." The 11th

European Public Health Conference "Winds of change: towards new ways of improving public health in Europe." November 28–December 1, 2018. Liubliana, Slovenia.

8. Steponaviciene L, Vincerzevskiene I, Smailyte G. "Overall and breast cancer mortality in breast cancer patients by participation in mammography screening program in Lithuania." The 16th St.Gallen International Breast Cancer Conference. March 20–23, 2019. Vienna, Austria.

9. Steponaviciene L, Vincerzevskiene I, Smailyte G. "Breast cancer screening program implementation in Lithuania." International Cancer Screening Conference. June 3–5, 2019. Rotterdam, The Netherlands.

7. SUMMARY IN LITHUANIAN

7.1 Darbo aktualumas

Nuolat daugėja šiuolaikinės medicinos laimėjimų kuriant įvairias priemones, skirtas išvengti vėžio, jį gydyti ir išgydyti, tačiau onkologinės ligos išlieka itin aktuali visuomenės sveikatos problema. Pasaulyje onkologinės ligos – viena pagrindinių mirčių ir neįgalumo priežasčių.

Krūties vėžys yra tarp aktualiausių moterų sveikatos problemų pasaulyje ir Lietuvoje. Tai antra pagal dažnį piktybinė liga po plaučių vėžio ir dažniausia moterų piktybinė liga visame pasaulyje. Kasmet pasaulyje diagnozuojama daugiau kaip 1,5 mln. naujų krūties vėžio atvejų. 2012 metais naujų atvejų buvo apie 1,7 mln. (25 proc. visų vėžio atvejų) [http://globocan.iarc.fr]. Lietuvoje, kaip ir visame pasaulyje, krūties vėžys yra dažniausia piktybinė moterų liga. Paskutiniais Lietuvos vėžio registro duomenimis, 2012 m. Lietuvoje nustatyti 1526 krūties vėžio atvejai (18 proc. visų moterų piktybinių navikų) [http://www.nvi.lt/index.php?1014526156]. Palyginti su kitomis Europos Sąjungos (ES) šalimis, Lietuvos moterų standartizuotas sergamumo krūties vėžiu rodiklis yra maždaug perpus mažesnis (65,2 atv./100 000 gyv.) nei Prancūzijoje (118,6 atv./100 000 gyv.), Olandijoje (131,3 atv./100 000 gyv.), Suomijoje (121,0 atv./100 000 gyv.), bet mirtingumas nuo krūties vėžio Lietuvoje ir šiose šalyse yra beveik vienodas (23,4; 23,7; 26,0; 19,7 atv./100 000 gyv. atitinkamai) [http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=46&Gender=2].

Sergamumą krūties vėžiu galima sumažinti taikant pirminės vėžio profilaktikos priemones. Pirminės profilaktikos tikslas – sumažinti sergamumą veikiant jį lemiančius veiksnius. Siekiant sumažinti mirtingumo dėl krūties vėžio ekonominę bei socialinę naštą, sistemingai ieškoma būdų mirtingumui mažinti. Mirtingumą nuo krūties vėžio galima sumažinti taikant antrinės profilaktikos

priemones. Didelių gyventojų grupių, kurias sudarantys žmonės nejaučia jokių ligos simptomų ir laiko save sveikais, tyrimai siekiant aptikti vėžį ar ikivėžinius pokyčius vadinami atrankinės patikros tyrimais. Atrankinės patikros tyrimas dėl krūties vėžio neapsaugo nuo krūties vėžio išsivystymo, bet leidžia nustatyti krūties vėžį anksčiau, kai yra galimas efektyvus gydymas bei galima taikyti mažiau agresyvias gydymo priemones. Taip prailginama susirgusiųjų išgyvenimo trukmė bei užtikrinama geresnė jų gyvenimo kokybė. Šiuo metu atliekant moterų atrankinę patikrą dėl krūties vėžio rekomenduojama naudoti rentgeninį krūtų tyrimą – mamografiją, kaip tyrimą, pasižymintį didžiausiu jautrumu ir specifiškumu [Greif JM, 2010].

Mamografinės patikros veiksmingumas buvo įvertintas randomizuotuose kontroliuojamuose tyrimuose. Pirmasis tyrimas pradėtas JAV 1963 m. [Shapiro S, 1997]. Vėliau panašūs tyrimai atlikti kitose šalyse. Gauti rezultatai leido nustatyti, kiek mamografinė patikra efektyvi mažinant mirtingumą nuo krūties vėžio. Skirtingų autorių duomenimis, mirtingumas vykdant mamografinę patikrą gali sumažėti 20–35 proc. [Marmot MG, et al. 2013; Gotzsche PC, et al. 2011]. Randomizuotų kontroliuojamų tyrimų rezultatai parodė, kad vykdoma mamografinė patikra gali reikšmingai sumažinti mirtingumą nuo krūties vėžio, todėl daugelyje Europos šalių nacionaliniu arba regioniniu lygmeniu buvo pradėtos atrankinės mamografinės patikros (angl. *screening mammography*) (AMP). Njor su bendraautoriais atlikę 20 tyrimų apžvalgą 2012 m. nustatė, jog AMP turi įtakos mirtingumo sumažėjimui Europos šalyse ir kad moterų, pakviestų dalyvauti AMP, mirtingumas sumažėjo 26 proc. [Njor S, et al. 2012]. Broeders su bendraautoriais atliko išsamią visų stebėjimo tyrimų, kuriuose vertinta AMP įtaka mirtingumo nuo krūties vėžio sumažėjimui, apžvalgą ir nustatė, kad Europoje vykdoma AMP sumažina mirtingumą 25–31 proc. tarp moterų, pakviestų dalyvauti atrankinėje patikroje, bei 38–48 proc. tarp moterų, dalyvavusių patikroje [Broeders M, et al. 2012].

AMP, vykdomos bendroje populiacijoje, efektyvumas gali skirtis nuo veiksmingumo, nustatyto klinikinių tyrimų metu [10]. Skirtumai gali atsirasti dėl skirtingo personalo, dalyvaujančio AMP vykdyme profesionalumo, dėl AMP dalyvaujančių moterų skirtingų charakteristikų, dėl skirtingos mamogafinės technikos ir kt. [Gabe R, et al. 2005; van Schoor G, et al. 2011]. Pažymėtina, kad mamografija yra tik vienas elementas visos įvykių sekos, kuri leidžia diagnozuoti vėžį arba užtikrina, kad vėžio nėra. Pradėjus vykdyti AMP bendrose populiacijose, supratus, kad tai sudėtingas kompleksinis procesas, turintis ir nepageidaujamų poveikių (hiperdiagnostika, rentgeno spinduliuotės, skausmo patiriamo tyrimo metu, papildomų diagnostinių procedūrų bei psichologinio streso poveikis), bei supratus, kaip svarbu užtikrinti tinkamą atrankinių tyrimų kokybę buvo dedamos pastangos sukurti kokybės užtikrinimo standartus. Dar 1989 metais Day su bendraautoriais paskelbė svarbiausius teisingai organizuotos AMP efektyvumo matavimo rodiklius, kurie yra būtini norint užtikrinti mirtingumo nuo krūties vėžio sumažėjimą [Day NE, et al. 1989]. Taigi jau 9-ajame dešimtmetyje buvo suprasta, kad reikalingos atrankinės mamografinės patikros programos (AMPP), kurios leis vykdyti atrankinę mamografinę patikrą organizuotai, laikantis tam tikrų kokybės standartų. Apibendrinus daugelio klinikinių tyrimų duomenis bei įvairių šalių patirtį vykdant AMP, 2006 m. Europos Sąjungoje anksčiau skelbtų ir peržiūrėtų gairių pagrindu buvo išleistos ketvirtosios išsamios multidisciplininės rekomendacijos, kuriose nurodomos priemonės užtikrinančios vykdomos AMPP kokybę [Perry N, et al. 2006]. Šiame dokumente labai išsamiai aptariama AMPP eiga, būtinos sąlygos, kad AMPP būtų vykdoma efektyviai. Kiekvienoje rekomendacijų dalyje labai aiškiai nurodomi rodikliai (jų minimalios bei pageidautinos reikšmės), kurių stebėsena garantuoja sklandžią programos eigą ir gerą kokybę bei leidžia tikėtis, kad tokia programa bus efektyvi, t.y. bus pasiektas mirtingumo nuo krūties vėžio sumažėjimas. AMPP vykdymas vertinamas pagal daug kriterijų, kuriuos galima būtų suskirstyti į 2

pagrindines grupes: programos vykdymo rodikliai, kurie būtini siekiant įvertinti ir užtikrinti, kad programa vykdoma teisingai, pagal esamas rekomendacijas, bei programos įtakos rodikliai, kurie atspindi AMPP vykdymo įtaką krūties vėžio epidemiologinių rodiklių pokyčiams. Lietuvoje AMPP pradėta vykdyti dar 2005 metais, tačiau nei programos eiga, nei jos efektyvumas iki šiol nebuvo tirti.

7.2 Darbo tikslas

Įvertinti Lietuvoje vykdomos atrankinės mamografinės patikros programos eigą ir jos įtaką krūties vėžio epidemiologinės situacijos pokyčiams Lietuvoje.

7.3 Darbo uždaviniai

1. Įvertinti atrankinės mamografinės patikros programos Lietuvoje vykdymo rodiklius.
2. Įvertinti sergamumo ir mirtingumo bei sergamumo ankstyvųjų ir pažengusiųjų stadijų krūties vėžiu pokyčius iki atrankinės mamografinės patikros programos vykdymo pradžios ir jos vykdymo metu.
3. Nustatyti krūties navikų patologinių charakteristikų skirtumus atrankinėje mamografinės patikros programoje dalyvavusių ir nedalyvavusių moterų grupėse.
4. Įvertinti intervalinių navikų santykinį dažnį.
5. Nustatyti atrankinės mamografinės patikros programos jautrumą.

7.4 Ginamieji teiginiai

1. Organizuotai vykdoma atrankinė mamografinės patikros programa gali sumažinti mirtingumą nuo krūties vėžio. Tam, kad šis tikslas būtų pasiektas, būtina nuolatinė atrankinės mamografinės patikros programos vykdymo stebėsena.

2. Atrankinės mamografinės patikros programos stebėsenai svarbiausi yra jos vykdymo (dalyvavimo dažnis, mamogramų kartojimo dėl techninių priežasčių dažnis, papildomų kvietimų dažnis ir kt.) ir poveikio (mirtingumo mažėjimas, intervalinių navikų dažnis, navikų stadijos ir kt.) rodikliai.

3. Intervalinių navikų stebėjimas yra būtinas procesas, siekiant vertinti atrankinės mamografinės patikros programos efektyvumą ir jautrumą.

7.5 Darbo mokslinis naujumas

Lietuvoje AMPP vykdoma nuo 2005 metų, tačiau iki šiol nebuvo atlikta išsamaus ir nuoseklaus programos vykdymo ir jos įtakos krūties vėžio epidemiologinei situacijai vertinimo.

Lietuvoje atliktuose darbuose analizuota tik Kauno regione vykdomos AMPP radiologų darbo kokybė ir pacienčių, kurioms nustatytas krūties vėžys, išgyvenamumas, etiniai AMPP aspektai arba kaštai dėl krūties vėžio. Iki šiol apimančio visoje Lietuvoje vykdomos AMPP tiek proceso, tiek poveikio rodiklių vertinimo tyrimo, kuriame naudojami šiuolaikiniai vėžio epidemiologijos metodai, atlikta nebuvo.

Pirmą kartą nuo pat AMPP vykdymo Lietuvoje pradžios apskaičiuotas intervalinių krūties navikų santykinis dažnis ir Lietuvoje vykdomos AMPP jautrumas. Pirmąkart įvertinta AMPP įtaka sergamumo krūties vėžiu, nustatomos ligos stadijų pasiskirstymo ir mirtingumo pokyčiams Lietuvoje. Pirmą kartą nustatyti AMPP dalyvavusių ir nedalyvavusių moterų krūties navikų patologinių charakteristikų skirtumai.

7.6 Išvados

1. Atrankinėje mamografinės patikros programoje Lietuvoje dalyvauja tik apie pusę rekomenduojamo dalyvauti moterų skaičiaus. Krūties navikai, nustatyti vykdant atrankinę mamografinę patikrą, sudaro tik 25 proc. visų krūties navikų, diagnozuotų 50–69 metų amžiaus moterims, o I stadijos krūties navikai sudaro tik 49 proc. visų nustatytų navikų.
2. Lietuvoje sergamumas krūties vėžiu didėja, o mirtingumas nuo šios ligos mažėja nežymiai. Didėja, diagnozuotų ankstyvų stadijų krūties navikų skaičius ir mažėja nustatytų vėlyvų stadijų navikų, tačiau atrankinės mamografinės patikros programos įtaka šiems pokyčiams nebuvo nustatyta. Tiriamuoju laikotarpiu nustatyti pokyčiai gali atspindėti didesnio žinomumo apie krūties vėžį, diagnostikos tobulėjimo ir didesnių efektyvaus gydymo galimybių įtaką.
3. Moterims, kada nors dalyvavusioms atrankinėje mamografinės patikros programoje, diagnozuoti navikai buvo mažesni, geriau diferencijuoti, ankstyvesnių stadijų, rečiau su metastazėmis limfmazgiuose.
4. Intervalinių navikų santykinis dažnis Lietuvoje 2006–2012 metais buvo 0,25. Šis dažnis iš esmės nesiskiria nuo kitų šalių publikuotų duomenų.
5. Bendras Lietuvoje vykdomos atrankinės mamografinės patikros programos jautrumas siekia 75 proc. ir yra panašus kaip ir kitose Europos šalyse. Didžiausias atrankinės mamografinės patikros programos jautrumas buvo tarp vyriausių programos dalyvių ir esant duktalinei naviko histologijai.

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