Ph.D. Thesis

ANALYSIS OF CONTRIBUTING FACTORS OF THE BREAST CANCER MORTALITY RATE IN HUNGARY BETWEEN 2002 AND 2014

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Ph.D. Thesis

Analysis of contributing factors of the breast cancer mortality rate in Hungary between 2002 and 2014

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LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PHD THESIS

I. **Újhelyi, M., D. Pukancsik, P. Kelemen, E. Kovács, I. Kenessey, N. Udvarhelyi, M. Bak, T. Kovács and Z. Mátrai**

Does breast screening offer a survival benefit? A retrospective comparative study of oncological outcomes of screen-detected and symptomatic early stage breast cancer cases.

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II. **Újhelyi M, Pukancsik D, Kelemen P**, **Kovács E, Kenessey I, Bak M, Kásler M, Kovács T, Mátrai Z**

Barriers to Organized Mammography Screening Programs in Hungary: A Questionnaire-based Study of 3 313 Women

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III. **Mátrai Z, Kenessey I, Sávolt Á, Újhelyi M, Bartal A, Kásler M**

Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary: a questionnaire study of 500 cases.

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IV. **Újhelyi M, Pukancsik D, Kelemen P, Sávolt Á, Gődény M, Kovács E, Udvarhelyi N, Bak M, Polgár C, Rubovszky G, Kásler M, Mátrai Z**

Breast cancer care quality analysis of the National Institute of Oncology in Hungary according to the requirements of European Society of Breast Cancer Specialists (EUSOMA)

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OTHER PUBLICATIONS RELATED TO THE TOPIC OF THE THESIS

V. **Pukancsik D, Kelemen P, Gulyás G, Újhelyi M, Kovács E, Éles K, Mészáros N, Kenessey I, Pálházi P, Kovács T, Kásler M, Mátrai Z.**
Clinical experiences with the use of ULTRAPRO® mesh in single-stage direct-to-implant immediate postmastectomy breast reconstruction in 102 patients: A retrospective cohort study.
Eur J Surg Oncol. 2017 Jul;43(7):1244-1251
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VI. **Pukancsik D, Kelemen P, Újhelyi M, Kovács E, Udvarhelyi N, Mészáros N, Kenessey I, Kovács T, Kásler M, Mátrai Z.**
Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy: An aesthetic and functional prospective cohort study.
Eur J Surg Oncol. 2017 Feb;43(2):303-310.
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VII. **Pukancsik D, Kelemen P, Sávolt Á, Újhelyi M, Kovács E, Zaka Z, Kásler M, Mátrai Z.**
Evaluation of clinicopathological findings and cosmetic outcome of 100 immediate postmastectomy breast reconstruction cases
Orv Hetil. 2016 Nov;157(46):1830-1838.
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VIII. **Mátrai Z, Tóth L, Polgár C, Láng I, Gõdény M, Sinkovics I, Horváth Z, Bidlek M, Udvarhelyi N, Bartal A, Sávolt A, Ujhelyi M, Kásler M.**
Sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer
Magy Onkol. 2011 Jun;55(2):73-84

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LIST OF ABBREVIATIONS

ALND:	axillary lymph node dissection
BCS:	breast conserving surgery
CT:	computed tomography
DCIS:	ductal carcinoma in situ
DFS:	disease-free survival
DM:	diagnostic mammography
DSC:	designated screening centre
EIC:	extensive intraductal component
ER:	estrogen receptor
ESMO:	European Society of Medical Oncology
ET:	endocrine therapy
FISH:	fluorescent in situ hybridization
HER2:	human epidermal growth factor 2
IHC:	immunohistochemical
ILC:	invasive lobular carcinoma
ILS:	Invitation Letter for Screening
MRI:	magnetic resonance imaging
NIO	National Institute of Oncology
OS:	overall survival
OMSP:	organized mammography screening programme
PMRT:	postmastectomy radiotherapy
PR:	progesterone receptor
RCTs:	randomized controlled trials
ROLL:	radio-guided occult lesion localization
RT:	radiotherapy
SEER:	Surveillance, Epidemiology, and End Results
SCR:	screened group
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy
SYM:	symptomatic group
TN:	triple negative

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1. INTRODUCTION

1.1 Breast cancer incidence and mortality

Breast cancer is one of the most prevalent malignancies and remains a main cause of cancer death for women in the developed world. Across Europe, there is an 8% chance for a woman to suffer from breast cancer before the age of 75 while sustaining a corresponding 2% chance of dying from the disease.[1] According to the database of the World Health Organization (WHO) 1.7 million new cases (25 % of all new cases in women) and 0.5 million (15 % of all cancer deaths in women) deaths of breast cancer were registered over the world in 2012. [2] The Hungarian National Cancer Registry recorded nearly 7,900 new cases of breast cancer in women, with more than 2,100 deaths in 2014.[3]

1.2 Breast cancer screening

Breast cancer is highly heterogeneous in its pathological characteristics, that comprising several molecular, genetic and biological subtypes with different aetiology, therapeutic indications, and clinical outcomes.[4] Most breast cancer deaths are caused by an advanced disease that has already spread to the regional lymph nodes or distant organs at the diagnosis. An important public health goal is to disclose breast tumours before they become symptomatic, optimally during stage 0 or stage I. Therefore, many countries have implemented the organized mammography screening programme (OMSP) in order to detect breast cancer at an early stage and reduce breast cancer mortality. [5-7] The efficacy of mammography screening in preventing breast cancer deaths has been shown in randomized controlled trials, with a mortality rate reduction from 17% to 32% [8-12]The Hungarian nationwide OMSP for women 45-65 years of age, with a biannual screening interval was implemented in January 2002 [13]

1.3 Problems related to Hungarian the breast cancer mortality rate in the last decade

Despite the well-organized decade-old screening programme while not statistically significant, the Hungarian incidence of breast cancer has been increasing since the implementation of the programme.[14] Again a crucial problem is that **the breast cancer mortality in Hungary did not change significantly between 2002 and 2014** despite of OMSP, with the aim of mortality reduction.[3] (Figure 1)

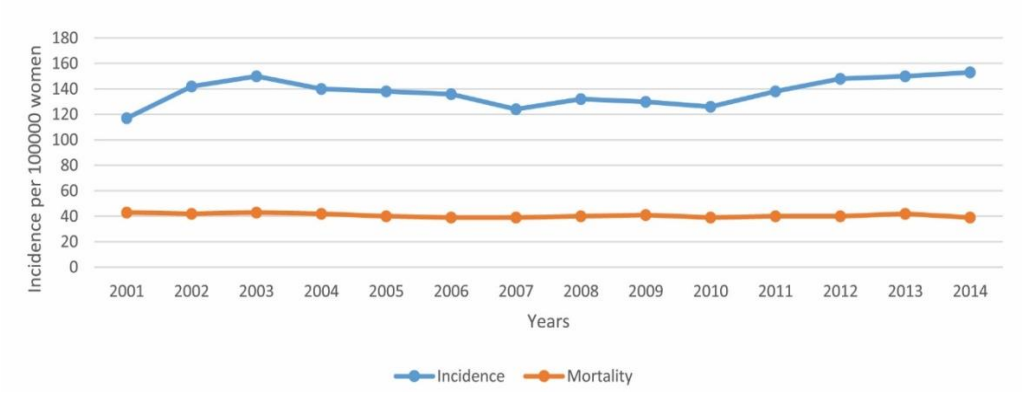

Figure 1: *Breast cancer incidence and mortality per 100,000 women in Hungary between 2001 and 2014*[3]

The Swedish Two-County Trial of mammography screening program for breast cancer was initiated in 1977. The first mortality results were published by László Tabár et al. in 1985, showing a significant 31% reduction in breast cancer mortality associated with an invitation to screening between 1977 and 1984.[9]

The UK breast screening programme was introduced in 1988 inviting women aged 50–64 every 3 years. In the absence of screening or other effects (improved treatment with tamoxifen and chemotherapy) the total reduction in mortality from breast cancer in first decade in women aged 55-69 was estimated as 21.3% and mortality is still decreasing.[15](Figure 2) In 2012/2013 around three-quarters (74%) of women in the UK who are invited for breast screening are screened adequately (with a definitive usable result) within 6 months of invitation.[16] In the USA the first national guidelines for breast cancer screening were issued by the American College of Radiology in 1976.[17] Prevalence estimates vary but range from 64% to 81% of the eligible population screened regularly.[18]

The incidence of breast cancer increased from 102 / 100,000 to 130.4 / 100,000 women and the mortality decreased from 31.8 /100 000 to 20.7 / 100,000 women between 1976 and 2013. [19]

One of the **main public health issues is that the mortality of breast cancer did not change significantly in Hungary** compared to UK and US between 2004 and 2013. [3,16,19] (Figure 2)

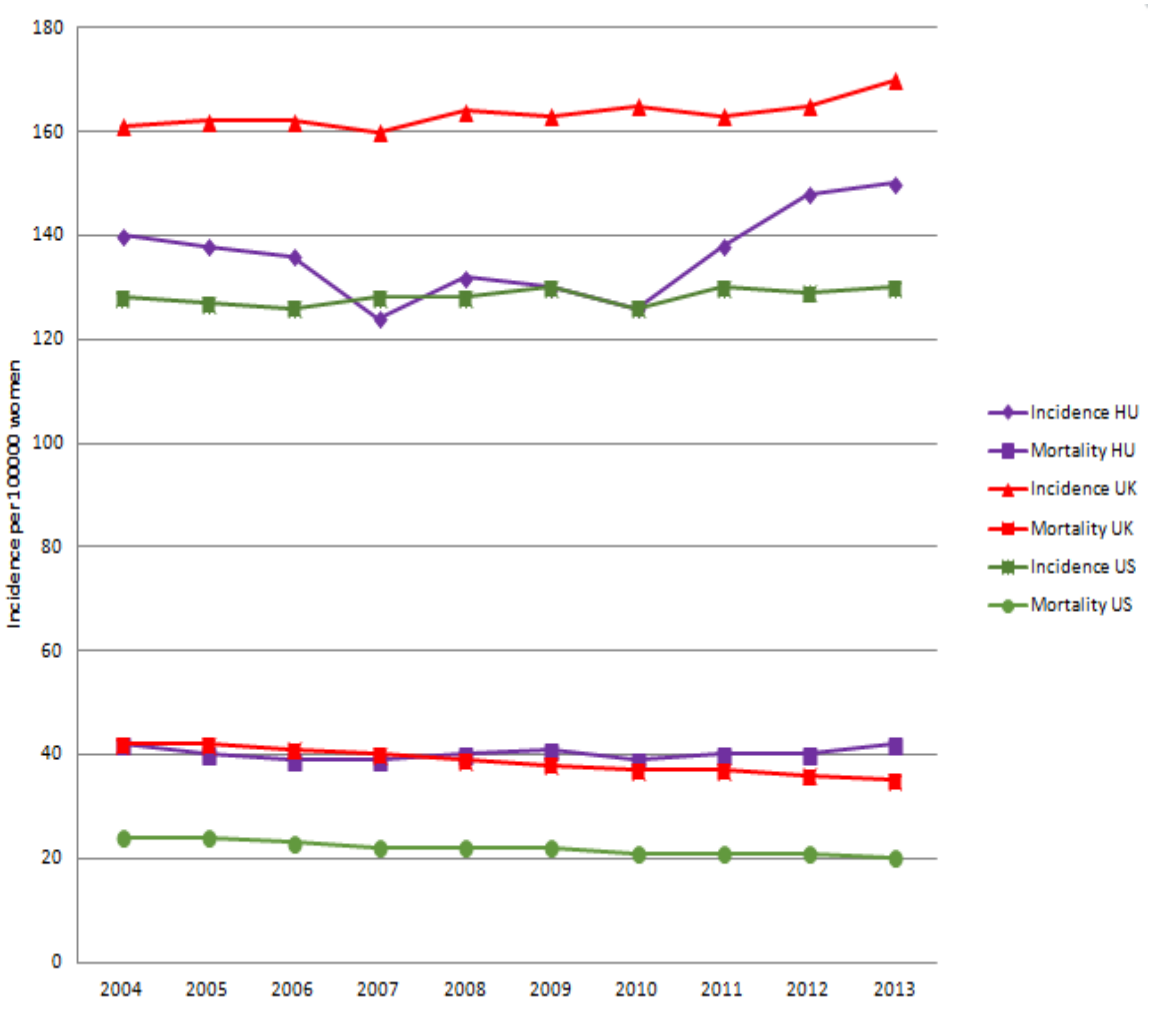

Figure 2: *Breast cancer incidence and mortality per 100,000 women in Hungary, UK, and US between 2004 and 2013*[3,16,19]

Breast cancer-related mortality mainly depends on the stage of breast cancer at the time of diagnosis, and oncological outcomes are generally more favourable during early stages of disease. One of the most important roles of OMSP is to reduce the number of advanced breast cancer cases. The incidence of advanced tumour stages represents one of the

most relevant surrogate parameters for screening effectiveness. OMSP as a main public health tool for secondary breast cancer detection can decrease the percentage of advanced breast cancer cases and thus could reduce breast cancer-related mortality.[20-22]

Another **main public health issue is that the Hungarian stage based cross-sectional view of incidence based breast cancer cases has not been analysed** yet. It is important to understand the cause of Hungarian constant mortality rates of the decade following the implementation of OMSP. There is a **pronounced need to assess a proportion of the early staged and advanced breast cancer cases**, which has not been examined properly to date.

The evaluation of breast cancer care in the National Institute of Oncology (NIO), Hungary based on the Society of Breast Cancer Specialists (EUSOMA) requirements of breast unit quality indicators with the large number of cases presents representative clinico-pathological data on the Hungarian stage based breast cancer incidence.[23] This cross-sectional view of Hungarian breast cancer population might provide associated information on the cause of relatively high breast cancer mortality rate compared to the USA and the UK.

Eighteen European countries have implemented national or regional population-based mammography screening programmes, to detect breast cancers at a pre-clinical stage.[24] There is no consensus about the exact effect of mammography screening on breast cancer mortality reduction, as the reported estimates vary.[25] Some recent studies have questioned the efficacy of early stage tumour detection on mortality reduction.[26, 27] Some authors believe that locally advanced breast cancer diagnosis and effective adjuvant therapy may play greater roles in reducing breast cancer mortality than screening.[28] Other studies concluded that OMSP by decrease of the percentage of advanced breast cancer cases reduces breast cancer-related mortality.[20-22] Consequently the incidence of advanced tumour stages might represent one of the most relevant surrogate parameters for screening effectiveness. The clinical outcomes of early stage breast cancer cases between patients who underwent mammography screening and non-screened symptomatic patients had not been analysed before.

Secondly, the participation rate on OMSP is an important factor in breast cancer related mortality reduction. According to the WHO, the breast screening adherence rate should be at least 70% in order to decrease breast cancer mortality.[29] Despite the fact that screening is invitational and free of charge, **the participation rate of the Hungarian OMSP has never reached the required minimum 70% participation rate and it has not even**

reached 35 %, which could have effect on breast cancer related mortality. From 2002 to 2003, 33.95% of the population attended the OMSP and 22.05% of the target population received a diagnostic mammography (DM). Thus, the total screening and diagnostic coverage of mammography exams was 53.46%.[30] From 2004 to 2005, 29.5% of the target population participated in the OMSP and 23.2% had a DM; in this period, the total mammography adherence rate decreased to 50.8%. In 2006-2007, the total coverage of mammography declined to 49.7%, with a 29.4% participation rate in the OMSP and 21.8% of the population having received a DM. From 2008 to 2009, the adherence rate was 31.2% and 20.4% of the target population having a DM, for a total coverage of 50.1%. The attendance rate of the Hungarian OMSP did not change significantly between 2002 and 2009.[30-33] (Figure 3)

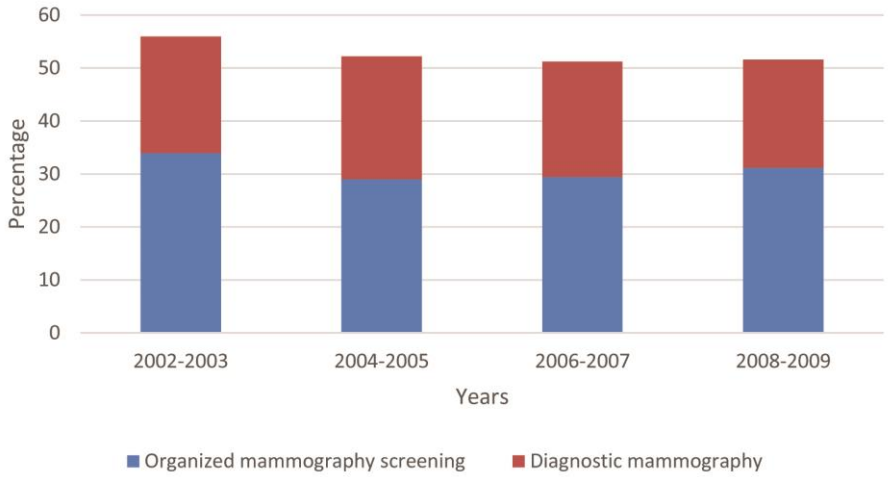

Figure 3: *The attendance rate of the Hungarian organized mammography screening programme and the percentage of diagnostic mammography performed between 2002 and 2009. [30-33]*

The association between marital status, education level, socioeconomic characteristics, knowledge, and beliefs about breast cancer and mammography screening have not been properly analysed to date. There is an urgent public health need to explore the barriers to the OMSP. [34] It is important to have a validated instrument to answer this question. There is also a pronounced **public health need to have appropriate knowledge on information channels to reach the target population** about the importance of breast screening.

Neighbouring Central-Eastern European countries such as Austria**, Bulgaria, Latvia, Poland and the Czech Republic have similar living standards, and also present low**

breast screening coverage rates comparable to those in Hungary therefore the problem of low participation rate is European / international. [24, 35] (Table 1)

Table 1: *Breast cancer screening programmes in 2010 and last update: coverage by test, coverage by invitation, participation rate (Austria, Bulgaria, Latvia, Poland and the Czech Republic)* [35]

Country	Update period	Annual eligible population	Number of invitations	Number of women screened	Coverage by invitation (%)	Coverage by test (%)	Participation rate (%)
Austria	2010	200,000	200,000	27,000	100.0	13.5	**13.5**
	2014	1,500,000	1,500,000	600,000	100.0	40.0	**40.0**
Bulgaria	2013–2014	1,057,000	123,647	10,392	11.7	1.0	**8.4**
Czech Republic	2013	878,576	521,187[a]	538,997	28.7	61.3	**13.4**
	2010	203,336	196,578	38,148	96.7	18.8	**19.4**
Latvia	2014	159,223	142,168	51,060	89.3	32.1	**35.9**
	2010	2,522,421	2,419,459	945,283	95.9	37.5	**39.1**
Poland	2014	2,668,119	2,749,919	1,207,214	103.1	45.2	**43.9**

Increased knowledge regarding the barriers to mammography screening may provide information to extend our knowledge of breast cancer screening and effective treatment in Hungary and in the above mentioned Central-Eastern European countries.

2. OBJECTIVES OF THE THESIS

2.1 To evaluate quality cross-sectional view of stage based breast cancer incidence for the first time in Hungary.

2.2 To analyse the differences between screen-detected and symptomatic early stage breast cancer cases for the first time in Hungary.

2.3 To compare the overall and disease free survival between screen-detected and symptomatic early stage cases breast cancer cases for the first time in Hungary.

2.4 To examine the factors associated with women's screening behaviours, beliefs, and barriers leading to low adherence rates in the Hungarian organized mammography screening programme and to acquire information on the appropriate level of necessary intervention to increase screening participation for the first time in Hungary.

2.5 To determine suitable information channels to reach the breast screening target population.

3. PATIENTS AND METHODS

3.1 ANALYSIS OF BREAST CANCER CARE QUALITY AT THE NATIONAL INSTITUTE OF ONCOLOGY BASED ON REQUIREMENTS OF THE EUROPEAN SOCIETY OF BREAST CANCER SPECIALISTS

To answer the first question, database has been created and approved by the institutional ethical committee with the aim of evaluating the Hungarian quality cross-sectional view of stage based breast cancer incidence. According to a dedicated breast unit quality analysis of uniformed criteria of European Society of Breast Cancer Specialists (EUSOMA) 119 clinico-pathological data of multimodality treated breast cancer cases were retrospectively analysed from the prospectively kept database of the NIO, Budapest between 1 June 2011 and 31 May 2012.[23]

According to the updated international European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up, all patients received multimodality oncology treatments and a follow-up at the NIO during the investigation period.[36, 37] The diagnosis of breast cancer was based on clinical examination in combination with imaging (mammogram, breast and regional lymph node ultrasound) and was confirmed via pathological (core biopsy or fine-needle aspiration cytology) assessment. magnetic resonance imaging (MRI) was used in cases of breast implants, invasive lobular carcinoma (ILC), the suspicion of multifocality/multicentricity, or large discrepancies between conventional imaging and the clinical examination. Early breast cancer was defined as tumours of not more than five centimetres in the largest diameter, with either non-palpable or palpable but not fixed lymph nodes and with no evidence of distant metastases. This corresponds to tumours that are pTis-2, pN0-1, M0 (Stage 0-IIB, except pT3pN0 tumours) as currently defined by the Union for International Cancer Control (UICC) TNM classification of malignant tumours.[38]

For surgical procedures, breast conserving surgery (BCS), mastectomy, sentinel lymph node biopsy (SLNB) with dual radio-colloid/blue dye technique were used. In sentinel lymph node (SLN)-positive cases or for clinically positive axillary lymph nodes, axillary lymph node dissection (ALND) was used. In case of BCS, palpable tumours were resected via a wide

excision and non-palpable tumours were resected via a wide excision using radio-guided occult lesion localization (ROLL) technique, with a minimum microscopical surgical margin of 1 mm. Postoperative pathological assessments included the number, the location and the size of the tumours removed, the total number of removed and positive lymph nodes, and the extent of metastases in the lymph nodes, such as isolated tumour cells, micrometastasis (0.2–2 mm) and macrometastasis. The report included the histological type and grade of the tumour, evaluation of the resection margins, vascular invasion, and a biomarker analysis, such as an immunohistochemical (IHC) evaluation of oestrogen receptors (ERs), progesterone receptors (PRs) and human epidermal growth factor 2 receptor (HER2) gene expression. HER2 gene amplification for tumours with an ambiguous (2+) IHC score was evaluated using a fluorescent in situ hybridization (FISH) technique. The minimum distance of the free margin was determined as 1 mm for invasive cancers and in situ carcinoma cases. The institutional breast cancer classification into surrogate intrinsic subtypes was based on the IHC assessment of ER, HER2 and Ki67 with a 14% cut-off during the investigation period between 2011 and 2012.

During the investigated period, the chemotherapy regimen was based on FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide) and taxanes. Chemotherapy was indicated in triple-negative, HER2-positive breast cancers and in high-risk luminal HER2-negative tumours. Depending on the individual recurrence risk and the selected regimen, chemotherapy was usually administered for six cycles. Endocrine therapy (ET) was based on tamoxifen or aromatase inhibitors in luminal cases for five years after the surgery. All HER-2 positive patients received adjuvant trastuzumab therapy, which was administered once per week during treatment with other chemotherapy medications, and then once every 3 weeks after treatment with the other medications for up to 52 weeks. Radiotherapy (RT) was performed using three-dimensional planning with CT. The adjuvant radiotherapy started on the fourth postoperative week or after the adjuvant chemotherapy. Patients who received breast conserving surgery were given whole breast radiotherapy and boost irradiation was indicated for patients who had unfavourable risk factors for local control. Postmastectomy radiotherapy (PMRT) was administered to patients with pT3–T4 tumours. Loco-regional RT was indicated for patients with more than three involved lymph nodes. Doses used for local and/or regional adjuvant

irradiation were 50 Gy in 25 fractions of 2.0 Gy with a typical boost dose of 16 Gy in 2 Gy single doses.

Medical records and pathology reports were reviewed, and information on the HER-2, ER and PR status of the patients were collected from the institutional database retrospectively, as well as data on age at the diagnosis, disease grade, stage, and other clinical covariates. The TNM classification was defined by the American Joint Cancer Committee (AJCC) and Union for International Cancer Control (UICC) Breast Cancer Staging 7th Edition.

3.2 THE STUDY OF COMPARISON OF CLINICAL OUTCOME OF SCREEN DETECTED AND SYMPTOMATIC BREAST CANCER CASES

To analyse the differences and compare the overall and disease free survival between screen-detected and symptomatic early stage cases breast cancer cases this study method has been designed. The study was performed in accordance with the Research Ethics Committee of the NIO. A written informed consent was always obtained for data collection. The inclusion period was from 1 January 2002 through 31 December 2009. Data were collected from the prospectively kept database of the NIO, Budapest.

Based on the Hungarian guideline on mammography screening the target population was invited for breast screening regionally by invitation letters.[39] Our investigated screened population represents the target population from the capital. Screened (SCR) breast cancer patients discovered by the mammography screening programme of the NIO were collected prospectively. Based on the international standards for breast screening, double-projection mammograms and double-read procedures were applied. A Siemens Mammomat 3000 mammography system was used for screening, diagnostics and stereotactic biopsy procedures. For suspicious and malignant cases, bimanual physical examination, breast and regional lymph node ultrasound and core biopsy or fine-needle aspiration cytology (FNAC) were used for further examination.[40]

The positively symptomatic (SYM) breast cancer patients with palpable tumours were collected randomly and prospectively from the institutional database by three researchers. The patients included in the SYM group were newly diagnosed breast cancer patients

corresponding to a **clinical stage** from 0 to II/A with a disease discovered by self-examination or via another physical breast examination by the general practitioner or gynaecologists within the inclusion period. The main reason for breast examination of SYM patients were the changes in the breast shape, skin retraction, nipple inversion, breast pain, a palpable lump, nipple discharge, unexplained redness, swelling or a lump around the collarbone or under the arm. Patients whose disease was discovered by screening were excluded from the SYM group. Patients in SYM group were collected mainly from the capital. The database was kept prospectively according to the standard methods of all disciplines involved in breast cancer diagnosis, treatment and follow-up, which included all relevant clinico-pathological data of the SCR and SYM patients. Some of the patients were included in clinical trials in both groups but nobody has left undertreated.

According to the updated international ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, all patients received multimodality oncology treatments and a follow-up at the NIO as it is described in a study method of "Breast cancer care quality analysis of the National Institute of Oncology according to the requirements of EUSOMA".[36, 41-44] Postoperative pathological examination and assessments, radiotherapy, hormonal therapy had not been significantly changed during the investigated period. Based on the institutional guidelines breast cancer classification into surrogate intrinsic subtypes was based on the IHC assessment of ER, HER2 and Ki67 with a 20 % cut-off during the investigation period between 2002 and 2009. Only biological therapy had been changed: from 2002 and 2006 for HER-2 positive patients with minimum diameter of 10 mm tumour or/and with regional metastasis, adjuvant trastuzumab was administered once per week during treatment with other chemotherapy medications, and then once every 3 weeks after treatment with the other medications for up to 52 weeks. From 2006 all HER-2 positive patients received adjuvant trastuzumab therapy.

Medical records and pathology reports were reviewed, and information on the HER-2, ER and PR status of the patients were collected from the institutional database retrospectively, as well as data on age at the diagnosis, disease grade, stage, death, and other clinical covariates. The TNM classification was defined by the AJCC/UICC Breast Cancer Staging 7th Edition [38] Patients with missing information were excluded. All patients were followed up, and their status was checked from their medical records. The follow-up was managed by regular visits with physical examinations every 3 months during the first 2 years, every 6

months from years 3–5, and annually thereafter. Annual mammography with ultrasound was performed. For cases of local, regional or distant relapse suspicion in the CT scan, PET/CT scans or MRI were used.

All causes of death were included in the analysis of the overall survival (OS). Disease-free survival (DFS) was calculated from the number of months elapsed from surgery until the date of the diagnosis of the first loco-regional or systemic recurrence. Patients' OS and DFS were calculated for the entire investigated period until the last visit. The OS and DFS between the SCR and SYM group were compared using the log-rank test and depicted using the Kaplan-Meier method. Time intervals were defined as the time elapsed from the first breast cancer therapy to the last control without an event or to event occurrence (loco-regional or distant relapse or death). Qualitative variables are expressed as a number and percentage, and quantitative variables are expressed as the median with minimum and maximum values. For comparison of qualitative data, a chi-square test or Fisher's exact test was applied. Asymmetrical numeric data were analysed using a Mann-Whitney test. Statistical significance was confirmed when P values were <0.05. Data analysis was performed using Statistica 12.0 (Statsoft, Tulsa, OK). [45]

3.3 THE STUDY OF INVESTIGATION OF THE SOCIOECONOMIC FACTORS AND BARRIERS ASSOCIATED WITH LOW ADHERENCE RATE ON MAMMOGRAPHY SCREENING PROGRAMME VIA QUESTIONNAIRE

This study was performed in accordance with the Research Ethics Committee of the NIO which conforms to the provisions of the Declaration of Helsinki. The study was performed without additional financial support at the NIO in Budapest between 2015 and 2016. The study received non-financial administrative support from the Hungarian AVON Cosmetics Company and the Mellrákinfó advocacy group.

A cross-sectional survey was designed to examine women's screening behaviour, beliefs, and barriers to OMSP. The Hungarian breast screening target population of women 45-65 years of age were interviewed anonymously using web-based and printed questionnaires containing 15 structured questions. The questionnaire was designed to assess and report on the psychometric and demographic properties of barriers leading to low participation rates. (Figure 4) The 15-item questionnaire was composed of four sections. The first five questions focused on education level, marital status, residence (capital, provincial town, or village) and county of residence. Three questions focused on mammography receptive behaviour, five questions directly addressed OMSP (receiving invitation letter, participation frequency in mammography screening, distance from screening centre), and two questions focused on barriers that prevented women from attending the screening programme.

The sample population was reached *via* e-mail and Facebook campaign through web-based questionnaires by the Hungarian AVON Cosmetics Company. The questionnaire link was secured by Hypertext Transfer Protocol Secure system. The survey's web-based link was sent to the e-mail contact list and Facebook followers of the Hungarian AVON Cosmetics Company. Printed forms were sent by mail and distributed at local social functions by the Mellrákinfó advocacy group and Hungarian AVON Cosmetics Company. Hungarian AVON used its own contacts to reach the target population.

To ensure that the study sample was representative of the screening population, only surveys from women 45-65 years of age were accepted. Answering the survey questions was voluntary and anonymous. The data protection law was followed and respected. Questionnaires with unreadable or unclear answers were excluded from the analysis.

All answers were statistically analysed in the context of marital status, educational level, and type of residence using chi-square test; *p*-values of less than 0.05 were considered to be significant. Statistical analysis was performed using PAST 1.86 and Statistica 12.0 (StatSoft, Tulsa, OK, USA). [45]

Q1: Age:				
Q2: Educational level:	Primary		Secondary	Tertiary
Q3: Residence:	Village		Provincial town	Capital
Q4: County:				
Q5: Marital status:	Unmarried	Married	Divorced	Widowed
Q6: Do you undergo any mammography examinations?	Yes		No	
Q7: If yes, how regularly?	Regularly		Occasionally	
Q8: If yes, how frequently?	Annually		Biennially	
Q9: Have you received Invitation Letter for Screening?	Yes		No	
Q10: When did you receive Invitation Letter for Screening?	Year:			
Q11: Do you undergo regular breast screening?	No		Regularly	Occasionally
Q12: Where was your last breast exam?	Organized mammography screening at designated screening centre		Opportunistic mammography screening outside of designated screening centre (medical office, private clinic, *etc.*)	
Q13: How far is the designated screening centre from your residence?	Close		Far	Very far
Q14: Why did you not undergo an organized mammography screening?	Because of fear of breast cancer.			
	Because of fear of mastectomy.			
	Because the designated screening centre is too far.			
	Because of my job.			
	Because I do not have enough information on mammography screening.			
	Because mammography examinations are harmful.			
	Because I undergo opportunistic mammography screening.			
	Because mammography examinations are painful.			
	Because examination of an intimate body part is embarrassing			
	Because of the expenses to get there.			
	Other			
Q15: What should be changed in order for you to attend the screening program?				

Figure 4: *Questionnaire containing 15 structured questions.*

To examine the appropriate information channels to reach the breast screening target population "Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary" questionnaire study was used.

A questionnaire containing 15 structured questions was given to 500 breast cancer patients on the day before undergoing mastectomy, with or without the axillary procedure, in

the Department of Breast and Sarcoma Surgery of the NIO between January 2010 and October 2011. The questions focused on the decision-making process, emotional impact of the malignant disease, breast loss, attitudes toward reconstruction, changes in family life and social connections, sexual well-being, importance of environmental conditions, patient knowledge regarding breast reconstruction**, sources of information**, and desire for an immediate or delayed procedure. Answering the survey questions was voluntary. The questionnaire and the study structure were approved by the institutional ethics committee. The results of information gathering on breast reconstruction in context of age and education were used in our investigation.

All answers were statistically analysed in the context of marital status, educational level, and type of residence using chi-square test; p values <0.05 were considered to be significant. Statistical analysis was performed using PAST 1.86 and Statistica 12.0 (StatSoft, Tulsa, OK, USA).[45]

4. RESULTS

4.1 ANALYSIS OF BREAST CANCER CARE QUALITY AT THE NATIONAL INSTITUTE OF ONCOLOGY BASED ON REQUIREMENTS OF THE EUROPEAN SOCIETY OF BREAST CANCER SPECIALISTS

During the study period 906 surgical procedures were performed with the indication of breast malignant, benign or recurrent tumours. The average age was 59 years (range 14-91 years). The comparison of clinical and pathological stages of breast cancer cases are shown in Table 2. In case of benign lesions, recurrent tumours the clinical stage was not determined.

Table 2: *Comparison of clinical and pathological stages of breast cancer cases in the National Institute of Oncology between 01.06.2011 and 31.05.2012*

Clinical stage	***n (%)***	***Pathological stage***	***n (%)***
0	*41 (4,5%)*	***0***	*67 (7,3%)*
IA	*376 (41,5%)*	***IA***	*256 (28,2%)*
		IB	*2 (0,2%)*
IIA	*236 (26%)*	***IIA***	*202 (22,2%)*
IIB	*115 (12,7%)*	***IIB***	*98 (10,8%)*
IIIA	*37 (4,1%)*	***IIIA***	*65 (7,1%)*
IIIB	*13 (1,4%)*	***IIIB***	*21 (2,3%)*
		IIIC	*32 (3,5%)*
IV	*9 (0,9%)*	***IV***	*5 (0,5%)*
		y0	*14 (1,5%)*
		yIA	*6 (0,6%)*
		yIIA	*10 (1,1%)*
		yIIB	*17 (1,8%)*
		yIIIA	*21 (2,3%)*
		yIIIB	*3 (0,3%)*
		yIIIC	*15 (1,6%)*
X	*79 (8,7%)*	***X***	*34 (3,7%)*
		Benign	*38 (4,1%)*
Total:	***906 (100%)***	***Total:***	***906 (100%)***

X: undetermined
y: stage after primary chemotherapy

The proportion of clinical early stage primary breast cancer cases (Stage 0-IIB, except T3N0) was 91.29 % (n=755) that decreased to 79.25 % (n=661) after surgical treatment based

on the postoperative pathology assessment (the data of pathological stage were used after primary chemotherapy). 819 (90.4 %) patients received primary surgical procedure and 87 (9.6 %) patients received primary chemotherapy. Types of surgical procedures are listed in Table 3.

Table 3: *Types of surgical procedures and their percentage distribution of breast cancer cases in the National Institute of Oncology between 01.06.2011 and 31.05.2012*

Surgical procedure	***n (%)***
Lumpectomy	*24 (2,6%)*
radio-guided (ROLL) wide excision	*13 (1,4%)*
wide excision	*28 (3,2%)*
radio-guided (ROLL) wide excision and SLNB	*217 (23,95%)*
radio-guided (ROLL) wide excision and ALND	*11 (1,2%)*
wide excision and SLNB	*110 (12,25%)*
quadrantectomy and SLNB	*118 (13,1%)*
wide excision and ALND	*30 (3,3%)*
quadrantectomy and ALND	*37 (4,1%)*
Mastectomy	*20 (2,2%)*
mastectomy and SLNB	*108 (11,9%)*
mastectomy and ALND	*173 (19,1%)*
ALND	*5 (0,5%)*
skin sparing mastectomy and SLNB	*7 (0,7%)*
skin sparing mastectomy and ALND	*5 (0,5%)*
Total:	***906 (100%)***

ROLL: radio-guided occult lesion localization,
SLNB: sentinel lymph node biopsy,
ALND: axillary lymph node dissection

The BCS rate was 64% (n=557) and the mastectomy rate was 36 % (n=311) in the case of primary surgical treatment in malignant diseases. For 560 (67.4 %, recurrent and benign cases excluded) patients were SLNB performed and the incidence of negative lymph nodes was 76.4 % (n=428) and positive was 23.6 % (n=132). The average of removed SLNs was 1.43 (range 1-7). In total for 388 (46.7 %, recurrent and benign cases excluded) patients ALND were performed. The average of removed lymph nodes via ALND was 12.67 (range 2-33). The percentage of negative lymph nodes was 51.5 % and 46.7 % for positive lymph

nodes. Proportion of patients with invasive cancer and ALND performed with at least 10 lymph nodes examined was 92.3 %.The average pathological tumour size was 27.4 mm (range 0-210 mm). The comparison of clinical and pathological tumour sizes is presented in Table 4.

Table 4: *Comparison of clinical and pathological tumour sizes of breast cancer patients in the National Institute of Oncology between 01.06.2011 and 31.05.2012*

Tumour size (mm)	***Clinical, n (%)***	***Pathological, n (%)***
<5	*27 (2,9%)*	*55 (6%)*
6-10	*185 (20,5%)*	*88 (9,8%)*
11-20	*343 (37,8%)*	*291 (32,2%)*
21-50	*297 (32,9%)*	*370 (40,9%)*
>50	*50 (5,5%)*	*94 (10,3%)*
X	*4 (0,4%)*	*8 (0,8%)*
Total:	***906 (100%)***	***906 (100%)***

X: lack of data

The incidence of benign lesions was 4.2 % (n=38), in situ carcinoma was 7,6 % (n=69), invasive carcinoma was 87.4 % (n=791), non-epithelial tumour was 0.2 % (n=2), other was 0.3 % (n=3) and undetermined was 0.3 % (n=3). The incidence of vascular invasion was 29.4 % (n=266). According to the breast cancer subtypes the number of Luminal-A surrogate subtype tumours were 354 (40.8 %), Luminal-B surrogate subtype tumours were 315 (36.2 %), triple negative (TN) cases were 116 (13.4 %) and HER-2 over-expressed tumours were 16 (1.8 %).

Proportion of patients with invasive cancer who received postoperative radiotherapy after surgical resection of the primary tumour and appropriate axillary staging/ surgery in the framework of BCT was 94.7 % (n=460). Proportion of patients with endocrine sensitive invasive carcinoma who were offered endocrine therapy was 99.8 % and the proportion of patients with ER/PR negative invasive tumours ≥ 2 cm and/or Node+ disease, who received adjuvant chemotherapy, was 98.9%. The chemotherapy regiments and their percentage distribution are presented in Table 5.

Table 5: *Chemotherapy regiments and their percentage distribution offered for breast cancer patients in the National Institute of Oncology between 01.06.2011 and 31.05.2012*

Chemotherapy regiments	***n(%)***
AC (doxorubicin, cyclophosphamid)	*30 (8,6%)*
CMF 1-8 (cyclophosphamid, methotrexat, fluorouracil)	*5(1,4%)*
EPI+CMF 1-8 (epirubicin, cyclophosphamid, methotrexat, fluorouracil)	*1 (0,2%)*
FAC (fluorouracil, doxorubicin, cyclophosphamid)	*106 (30,7%)*
FEC (fluorouracil, epirubicin, cyclophosphamid)	*19 (5,%)*
EC (epirubicin, cyclophosphamid)	*31 (8,9%)*
ADM-TXT (doxorubicin docetaxel)	*9 (2,6%)*
EPI-TXT (epirubicin, docetaxel)	*10 (2,8%)*
A-TAX (doxorubicin, paclitaxel)	*5 (1,4%)*
Other	*129 (37,3%)*
Undetermined	*0 (0%)*

Other: Chemotherapy regiments are listed based on EUSOMA sub-partition, biological treatment is not listed

Based on EUSOMA quality indicators the breast cancer care of the NIO is presented in Table 6. According to EUSOMA quality indicators the breast cancer care of the NIO is eligible.

Table 6: *According to EUSOMA quality indicators the breast cancer care in the National Institute of Oncology between 01.06.2011 and 31.05.2012*

Indicator	***Mandatory***	***Minimum Standard***	***Target***	***National Institute of Oncology***
Preoperative diagnosis (proportion of B5/C5 in cancers)	*M*	*80 %*	*90 %*	***85,1%***
Proportion of invasive cancer cases with primary surgery, for which the following prognostic/predictive parameters have been recorded: Histological type, Grading, ER & PR,	*M*	*90%*	*98%*	***97,9%***

Pathological stage (T and N), Size in mm for the invasive component.				
Proportion of non-invasive cancer cases for which the following prognostic/predictive parameters have been recorded: Dominant Histological pattern, Grading,	*M*	*80 %*	*98%*	***89,1%***
Proportion of patients with invasive cancer and axillary clearance performed with at least 10 lymph nodes examined	*M*	*85%*	*98%*	***92,3%***
Proportion of patients (invasive cancer M0) who received postoperative radiotherapy after surgical resection of the primary tumour and appropriate axillary staging/ surgery in the framework of BCT.	*M*	*90 %*	*95 %*	***94,7%***
Proportion of patients with invasive breast cancer not greater than 3 cm (total size, including DCIS component) who underwent BCT.	*M*	*70 %*	*80 %*	***80,9%***
Proportion of patients with non-invasive breast cancer not greater than 2 cm who underwent BCT	*M*	*70 %*	*80 %*	***100%***
Proportion of patients with DCIS who do not undergo axillary clearance	*M*	*93 %*	*98%*	***100%***
Proportion of patients with endocrine sensitive invasive carcinoma who received hormonal therapy, out of the total number of patients with this diagnosis	*M*	*80 %*	*90 %*	***99,8%***
Proportion of patients with ER/PR negative invasive tumours ≥ 2 cm and/or Node+ disease, who received adjuvant chemotherapy	*M*	*80%*	*90%*	***98,9%***

4.2 THE STUDY OF COMPARISON OF CLINICAL OUTCOME OF SCREEN DETECTED AND SYMPTOMATIC BREAST CANCER CASES

During the inclusion period the NIO as an accredited regional mammography screening centre covered around 2% of the Hungarian target population. [39] During that period 47,718 women were examined by OMSP, and a total of 298 patients were diagnosed with breast cancer, which formed the SCR group.

For the SYM group, a total of 331 patients were collected randomly from 5351 symptomatic breast cancer patients during the same period. Patients with missing information or who were lost to follow-up were excluded. In total, we analysed data from 279 patients in the SCR group and from 316 patients in the SYM group. The median follow-up was 65 months (range: 13-130 months) for the SCR group and 80 months (range: 18-150 months) for the SYM group. The general characteristics and the clinical stages of the two groups are presented in Table 7.

Table 7: *General characteristics of the SCR and SYM groups*

	SCR Group, n (%)	***SYM Group, n (%)***	***P value***
Median age (years; range)	57; 45-65	56,5; 45-65	**0,453**[a]
Median follow-up	65; 13-130	80; 18-150	**0,0001**[a]
Clinical Stage			**$1{,}6*10^{-7}$**[a]
0	22 (7.8 %)	4 (1.2 %)	
I	125 (44.8 %)	101 (31.9 %)	
II	102 (36.5 %)	149(47.1 %)	
III	26 (9.3 %)	60 (18.9 %)	
IV	4 (1.4 %)	2 (0.6 %)	
Median tumour size	19; 1-170	24; 1-182	**p<0.00001**[b]
pT category			**$4{,}4*10^{-7}$**[a]
pTis	22 (7.8%)	4 (1.2%)	
pT1mi	4 (1.4%)	1 (0.3%)	
pT1	157 (56.2%)	135 (42.7%)	
pT2	81 (29%)	148 (46.8%)	
pT3	13 (4.6%)	22 (6.9%)	
pT4	2 (0.7%)	6 (1.8%)	
Histology			**$7.2*10^{-5}$**[c]
Non-invasive	22 (8 %)	4 (1.3%)	
Invasive	257 (92 %)	312 (98.7 %)	
Regional lymph node			**0.0006**[a]
pN0+pN1mi	187 (67 %)	168 (53.1 %)	

pN1-pN3	92 (33 %)	148 (46.9 %)	
Distant metastasis at the time of breast cancer detected			**0.315**[a]
M0	266 (95.3 %)	311 (98.4 %)	
M1	4 (1.4 %)	2 (0.6 %)	
Missing	9 (3.2 %)	3 (0.9 %)	
Distant metastasis for the entire investigated period			**0.013**[a]
M0	242 (86.8 %)	258 (81.7 %)	
M1	28 (10 %)	55 (17.4 %)	
Missing	9 (3.2 %)	3 (0.9 %)	
EIC			**p<0,001**[a]
Presence	171 (61.3 %)	79 (25 %)	
Absence	50 (17.9 %)	236 (74.7%)	
Missing	58 (20.8 %)	1 (0.3 %)	
Vascular invasion			**0.001**[c]
Presence	77 (27.6 %)	139 (44 %)	
Absence	172 (61.6 %)	175 (55.4 %)	
Missing	30 (10.8 %)	2 (0.6 %)	
Perineural invasion			**8.2 *10^{-8}**[a]
Presence	31 (11.1 %)	100 (31.7 %)	
Absence	216 (77.4 %)	214 (67.7 %)	
Missing	32 (11.5 %)	2 (0.6 %)	
IHC surrogate subtypes			**0.003**[a]
Luminal-A	202 (72.4 %)	221(69.9 %)	
Luminal-B	23 (8.2 %)	37 (11.7 %)	
Her2 overexp.	20 (7.2 %)	12 (3.8 %)	
Triple negative	15 (5.4 %)	42 (13.3 %)	
Missing	19 (6.8 %)	4 (1.3 %)	

[a]***Chi-square test,*** [b] ***Mann-Whitney test,*** [c] ***Fisher's exact test***

EIC: extensive intraductal component,

IHC: immunohistochemical,

HER2: human epidermal growth factor 2

Tumour size

The SCR group presented a significantly smaller median pathological tumour size than the SYM group (**P<0.00001,** Mann-Whitney test) (Figure 5), and significant differences were observed using the pT classification (**P=1.6*10-7,** Chi-square test). (Table 7)

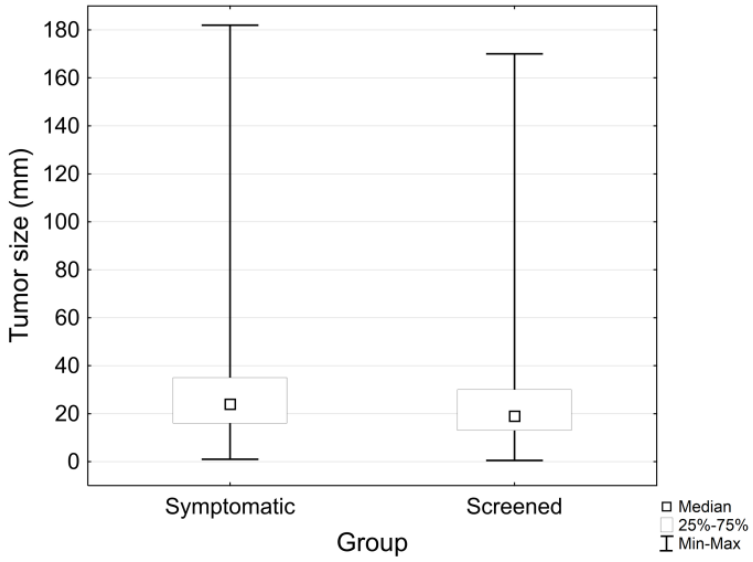

Figure 5*: Tumour sizes in the SCR and SYM groups. (Mann-Whitney test; P<0.00001).*

Histology and subtypes

The incidence of pTis was significantly higher in the SCR than in the SYM group (**P =7.2*10^{-5}**). The incidence of extensive intraductal component (EIC) in the SCR group was statistically higher than in the SYM group (**P=6.7*10^{-33}**). The SYM group presented significantly more vascular invasion than the SCR group (**P=0.001**). The incidence of perineural invasion in the SYM group was statistically higher than in the SCR group (**P=8.2*10^{-8}**). (Table 7)

Significant differences in the clinical characteristics were observed based on breast cancer subtype (**P=0.003**). The number of triple negative (TN) cases was higher in the SYM

group. The number of Luminal-A type tumours was statistically higher in the SCR group than Luminal-B type tumours compared to the SYM group. (Table 7)

Regional and distant metastases

The incidence of regional lymph node metastasis was significantly lower in the SCR group (**P =0.0006). The incidence of distant metastases was significantly higher in the SYM group than in the SCR group** for the entire investigated period **(P=0.013).** (Table 7)

Treatment

The incidence of chemotherapy was 17% greater in the SYM group than in the SCR group ($P=2.9*10^{-5}$, Chi-square test). The BCS rate was 75.9% (n=211) in the SCR group and 74.7% (n=236) in the SYM group (P=0.79; chi-square test). Significant differences were not observed for the type of surgery, in RT and in HT. (Table 8**)**

Table 8: *Differences in therapies between the SCR and SYM groups*

	SCR Group, n (%)	***SYM Group, n (%)***	***P value***
Chemotherapy			**$2.9*10^{-5}$**[a]
Given	111 (39.8 %)	180 (57 %)	
Not given	168 (60.2 %)	136 (43 %)	
Radiotherapy			**0.039**[a]
Given	247 (88.5 %)	295 (93.4 %)	
Not given	32 (11.5 %)	21 (6.6 %)	
Endocrine therapy			**1**[a]
Given	225 (80.6 %)	255 (80.7 %)	
Not given	54 (19.4 %)	61 (19.3 %)	
Surgery			**0.384**[a]
BCS	211 (75.9 %)	236 (74.7 %)	
Mastectomy	67 (24.1 %)	80 (25.3 %)	

[a]***Chi-square test***

BCS: breast conserving surgery

Overall survival

The SCR group did not exhibit significantly better OS rates than the SYM group (**P=0.717**; log-rank). (Figure 6)

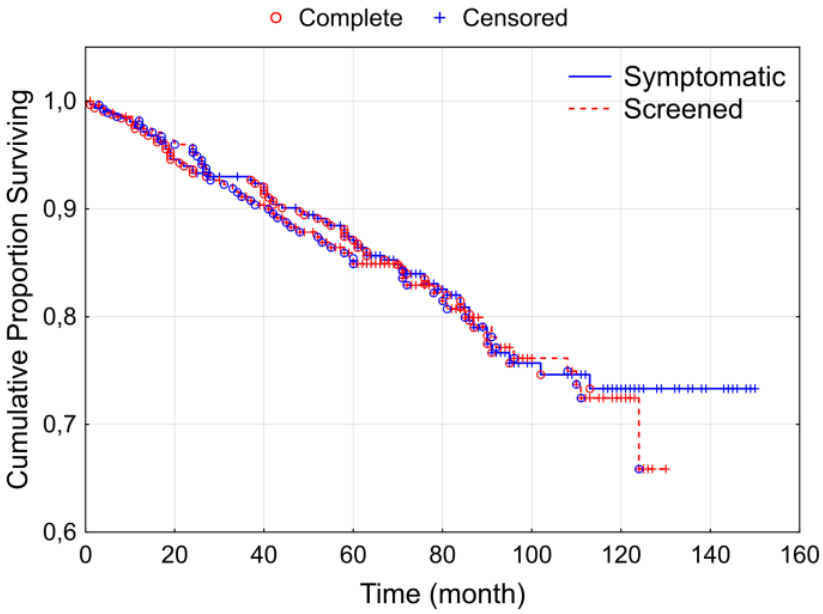

Figure 6: *Kaplan-Meier curve for the OS of the SCR and SYM groups.*

Disease-free survival (DFS)

The SCR group did not exhibit significantly better DFS rates than the SYM group. (**P=0.081**; log-rank). (Figure 7)

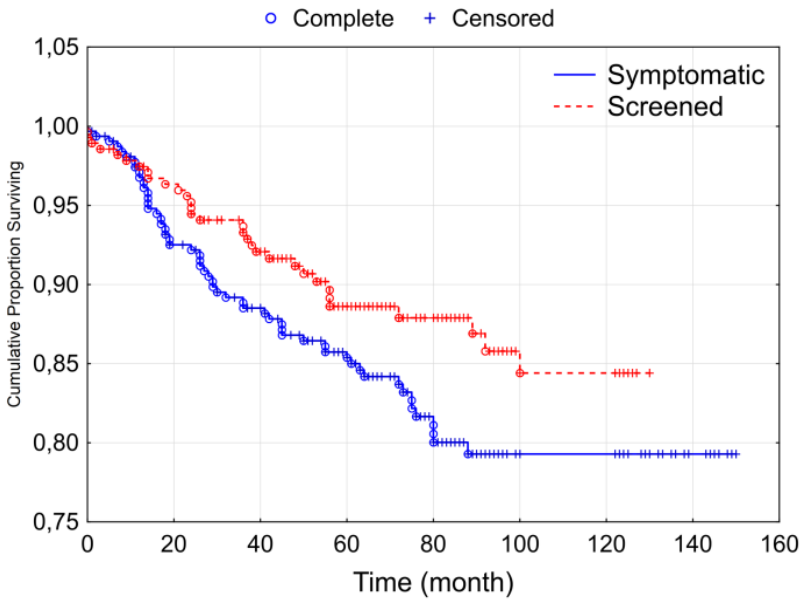

Figure 7: *Kaplan-Meier curve for the DFS for the SCR and SYM groups.*

4.3 THE STUDY OF INVESTIGATION OF THE SOCIOECONOMIC FACTORS AND BARRIERS ASSOCIATED WITH LOW ADHERENCE RATE ON MAMMOGRAPHY SCREENING PROGRAMME VIA QUESTIONNAIRE

A total of 58,839 questionnaire links were sent *via* e-mail, 21,501 links were sent by Facebook campaign, 500 printed questionnaires were mailed, and 293 questionnaires were completed at social events. A total of 12,345 links were opened *via* e-mail and 5,739 links were opened *via* Facebook. Overall, 1,774 women 45-65 years of age completed the survey by e-mail, 1,262 on Facebook, 76 forms by mail and 201 at social events. The online response rate was 18.32% and 15.2% for mailed forms. A total of 3,313 women between 45 and 65 years of age completed the questionnaire. The demographic characteristics of the respondents are summarized in Table 9. The majority of responders were married, had completed secondary school or lived in provincial towns. Descriptive statistical analysis of the answers for structured questions (Q6-Q14) of the questionnaire is shown in Table 10.

Table 9: *Responders' demographic characteristics*

Number of responders	***n = 3,313***	***%***
Marital status		
Unmarried	*153*	*4.62%*
Married	*1945*	*58.71%*
Divorced	*833*	*25.14%*
Widowed	*336*	*10.14%*
No answer	*46*	*1.39%*
Educational level		
Primary	*173*	*5.22%*
Secondary	*2106*	*63.57%*
Tertiary	*1005*	*30.34%*
No answer	*29*	*0.88%*
Place of residence		
Capital	*693*	*20.92%*
Provincial town	*1979*	*59.73%*
Village	*612*	*18.47%*
No answer	*29*	*0.88%*

Table 10: *Descriptive statistical analysis of the responses to structured questions (Q6-Q14) of the questionnaire*

Q6: Do you undergo any mammography examinations?	***N***	***%***
Q7: If yes, how regularly?		
Q8: If yes, how frequently?		
Yes, annually.	*952*	*28.74%*
Yes, biennially.	*1485*	*44.82%*
Yes, occasionally.	*540*	*16.30%*
No.	*290*	*8.75%*
No answer	*46*	*1.39%*
Q9: Have you received an Invitation Letter for Screening?		
Yes.	*2194*	*66.22%*
No.	*1073*	*32.39%*
No answer	*46*	*1.39%*
Q11: Do you receive regular breast screening?		
Regularly.	*2359*	*71.20%*
Occasionally.	*320*	*9.66%*
No.	*560*	*16.90%*
No answer	*74*	*2.23%*
Q12: Where was your last breast exam?		
Organized mammography screening in a designated screening centre.	*1590*	*47.99%*
Opportunistic mammography screening not in a designated screening centre (medical office, private clinic, etc.).	*1482*	*44.73%*
No answer	*241*	*7.27%*
Q13: How far is the designated screening centre from your residence?		
Close.	*2221*	*67.04%*
Far.	*884*	*26.68%*
Very far.	*58*	*1.75%*
No answer	*150*	*4.53%*
Q14: Why did you not undergo an organized mammography screening?		
Because of fear of breast cancer.	*28*	*3.58%*
Because of fear of mastectomy.	*16*	*2.04%*
Because the designated screening centre is too far.	*87*	*11.11%*
Because of my job.	*148*	*18.90%*
Because I do not have enough information on mammography screening.	*43*	*5.49%*
Because mammography examinations are harmful.	*117*	*14.94%*
Because I undergo opportunistic mammography screening	*109*	*13.92%*
Because mammography examinations are painful.	*144*	*18.39%*
Because examination of an intimate body part is embarrassing.	*36*	*4.60%*
Because of the expenses to get there.	*38*	*4.85%*
Other:	*276*	*35.25%*

The questions that focused on barriers to participation were also systematically analysed. A total of 1,042 women responded to the questions regarding their reasons for not undergoing breast screening. Briefly, the main barriers to participation in the OMSP were work absenteeism (18.9%), fear of painful examination (18.39%) and false beliefs regarding mammography screening (14.94%). Of survey respondents, 13.92% of those who did not attend the OMSP underwent opportunistic screenings; 11.11% answered that their designated screening centre (DSC) was too far from their home. Only 5.49% of those who did not participate in screening reported not having enough information on mammography screening and 4.85% answered that it was too expensive to get to the screening centre. Fear of breast cancer diagnosis prevented 3.58% of non-participants from attending the OMSP, and 2.04% did not participate for fear of mastectomy.

Based on patient marital status and place of residence, the responses were analysed to compare a number of criteria. (Table 11) There was a significant association (P=0.029) between the responders' marital status and OMSP attendance, with married women attending breast screenings more frequently than single women. There was also a significant difference (P=0.038) between the place of residence and the frequency of mammography examination: women from the capital or from provincial towns more frequently underwent and were more compliant with screening than women who lived in villages. There was a significant association between the responders' residence and the distance from the DSC (P<0.0001): women living in the capital or provincial towns had better access to their DSC than those living in villages.

There was a significant association between the place of residence and the travel expenses incurred to reach the DSC (P=0.009). (Table 12) Compared to those living in the capital, women in rural populations reported financial difficulties in travelling to their DSC. Female residents of the capital were more likely to choose opportunistic screening compared to those living in rural areas (P=0.005). Barriers such as lack of information on mammography screening (P=0.001) and fear of breast loss (P=0.003) were also significantly associated with lower education level. Educated women were less likely to fear breast cancer and more likely to have sufficient information regarding mammography screening compared to interviewed women with lower levels of education. In the current study, married marital status appeared to be a protective factor against barriers such as feeling embarrassed about the examination (P=0.0002) and expenses incurred to reach the DSC (P<0.0001).

Table 11: *Significant associations between patient marital status, residence, and responses to the questionnaire (by response to questions 3, 5-8, and 13)*

Factor		***Response***			***p-Value*** [a]
Screening		***Regularly***	***Occasionally***	***No***	***P***
Unmarried		*97*	*21*	*30*	
Married		*1438*	*165*	*320*	*0.029*
Divorced		*588*	*89*	*148*	
Widow		*228*	*42*	*60*	
Mammogram	***Annually***	***Biennially***	***Occasionally***	***No***	
Capital	*221*	*285*	*123*	*60*	
Provincial town	*565*	*925*	*317*	*160*	*0.038*
Village	*166*	*275*	*100*	*70*	
Distance from DSC		***Close***	***Far***	***Very far***	
Capital		*476*	*184*	*7*	
Provincial town		*1413*	*450*	*35*	9.5×10^{-17}
Village		*332*	*250*	*16*	

DSC: Designated screening centre, [a]*Chi-square*

Table 12: *Statistical analysis of significant barriers to undergoing mammography screening associated with socioeconomic status (answer to question 14: Why did you not undergo an organized mammography screening?).*

			Response, n		
Answer to Q14	***Factor***	***Status***	***Chosen***	***Not chosen***	***p-Value*** [a]
Because I attend other mammography screening	*Location*	*Capital*	*39*	*147*	*0.005*
		Provincial town	*50*	*401*	
		Village	*20*	*126*	
Because of the expenses to get there	*Location*	*Capital*	*3*	*183*	*0.009*
		Provincial town	*22*	*429*	
		Village	*13*	*133*	
	Marital status	*Unmarried*	*2*	*44*	2.1×10^{-5}
		Married	*10*	*421*	
		Divorced	*12*	*198*	
		Widowed	*13*	*78*	
Because of fear of mastectomy	*Education*	*Primary*	*4*	*43*	*0.003*
		Secondary	*10*	*487*	
		Tertiary	*2*	*237*	
Because I do not have enough information	*Education*	*Primary*	*8*	*39*	*0.001*
		Secondary	*26*	*471*	
		Tertiary	*9*	*230*	
Because undergoing examination of an intimate body part is embarrassing	*Marital status*	*Unmarried*	*3*	*43*	*0.0002*
		Married	*12*	*419*	
		Divorced	*8*	*202*	
		Widowed	*12*	*79*	

[a] *Chi-square*

According to "Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary" questionnaire study to examine the appropriate information channels a higher proportion of patients under age 35 gained

information over the Internet, while in older age groups the surgeon was an important source of information. Surgeons were the primary source of information for most patients ($P=2.9\times10^{-5}$). However, if the surgeon and Internet resources were compared with the exclusion of the other sources (e.g., fellow patients, TV, radio, and newspapers), the Internet was the most effective forum for orientation (P=0.019). (Figure 8)

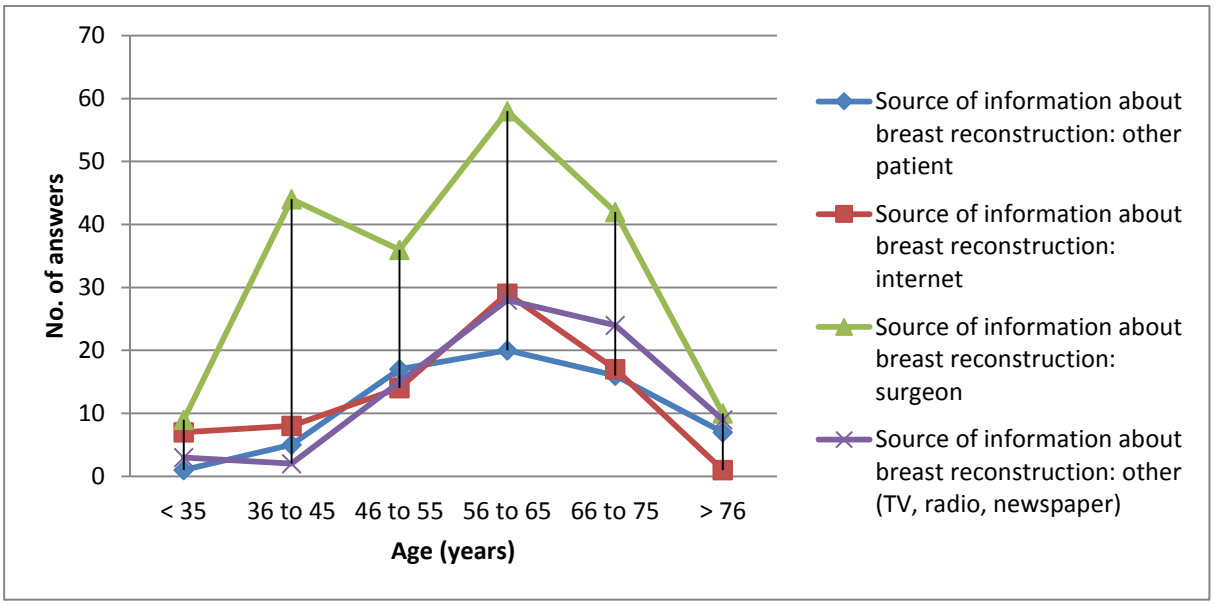

***Figure 8**: Sources of information and knowledge on breast reconstruction.*

As expected, those with higher educational backgrounds were the most informed ($P=1\times10^{-5}$). (Figure 9)

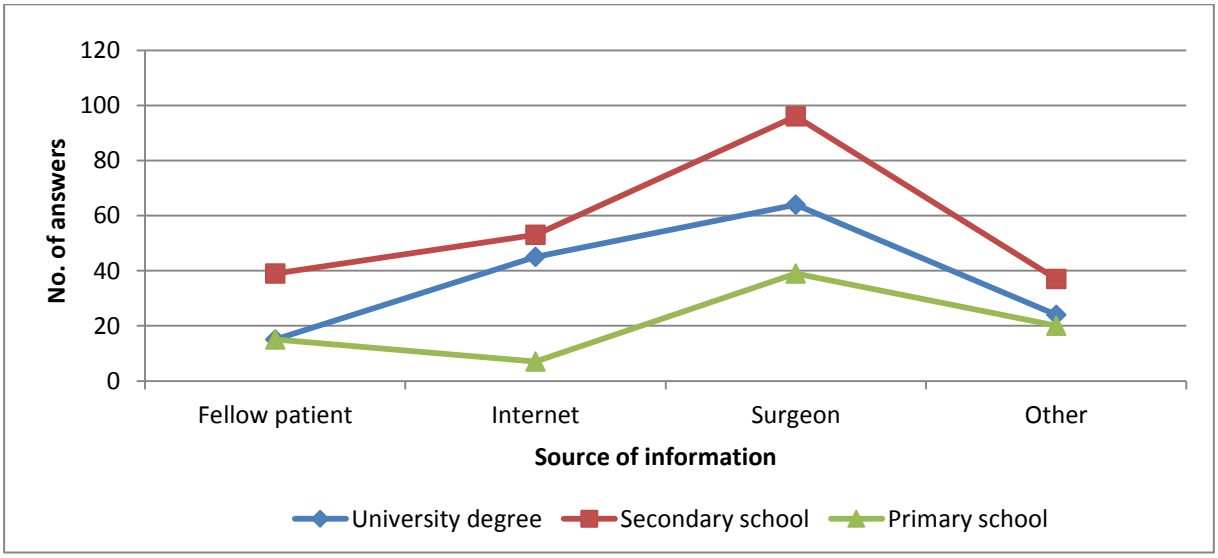

***Figure 9**: Awareness in the context of education and source of information*

5. DISCUSSION

5.1 ANALYSIS OF BREAST CANCER CARE QUALITY AT THE NATIONAL INSTITUTE OF ONCOLOGY BASED ON REQUIREMENTS OF THE EUROPEAN SOCIETY OF BREAST CANCER SPECIALISTS

Applying minimum requirements and quality indicators is essential to improve organisation, performance and outcome in breast care. Efficacy and compliance have to be constantly monitored to evaluate the cross-sectional view of breast cancer stages with the quality of patient care and to allow appropriate corrective actions leading to improvements in patient care. According to our results the diagnostic modalities and multimodality care of breast cancer of the NIO breast unit meets the critical mass and minimum standards of EUSOMA criteria. [23] (Table 6)

The evaluation of institutional breast cancer care based EUSOMA quality indicators provides quality representative cross-sectional view of the Hungarian stage based breast cancer incidence. The limitation of this study is the underrepresented proportion of Stage IV breast cancer cases.

Despite the fact that almost 10 % of patients received primary chemotherapy the study presented relatively low amount of early stage breast cancer cases. According to the postoperative pathological assessment (the data of pathological stage were used after primary chemotherapy as well) the proportion of primary early stage (Stage 0-IIB, except T3N0) breast tumour cases decreased from 91.29 % clinical stage rate to 79.25 % pathological stage rate. During the study period the proportion of clinical Stage I invasive breast cancers was lower (45.45%) compared to data of US Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review (CSR) where the average percentage of clinical Stage I invasive breast cancers was 48 % between 2004 and 2011 and in Sweden it was 47.36 % between 2004 and 2009.[46, 47] The percentage of pT1 tumours was lower (48.39 %) and pT2 tumours was higher (41.23 %) compared to US (pT1: 64.4 % and pT2: 30.9 %) and compared to Swedish statistics (pT1: 50.75 % and pT2: 31.21 %) between 2004 and 2009. [47, 48] The average tumour size was 27.4 mm during the investigation period in Hungary

compared to US statistics where the average tumour size was 21.6 according to the SEER database.[19]

The incidence of negative lymph nodes was 51.5 % and positive was 46.7 %. Compared to US (65 % and 33.4 %) and Swedish (69.44% and 24.57 %) statistics the proportion of negative lymph nodes was higher than in Hungary.[47, 48]

Significant differences in type of breast surgery (BCS or mastectomy) were not observed compared to US statistics. In our analysis BCS rate was 64% and the mastectomy rate was 36 % in case of primary surgical treatment in malignant diseases. According to the SEER database rate was 63% and the mastectomy rate was 37 % between 2005 and 2007.[49]

According to our statistics Hungarian breast cancer cases represented higher tumour size, tumour stage and percentage of positive lymph nodes compared to Swedish and US statistics. This quality representative cross-sectional view of stage based breast cancer cases suggests that the relatively higher mortality rate in Hungary could be associated to higher tumour stages at the diagnosis. Further investigation is needed to improve the knowledge regarding the representative cross-sectional view of stage based breast cancer cases to allow appropriate corrective actions leading to improvements in patient care.

5.2 THE STUDY OF COMPARISON OF CLINICAL OUTCOME OF SCREEN DETECTED AND SYMPTOMATIC BREAST CANCER CASES

A decrease in mortality is the ultimate goal for any screening program, and the advantages of early cancer detection are obvious. [50] Randomized controlled trials (RCTs) that have evaluated mammography screening have demonstrated a reduction in breast cancer mortality [8-10], but unfortunately, the randomized trials are uninterpretable in the modern era, as they were conducted before the era of breast cancer units, before IHC evaluation of receptor statuses to define breast cancer IHC surrogate subtypes, and before the use of modern chemotherapy regimens, given that biological and hormonal therapy are now widely used in breast cancer treatment. Therefore, the impact of mammographic screening on reducing breast cancer mortality has become an intensively researched topic. A few recent studies have questioned the impact of early detection on mortality reduction and cast doubt on costs for a procedure that yields minimal benefit.[26, 27, 51-53]

According to the study database, patients in the SCR group were six times more likely to be diagnosed with DCIS and smaller invasive tumours compared to patients in the SYM group. The proportion of stage I cases was 12% higher in the SCR group, and the number of cases with regional lymph node metastasis was approximately 14% lower in the SCR group compared to the SYM group. Hofvindet al. compared the stage-specific breast cancer incidence rates among participants and non-participants of a population-based mammographic screening program. They found similar results, and according to their study, participants in the screening program were three times more likely to be diagnosed with DCIS and early-stage invasive breast cancer and were less likely to be diagnosed with advanced stage breast cancer. The number of stage I cases was 10% higher in the participating group compared to the non-participating group. The number of cases with regional lymph node metastasis was 9% lower in the participating group compared to the non-participating group.[54]

In this study, the percentage of pT1 tumours was 13.5% greater in the SCR group compared to the SYM group. Kalager et al. compared the basic characteristics of women with breast cancer in Norway from 1985 to 2004, diagnosed before (pre-programme) and after (post-programme) the introduction of a population-based mammography screening

programme in their county of residence. The incidence of pT1 tumours was 11% greater in the participating group compared to the non-participating group. [55]

According to our investigation, the pathological median tumour size was 19 mm in the SCR and 24 mm in the SYM group. Fernandez et al. compared the mortality and recurrence patterns of breast cancer patients diagnosed under a screening program versus comparable non-screened breast cancer patients from the same population from 2002 to 2012, and the mean tumour size was 16.2 mm for the screened group and 27.7 mm for the non-screened group. [56] Dillon et al. compared screen-detected patients versus symptomatic patients with breast cancer and found a 16-mm median tumour size in the screen-detected group and a 22-mm median tumour size in the symptomatic group. [57]

The proportion of regional lymph node involvement was 33% in the SCR group and 46.9% in the SYM group. Dillon et al. found the same result. [57] Fernandez et al. reported a 24.6% lymph node metastasis rate in the screened group and a 38.9% rate in the non-screened group.[56] According to the study database, the prognostic tumour characteristics were better in women who participated in the screening program compared to those who did not. The percentage of TN tumours was 7.9% lower in the SCR group than in the SYM group. Fernandez et al. found a 6.4% difference between the two groups.[54, 56, 57]

According to the study database, significant differences between the two groups in OS and DFS were not observed during the investigated period. Miller et al. compared breast cancer incidence and mortality up to 25 years in women aged 40-59 who did or did not undergo mammography screening in Canada. Differences between the two groups in survival were not observed during the entire study period. [58] In cited biased investigations, the results of a clinical breast examination performed by nurses on all patients in the study were known when the patients were assigned to the screening or to the control group. Other biases of the study include that the patients were not randomized nor was the study double-blinded, as they should have been with proper methodology.[59, 60]

The question arises what the reason is for not finding any differences in OS or DFS between the SCR and SYM subgroups. There is a trend of the DFS in favour of the SCR group but it has not reached the statistical significance. The amount of distant metastases was higher in SYM group (17%) compared to SCR group (10%) and as the metastatic breast cancer is an incurable disease, probably, a longer follow-up period might show the statistical

significance of DFS and/or OS in favour of the SCR group. But since metastatic breast cancer is still generally an incurable disease with 1 or 2-year average OS the long term follow-up data are limited. We assume that early breast cancer detection is potentially not the main factor being responsible for reducing mortality in breast cancer. Modern multimodality cancer treatments may play a major role in breast cancer survival. In our investigation**,** the incidence of chemotherapy was 17% greater in the SYM group than in the SCR group.

Adjuvant therapy could be translated into improved outcomes for patients in the SYM group, but it is important to investigate the short and long-term impact on quality of life (QOL) of systemic therapy. Jeffe et al. concluded that chemotherapy had a short-term negative impact on QOL after definitive surgical treatment, and QOL rebounded after completion of adjuvant treatment.[61] Grimison et al. reached a similar conclusion that adjuvant chemotherapy has an acute detrimental effect on QOL, with longer and more intense regimens causing worse and more persistent effects. Most aspects of QOL recover rapidly after chemotherapy ends without long-term residual effects for the majority of patients. [62]In our investigation, the OS and DFS were not worse in the SYM group, but that may be achieved by a significant reduction in QOL due to the more aggressive treatments required. However, the cost effectiveness should be mentioned in the two groups. Mittmann et al. calculated the health system costs for stage-specific breast cancer, and they demonstrated a significant correlation between the stage of breast cancer and the treatment costs.[63]

A limitation of this study is the follow-up period. After 10 years of a national screening programme, a mortality analysis would be valuable in evaluating the program's effectiveness. In our investigation, the median follow-up time of 65 and 85 months might be too short to show the real advantages of the screening programme. However, in RCTs, there was a reduction in mortality after 4 years, with an increasing effect up to 10 years. [12] Another limitation of our study is that some of the women in the SYM group might have undergone opportunistic screening, potentially resulting in an underestimation of the benefit of screening.

This study design did not focus on interval breast cancer cases or the effectiveness of organized mammography breast screening programme, our study focused only on the oncological outcome of early stage screen-detected and early stage symptomatic breast cancer cases.

5.3 THE STUDY OF INVESTIGATION OF THE SOCIOECONOMIC FACTORS AND BARRIERS ASSOCIATED WITH LOW ADHERENCE RATE ON MAMMOGRAPHY SCREENING PROGRAMME VIA QUESTIONNAIRE

To improve breast cancer screening attendance among Hungarian women, it is imperative to have a valid instrument for exploring and understanding the factors associated with their screening behaviour. Our questionnaire has the appropriate psychometric properties to provide insights into tailor-made strategies designed to address the needs of the screening target population.

Our findings highlight that the main reasons for not attending the OMSP were work absenteeism, fear of pain associated with the examination, and false beliefs regarding mammography screenings. Reducing barriers such as work absenteeism, a paid day off might increase women's willingness to participate in the OMSP. It would be important for employers also to participate in helping their employees utilize preventative measures.

According to the results of our questionnaire study, women with lower levels of education - mainly those who completed only primary school (were less likely to have sufficient information on breast screening, and they were more likely to fear of mastectomy compared to women with higher levels of education) mainly those who had completed secondary school or university. According to the questionnaire study "Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary" education level and awareness showed significant associations. Ackerson et al. summarized in a systematic review that lower screening adherence rates were also associated with lower levels of education and women from lower socioeconomic backgrounds focused on the perceived negative aspects of screening and the intrinsic costs.[64]

There is a need for a multi-pronged strategy to inform and educate women about breast awareness and bring about a behavioural change. It may be beneficial to provide more information about breast cancer, breast cancer treatment, and the importance of mammography screening through health awareness education in primary school or through alternative information channels such as magazines, TV advertisements, online sites and brochures. Other authors with similar findings came to the same conclusion.[64] According to the "Evaluation of patient knowledge, desire, and psychosocial background regarding

postmastectomy breast reconstruction in Hungary" questionnaire study the source of information on breast reconstruction was correlated with the level of education and most information coming from the medical staff, doctors or from the Internet. A higher proportion of patients under age 35 gained information over the Internet; while in older age group of patients (aged 35-65 years) received that information from the surgeon and medical staff. As the younger population is the future target population they should be informed through the internet (probably social media) to promote the importance of breast screening. Consequently, the patient navigator system, employing prevention nurses, general practitioners or other specialties could increase the willingness of the current target population, and the information channels such as the internet and social media could increase the willingness of future target population participating on mammography screening. Using appropriate information channels could provide feasible breast cancer awareness for current and for future screening target population.

Fear of pain in the examination was the second most common reason for avoiding mammography examinations. According to a previous study, discomfort was reduced when women were provided with written or verbal information, and when a breast cushion was used [65]. Providing verbal or written information, as well as supporting women during the examination, is a simple and easily achievable intervention and can help to reduce pain during screening mammography. Use of alternative breast compression strategies or premedication with acetaminophen has not been reported to significantly reduce breast pain and discomfort.[65]

It is important to note that half of the responders in the current study chose opportunistic screening and that 13.92% of non-participants chose a location other than their DSC for their mammography examinations. This finding is consistent with reports that opportunistic screening only covers half of the screened target population in Hungary[31-33]. The non-participants described other barriers such as long waiting times in clinics, unorganized DSCs, dissatisfaction with facility staff, difficulties in changing scheduled mammogram appointments, and a lack of concern about breast cancer. To increase screening attendance rates, these barriers should also be addressed. The environment and facility staff are important for women's satisfaction and for their willingness to attend their next screening. Similar barriers and suggestions have been described in other studies[66-69]. A patient navigator system could utilize prevention nurses to organize an effective screening

programme by offering education on breast awareness, screening invitation, and management of biennial mammogram appointments.[70]

Only two-thirds of the responders had received an Invitation Letter for Screening (ILS) in the previous 2 years, which is below the minimum 70% adherence rate required by the WHO to reduce breast cancer mortality. [29] Further investigations are needed to determine the causes for the lack of receiption of ILS.

According to the study, the fear of breast cancer and fear of mastectomy among non-attendees have not been emphasized as the main causes of avoiding the OMSP, but still important cause of non-participating. This finding is contrary to several previous studies in which the authors concluded that cancer anxiety and worry were associated with both the promotion and avoidance of breast cancer screening.[71, 72]

Married status appeared to be a protective factor against barriers, including embarrassment regarding the examination, financial challenges associated with travelling to the DSC and avoiding breast screening. Single women, mainly widows, were more likely to skip or were less likely to participate in the OMSP compared to married women. There is a strong positive association between relationship and participation behaviour in mammography screening, which is also supported by other authors [73]. Single women require special attention to inform them about the importance of breast screening, which could be addressed through well-organized patient navigation programmes, as well as breast cancer support groups and self-help organizations.

In subjective response to the question "*How far is the designated screening centre from your residence?",* one-quarter of the women answered far, while fewer than 2% answered very far. Excessive distance to reach the DSC was the fifth most frequent barrier to breast screening. A statistical comparative analysis indicated that living in villages or in single households was associated with lower participation rates because of financial difficulties and problems in travelling long distances to the DSC. Others concluded similarly that women living in rural areas were less likely to participate in OMSPs compared with those living in urban areas[74]. According to a previous interview-based survey, time required to travel to and distance from the DSC is an important factor for women [75]. Well-situated units with advanced promotion about public transportation and parking facilities may encourage greater uptake. Rural women require special attention because of their lower participation rates in mammography examination. Patient navigation, free public transport for the day of screening,

specialized round-trip bus lines, or mobile breast screening units may help to overcome these barriers.

The strength of our survey study was that the Hungarian mammography screening target population 45-65 years of age was interviewed regardless of whether the participants had received an ILS.

6. CONCLUSIONS

Early tumour detection is very important in breast cancer treatment and in clinical outcomes. As breast cancer mortality depends on the stage of the diagnosis and oncological outcomes are generally more favourable during early stages of the disease before symptoms appear in symptomatic diseases. Despite mammography screening, with the aim of mortality reduction, the breast cancer mortality in Hungary has not changed significantly since 2002.

Answering question 2.1. of the thesis: **According to the evaluation of institutional breast cancer care based on EUSOMA quality indicators Hungarian women with breast cancer represented higher tumour stage compared to western countries. The percentage of early stage breast cancer cases was lower compared to US and Sweden. This quality representative cross-sectional view of stage based breast cancer cases suggests that the relatively higher mortality rate in Hungary could be associated to higher tumour stages at the diagnosis.**

Answering questions 2.2. and 2.3. of the thesis: **According to the comparison of SCR and SYM groups patients with non-palpable early stage breast cancers diagnosed via population-based breast screening did not have better survival rates than those with symptomatic cancers. The reason why there were no differences in OS and DFS remains unclear. The potential drawback of symptomatic early stage tumours compared to non-palpable early stage tumours could be equalized by modern breast cancer molecular subtype-based personalized multimodality oncology treatments. There is a trend of the DFS in favour of the SCR group but it has not reached the statistical significance. The amount of distant metastases was higher in SYM group compared to SCR group and as the metastatic breast cancer is an incurable disease, probably, a longer follow-up period might show the statistical significance of DFS and/or OS in favour of the SCR group.** Further investigations and longer follow-up are needed to answer these questions.

The thesis does not suggest that mammography screening does not reduce breast cancer mortality, but supports the evidence that mammography screening reduces the rate of advanced breast cancers. As breast cancer deaths are caused mostly by an advanced disease that has already spread to the lymph nodes or distant organs, an important public health goal is to increase adherence rate on mammography screening. Increased knowledge regarding the

barriers to mammography screening provides information to extend our knowledge on breast cancer screening and effective treatment in Central-Eastern European countries.

Answering question 2.4. of the thesis: **Our findings highlight that the main reasons for women to not attend OMSP included work absenteeism, fear of painful examination, lack of information, and false beliefs regarding mammography screenings. Reducing barriers such as work absenteeism, a paid day off may increase women's willingness to attend the OMSP. In order to increase screening compliance, environment and facility staff are very important factors associated with the women's satisfaction and therefore their participation in future screenings. A patient navigator system employing prevention nurses could help to organize an effective screening programme by offering education on breast awareness, screening invitations, and managing appointments for biennial mammograms. Married women more regularly receive breast screening compared to single women; marital status seems to be a protective factor against barriers like embarrassment and financial difficulties that may prevent travelling to the DSC. Single women and rural female residents require special attention because of their lower participation rates in mammography exams. In these populations, patient navigation, free public transportation, specialized round-trip bus lines, or mobile breast screening units may help to decrease these screening barriers**.

Answering question 2.5. of the thesis: **In the following, using applicable information channels as the internet for the future screening target population and the patient navigation system, employing prevention nurses, general practitioners or other specialties could provide feasible breast cancer awareness for the current screening target population in conclusion of increased breast screening participation.**

ÖSSZEFOGLALÁS: A rosszindulatú emlődaganatok korai felfedezése jelentősen befolyásolja az onkológiai kezelést és a túlélést. A korai stádiumban, még tünetmentesen felfedezett emlőrákok esetében kedvezőbb az onkológiai kimenetel, ellentétben a lokálisan előrehaladott vagy már távoli áttétet adó esetekkel. Mortalitást csökkentő célja ellenére a szervezett lakossági mammográfiás szűrés érdemben nem csökkentette a halálozást Magyarországon.

Válasz az első célkitűzésre: A magyar emlőrák populáció EUSOMA egységes nemzetközi kritériumrendszere szerint végzett keresztmetszeti vizsgálata alapján a korai emlőrákok aránya kisebb volt összehasonlítva az Egyesült Államokkal vagy Svédországgal.

Válasz a második és a harmadik célkitűzésre: A vizsgáltunk alapján a mammográfiás emlőrák szűrés nem csökkentette a mortalitást a korai emlőrákos betegek esetében összehasonlítva a szimptomatikus korai emlőrákos esetekkel. A szimptomatikus emlőrákos betegek túlélését növelő faktorok között szerepe lehet a korszerű személyre szabott adjuváns terápiának és diagnosztikus modalitásoknak, melyek képesek kiegyenlíteni a későbbi diagnózis miatt kialakult különbségeket. Hogy választ kapjuk arra, hogy miért nem volt különbség a teljes és a betegségmentes túlélésben a két csoport között további vizsgálatokra van szükség. Vélhetően hosszabb utánkövetéssel a szűrésen kiemelt és a szimptomatikus csoportok között a teljes és/vagy betegségmentes túlélésben különbség adódhat a szűréses csoport javára. A kérdés megválaszolására további vizsgálatok szükségesek.

Válasz a negyedik célkitűzésre: A mammográfiás szűréstől való távolmaradás leggyakoribb okaként a munkahelyi hiányzást jelölték meg, továbbiakban gyakori okként a félelem a fájdalmas vizsgálattól és károsnak tartott mammográfiás vizsgálat került megnevezésre. A részvételi arányok növeléséhez elengedhetetlen a megfelelő információ biztosítása és oktatás az emlőrák szűrés fontosságáról és elérhetőségéről. Továbbá egy szervezett betegirányító rendszer, könnyen elérhető szűréssel kapcsolatos információs felületek, szabadnap biztosítása, elérhető távolságban lévő szűrőközpontok kialakítása a vidéki lakosság számára és a szűrésre ingyenes tömegközlekedés biztosítása javíthatja a mammográfiás szűréseken való részvételt.

Válasz az ötödik célkitűzésre: Az aktuális szűrésre behívott célcsoport az egészségügyi személyzettől, illetve kezelőorvosától szerzi a legtöbb információt, a jelenleg fiatalabb a jövőbeli szűrésre behívásra kerülő célcsoport pedig az internetről gyűjti azt. A megfelelő információs csatornák célzott alkalmazásával javítható a szervezett lakossági mammográfiás szűréseken való részvételi arány.

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REFERENCES

1. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.* Eur J Cancer, 2013. **49**(6): p. 1374-403.
2. Bernard W. Stewart and Christopher P. Wild (2014). World cancer report 2014.Lyon, France : International Agency for Research on Cancer
3. Hungarian National Cancer Registry: http://www.onkol.hu/hu/rakregiszter-statisztika
4. Perou, C.M., et al., *Molecular portraits of human breast tumours.* Nature, 2000. **406**(6797): p. 747-52.
5. Duffy, S.W., et al., *The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties.* Cancer, 2002. **95**(3): p. 458-469.
6. Tabar, L., et al., *Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality.* Cancer, 2001. **91**(9): p. 1724-31.
7. Hellquist, B.N., et al., *Effectiveness of population-based service screening with mammography for women ages 40 to 49 years.* Cancer, 2011. **117**(4): p. 714-722.
8. Andersson, I., et al., *Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial.* BMJ, 1988. **297**(6654): p. 943-8.
9. Tabar, L., et al., *Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare.* Lancet, 1985. **1**(8433): p. 829-32.
10. Kopans, D.B. and S.A. Feig, *The Canadian National Breast Screening Study: a critical review.* AJR Am J Roentgenol, 1993. **161**(4): p. 755-60.
11. Nystrom, L., et al., *Breast cancer screening with mammography: overview of Swedish randomised trials.* Lancet, 1993. **341**(8851): p. 973-8.
12. Nystrom, L., et al., *Long-term effects of mammography screening: updated overview of the Swedish randomised trials.* Lancet, 2002. **359**(9310): p. 909-19.
13. Boncz, I., et al., *The effect of an organized, nationwide breast cancer screening programme on non-organized mammography activities.* J Med Screen, 2008. **15**(1): p. 14-7.
14. Hungarian Central Statistical Office. http://www.ksh.hu/thm/2/indi2_8_1.html
15. Blanks, R.G., et al., *Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality.* BMJ, 2000. **321**(7262): p. 665-9.
16. NHS Breast Screening Programme (NHSBSP). Breast Screening Results from the NHSBSP 2012/13. London: Queen Mary University of London; 2014
17. Feig, S.A., *Mammography screening: published guidelines and actual practice.* Recent Results Cancer Res, 1987. **105**: p. 78-84.
18. Swan, J., et al., *Data and trends in cancer screening in the United States: results from the 2005 National Health Interview Survey.* Cancer, 2010. **116**(20): p. 4872-81.
19. Surveillance, Epidemiology, and End Results program. Available at http://www.seer.cancer.gov.
20. Weigel, S., et al., *Reduction of Advanced Breast Cancer Stages at Subsequent Participation in Mammography Screening.* Rofo, 2016. **188**(1): p. 33-7.
21. Autier, P., et al., *Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening.* J Clin Oncol, 2009. **27**(35): p. 5919-23.
22. Tabar, L., et al., *Significant reduction in advanced breast cancer. Results of the first seven years of mammography screening in Kopparberg, Sweden.* Diagn Imaging Clin Med, 1985. **54**(3-4): p. 158-64.

23. Ujhelyi, M., et al., *[Breast cancer care quality analysis of the National Institute of Oncology in Hungary according to the requirements of European Society of Breast Cancer Specialists (EUSOMA)].* Orv Hetil, 2016. **157**(42): p. 1674-1682.
24. Giordano, L., et al., *Mammographic screening programmes in Europe: organization, coverage and participation.* J Med Screen, 2012. **19 Suppl 1**: p. 72-82.
25. Lauby-Secretan, B., et al., *Breast-cancer screening--viewpoint of the IARC Working Group.* N Engl J Med, 2015. **372**(24): p. 2353-8.
26. Esserman, L., Y. Shieh, and I. Thompson, *Rethinking screening for breast cancer and prostate cancer.* JAMA, 2009. **302**(15): p. 1685-92.
27. Kalager, M., et al., *Effect of screening mammography on breast-cancer mortality in Norway.* N Engl J Med, 2010. **363**(13): p. 1203-10.
28. Autier, P., et al., *Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database*. Vol. 341. 2010.
29. Perry, N., et al., *European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document.* Ann Oncol, 2008. **19**(4): p. 614-22.
30. Boncz, I., et al., *[The attendance of the first screening round (2002-2003) of the Hungarian organized breast cancer screening program and its effect on the number of diagnostic and screening mammography].* Orv Hetil, 2005. **146**(38): p. 1963-70.
31. Boncz, I., et al., *[Attendance of the fourth (2008-2009) screening round of the Hungarian organized, nationwide breast cancer screening program].* Orv Hetil, 2013. **154**(50): p. 1975-83.
32. Boncz, I., et al., *[Participation rates in the third round (2006-2007) of the breast cancer screening program in Hungary].* Magy Onkol, 2013. **57**(3): p. 140-6.
33. Boncz, I., et al., *[Attendance in the second phase (2004-2005) of the Hungarian organized breast cancer screening program].* Orv Hetil, 2008. **149**(32): p. 1491-8.
34. Schueler, K.M., P.W. Chu, and R. Smith-Bindman, *Factors associated with mammography utilization: a systematic quantitative review of the literature.* J Womens Health (Larchmt), 2008. **17**(9): p. 1477-98.
35. Deandrea, S., et al., *Presence, characteristics and equity of access to breast cancer screening programmes in 27 European countries in 2010 and 2014. Results from an international survey.* Prev Med, 2016. **91**: p. 250-263.
36. Pestalozzi, B., M. Castiglione, and E.G.W. Group, *Primary breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up.* Ann Oncol, 2008. **19 Suppl 2**: p. ii7-10.
37. Aebi, S., et al., *Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2010. **21 Suppl 5**: p. v9-14.
38. L.H. Sobin, M.K.G., and. Ch. Wittekind, *TNM classification of malignant tumours. .* New York: John Wiley & Sons, Seventh Edition, 2009.
39. Boncz, I., et al., *Quality Control of the Hungarian Nationwide Mammography Screening Programme.* Value Health, 2014. **17**(7): p. A740.
40. Bak, M., et al., *[Quality assurance of fine-needle aspiration cytology of the organized mammography screening].* Orv Hetil, 2010. **151**(32): p. 1295-8.
41. Senkus, E., et al., *Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2013. **24 Suppl 6**: p. vi7-23.
42. Aebi, S., et al., *Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2011. **22 Suppl 6**: p. vi12-24.
43. Esmo, *ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer.* Ann Oncol, 2001. **12**(8): p. 1047-8.
44. Pestalozzi, B.C., et al., *ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer.* Ann Oncol, 2005. **16 Suppl 1**: p. i7-9.

45. Hammer O, H.D., Ryan PD, *PAST: Paleontological Statistics software package for education and data analysis.* Paleontological Electronica **4**(1): p. 9.
46. Iqbal, J., et al., *Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States.* JAMA, 2015. **313**(2): p. 165-73.
47. Abdoli, G., et al., *Breast cancer diagnosis and mortality by tumor stage and migration background in a nationwide cohort study in Sweden.* Breast, 2017. **31**: p. 57-65.
48. Zheng, Y.Z., et al., *Effect of tumor size on breast cancer-specific survival stratified by joint hormone receptor status in a SEER population-based study.* Oncotarget, 2015. **6**(26): p. 22985-95.
49. Jagsi, R., et al., *Patient-reported Quality of Life and Satisfaction With Cosmetic Outcomes After Breast Conservation and Mastectomy With and Without Reconstruction: Results of a Survey of Breast Cancer Survivors.* Ann Surg, 2015. **261**(6): p. 1198-206.
50. Senkus, E., et al., *Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2015. **26 Suppl 5**: p. v8-30.
51. Gotzsche, P.C. and M. Nielsen, *Screening for breast cancer with mammography.* Cochrane Database Syst Rev, 2011(1): p. CD001877.
52. Autier, P., et al., *Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database.* BMJ, 2011. **343**: p. d4411.
53. Berry, D.A., et al., *Effect of screening and adjuvant therapy on mortality from breast cancer.* N Engl J Med, 2005. **353**(17): p. 1784-92.
54. Hofvind, S., C.I. Lee, and J.G. Elmore, *Stage-specific breast cancer incidence rates among participants and non-participants of a population-based mammographic screening program.* Breast Cancer Research and Treatment, 2012. **135**(1): p. 291-299.
55. Kalager, M., et al., *Improved breast cancer survival following introduction of an organized mammography screening program among both screened and unscreened women: a population-based cohort study.* Breast Cancer Res, 2009. **11**(4): p. R44.
56. Garcia Fernandez, A., et al., *Mortality and recurrence patterns of breast cancer patients diagnosed under a screening programme versus comparable non-screened breast cancer patients from the same population: analytical survey from 2002 to 2012.* Tumour Biol, 2014. **35**(3): p. 1945-53.
57. Dillon, M.F., et al., *Surgical intervention in screen-detected patients versus symptomatic patients with breast cancer.* J Med Screen, 2004. **11**(3): p. 130-4.
58. Miller, A.B., et al., *Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial.* BMJ, 2014. **348**: p. g366.
59. Javitt, M.C., *The Canadian National Breast Screening Study: caveat emptor.* AJR Am J Roentgenol, 2014. **202**(5): p. W505.
60. Heywang-Kobrunner, S.H., et al., *Conclusions for mammography screening after 25-year follow-up of the Canadian National Breast Cancer Screening Study (CNBSS).* Eur Radiol, 2016. **26**(2): p. 342-50.
61. Jeffe, D.B., et al., *The Effects of Surgery Type and Chemotherapy on Early-Stage Breast Cancer Patients' Quality of Life Over 2-Year Follow-up.* Ann Surg Oncol, 2016. **23**(3): p. 735-43.
62. Grimison, P.S. and M.R. Stockler, *Quality of life and adjuvant systemic therapy for early-stage breast cancer.* Expert Rev Anticancer Ther, 2007. **7**(8): p. 1123-34.
63. Mittmann, N., et al., *Health system costs for stage-specific breast cancer: a population-based approach.* Curr Oncol, 2014. **21**(6): p. 281-93.
64. Ackerson, K. and S.D. Preston, *A decision theory perspective on why women do or do not decide to have cancer screening: systematic review.* J Adv Nurs, 2009. **65**(6): p. 1130-40.

65. Miller, D., V. Livingstone, and P. Herbison, *Interventions for relieving the pain and discomfort of screening mammography.* Cochrane Database Syst Rev, 2008(1): p. CD002942.
66. Sarwar, M.Z., et al., *Knowledge, attitude and practices amongst the Pakistani females towards breast cancer screening programme.* J Pak Med Assoc, 2015. **65**(10): p. 1075-8.
67. Khokhar, A., *Study on knowledge, experiences and barriers to mammography among working women from Delhi.* Indian J Cancer, 2015. **52**(4): p. 531-5.
68. Peipins, L.A., et al., *Impact of women's experiences during mammography on adherence to rescreening (United States).* Cancer Causes Control, 2006. **17**(4): p. 439-47.
69. Bairati, I., et al., *Development and validation of an instrument assessing women's satisfaction with screening mammography in an organized breast cancer screening program.* BMC Health Serv Res, 2014. **14**: p. 9.
70. Percac-Lima, S., et al., *Patient Navigation for Comprehensive Cancer Screening in High-Risk Patients Using a Population-Based Health Information Technology System: A Randomized Clinical Trial.* JAMA Intern Med, 2016. **176**(7): p. 930-7.
71. Antill, Y.C., et al., *Screening behavior in women at increased familial risk for breast cancer.* Fam Cancer, 2006. **5**(4): p. 359-68.
72. Pfeffer, N., *Screening for breast cancer: candidacy and compliance.* Soc Sci Med, 2004. **58**(1): p. 151-60.
73. Achat, H., G. Close, and R. Taylor, *Who has regular mammograms? Effects of knowledge, beliefs, socioeconomic status, and health-related factors.* Prev Med, 2005. **41**(1): p. 312-20.
74. Ouedraogo, S., et al., *European transnational ecological deprivation index and participation in population-based breast cancer screening programmes in France.* Prev Med, 2014. **63**: p. 103-8.
75. Linsell, L., et al., *Women's preferences for the delivery of the National Health Service Breast Screening Programme: a cross-sectional survey.* J Med Screen, 2010. **17**(4): p. 176-80.