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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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Summary

Introduction: Mammography screening reduces breast cancer mortality by up to 32%. However, some recent studies have questioned the impact of non-palpable breast cancer detection on mortality reduction. The aim of this study was to analyse the clinicopathological and long-term follow-up data of early stage screened and symptomatic breast cancer patients.

Patients and method: The institutional prospectively led database was systematically analysed for breast cancer cases diagnosed via the mammography screening program from 2002 to 2009. As a control group, symptomatic early stage breast cancer patients were collected randomly from the same database and matched for age and follow-up period. All medical records were reviewed retrospectively.

Results: Data from 298 breast cancer patients were collected from 47,718 mammography screenings. In addition, 331 symptomatic breast cancer patients were randomly selected. The screened group presented a significantly lower median tumour size ($P < 0.00001$). The incidence of negative regional lymph nodes was significantly higher in the screened group ($P < 0.0006$). The incidence of chemotherapy was 17% higher in the symptomatic group ($P = 4*10^{-5}$). At the median follow-up of 65 and 80 months, the screened group did not exhibit better overall ($P = 0.717$) or disease-free survival ($P = 0.081$) compared to the symptomatic group.

Conclusion: Our results do not suggest that mammography screening does not reduce breast cancer mortality but the mammography screening did not bring any significant improvement in patient overall or disease-free survival for the early stage breast cancer patients compared to the symptomatic group. The drawback of symptomatic early stage tumours compared to non-palpable tumours could be equalized by modern multimodality oncology treatments.

Keywords: Breast neoplasms; Mass screening; Mortality; Survival

Introduction

Oncological outcomes are generally more favourable during early stages of disease before symptoms appear in symptomatic (palpable) diseases. The goal of any screening program is to disclose breast tumours before they become palpable, optimally during stage 0. Mammography screening could bring about significant benefits in survival, which was the main reason for the implementation of breast screening programs in many countries.[1,2] Hungary

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organized a nationwide screening program for residents aged 45–65 years, with biannual screening commencing in January 2002.[3]

The efficacy of mammography screening in preventing breast cancer deaths was presented in some randomized controlled trials (RCTs), with reductions in mortality rate ranging from 17% to 32%.[4–7] On the contrary, some recent studies have questioned the efficacy of early stage tumour detection on mortality reduction.[8,9] Some authors believe that advanced breast cancer diagnosis and effective adjuvant therapy may play greater roles in reducing breast cancer mortality than screening.[10]

The aim of the present investigation was to compare the clinical outcomes of a group of patients that underwent mammography screening compared to a non-screened symptomatic group of early stage breast cancer patients.

Patients and method

This study was performed in accordance with the Research Ethics Committee of the National Institute of Oncology. Written informed consent was always obtained for data collection.

The inclusion period was from 1 January 2002 to 31 December 2009. Data were collected from the prospectively led database of the National Institute of Oncology, Budapest.

According to the Hungarian guideline on mammography screening the target population was invited for breast screening regionally by invitation letter.[11] Our investigated screened population represents the target population from the capital. Screened (SCR) breast cancer patients discovered by the mammography screening program of the National Institute of Oncology were collected prospectively. According to 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.[12]

The surely symptomatic (SYM) breast cancer patients with palpable tumours were collected randomly and prospectively from the institutional database by three researchers. The patients included to the SYM group were newly diagnosed breast cancer patients corresponding to a clinical stage from 0 to II/A with disease discovered by self-examination or via another physical breast examination by 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 led prospectively according to the standard methods of all disciplines involved in breast cancer diagnosis, treatment and follow-up, which included all relevant clinicopathological data of the SCR and SYM patients. Some of the patients were included in clinical trials from both groups but nobody has left undertreated.

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 National Institute of Oncology.[13–17]

The diagnosis of breast cancer was based on clinical examination in combination with imaging and was confirmed via pathological assessment. MRI was used in cases of breast implants, ILC, the suspicion of multifocality/multicentricity, or large discrepancies between conventional imaging and the clinical examination.

For surgical procedures, breast conserving surgery (BCS), mastectomy, sentinel lymph node (SLN) biopsy with dual radio-colloid/blue dye technique were used. In SLN-positive cases or for clinically positive axillary lymph nodes, axillary node clearance 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 microscopically surgical margin of 1 mm.

Postoperative pathological examination and assessments had not been significantly changed during the investigated period.[18] The 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. 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 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.

Hormone therapy (HT) was based on tamoxifen or aromatase inhibitors in luminal cases for five years after the surgery. From 2002 to 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.

Radiotherapy (RT) was performed using three-dimensional planning with CT. The adjuvant radiotherapy started on the fourth postoperative week or after the adjuvant chemotherapy. Whole breast radiotherapy for patients who received breast conserving surgery 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. Breast cancer therapy had not been changed significantly during the investigated period.

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 diagnosis, disease grade, stage, death, and other clinical covariates. The TNM classification was defined by the American Joint Cancer Committee (AJCC) Breast Cancer Staging 7th Edition. 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 date of the diagnosis of the first locoregional 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).

Results

During the inclusion period the National Institute of Oncology as an accredited regional mammography screening centre covered around 2% of Hungarian breast screening target population.[11]

During that period 47,718 women were examined by organized nationwide mammography screening program, 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 1.

Tumour size

The SCR group presented a significantly less median pathological tumour size than the SYM group ($\mathbf{P < 0.00001}$, Mann–Whitney test) (Fig. 1), and significant differences were observed using the pT classification ($\mathbf{P = 1.6*10^{-7}}$, Chi-square test) (Table 1).

Histology and subtypes

The incidence of pTis was significantly higher in the SCR than in the SYM group ($\mathbf{P = 7.2*10^{-5}}$) (Table 1). The incidence of extensive intraductal component (EIC) in the SCR group was statistically higher than in the SYM group ($\mathbf{P = 6.7*10^{-33}}$) (Table 1). The SYM group presented significantly more vascular invasion than the SCR group ($\mathbf{P = 0.001}$). The incidence of perineural invasion in the SYM group was statistically higher than in the SCR group ($\mathbf{P = 8.2*10^{-8}}$) (Table 1).

Significant differences in the clinical characteristics were observed according to breast cancer subtype ($\mathbf{P = 0.003}$). 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 1).

Table 1
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 (months; range)	65; 13–130	80; 18–150	0,0001[a]
Clinical Stage			$1,6*10^{-7}$[a]
0	22 (7.89%)	4 (1.26%)	
I	125 (44.80%)	101 (31.96%)	
II	102 (36.56%)	149 (47.15%)	
III	26 (9.32%)	60 (18.98%)	
IV	4 (1.43%)	2 (0.63%)	
Median tumour size (mm; range)	19; 1–170	24; 1–182	$P < 0.00001$[b]
pT stadium			$4,4*10^{-7}$[a]
PTis	22 (7.89%)	4 (1.27%)	
pT1mi	4 (1.43%)	1 (0.32%)	
pT1	157 (56.27%)	135 (42.72%)	
pT2	81 (29.03%)	148 (46.84%)	
pT3	13 (4.66%)	22 (6.96%)	
pT4	2 (0.72%)	6 (1.89%)	
Histology			$7.2*10^{-5}$[c]
Non-invasive	22 (8%)	4 (1.3%)	
Invasive	257 (92%)	312 (98.7%)	
Regional lymph node metastasis			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			$6.7*10^{-33}$[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%)	

EIC: extensive intraductal component, IHC: immunohistochemical, HER2: human epidermal growth factor 2.
[a] Chi-square test.
[b] Mann–Whitney test.
[c] Fisher's exact test.

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 1).

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 2).

Overall survival

The SCR group did not exhibit significantly better OS rates than the SYM group (**P = 0.717**; log-rank) (Fig. 2).

Disease-free survival (DFS)

The SCR group did not exhibit significantly better DFS rates than the SYM group (**P = 0.081**; log-rank) (Fig. 3).

Discussion

A decrease in mortality is the ultimate goal for any screening program, and the advantages of early cancer detection are obvious.[19]

Randomized controlled trials (RCTs) that have evaluated mammography screening have demonstrated a reduction in breast cancer mortality,[4–6] 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.[8,9,20–22]

According to our 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. Hofvind et al. compared the stage-specific breast cancer incidence rates among participants and non-participants of a

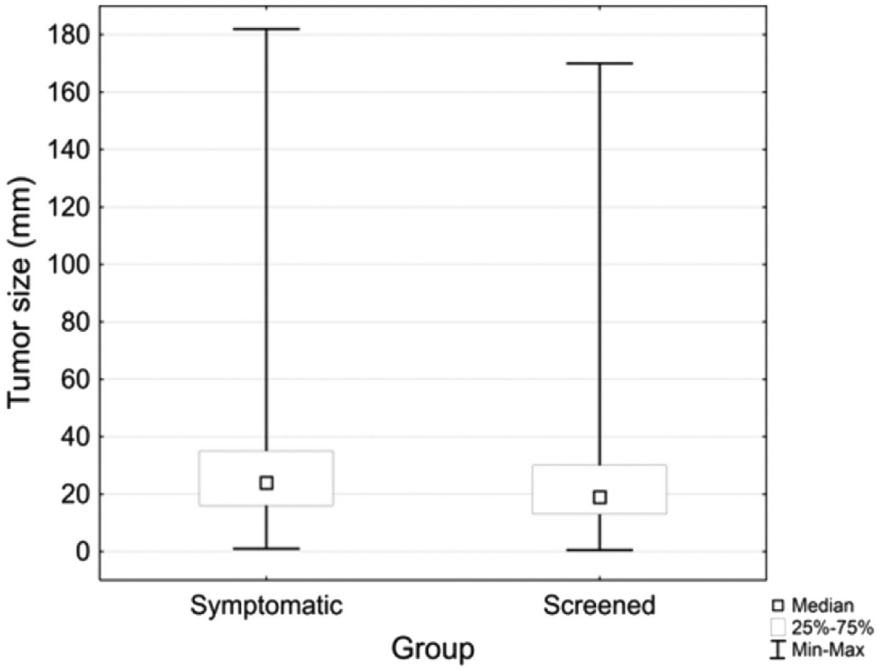

Figure 1. Tumour sizes in the SCR and SYM groups. (Mann–Whitney test; $P < 0.00001$).

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.[23]

In our 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-program) and after (post-program) the introduction of a population-based mammography screening program in their county of residence. The incidence of pT1 tumours was 11% greater in the participating group compared to the non-participating group.[24]

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.[25] 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.[26]

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.[26] 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.[25]

According to our 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.[23,25,26]

According to our 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.[27] 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 should have been the case with proper methodology.[28,29]

The question arises as to the reason that no differences in OS or DFS were found between the SCR and SYM

Table 2
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%)	
Hormonal 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%)	

BCS: breast conserving surgery.
[a] Chi-square test.

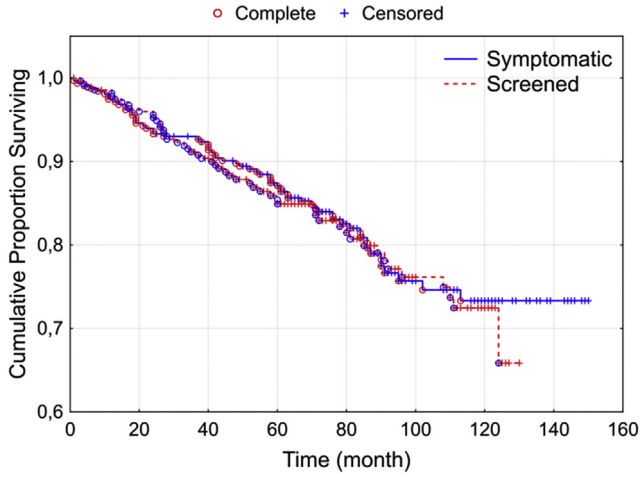

Figure 2. Kaplan–Meier curve for the OS of the SCR and SYM groups.

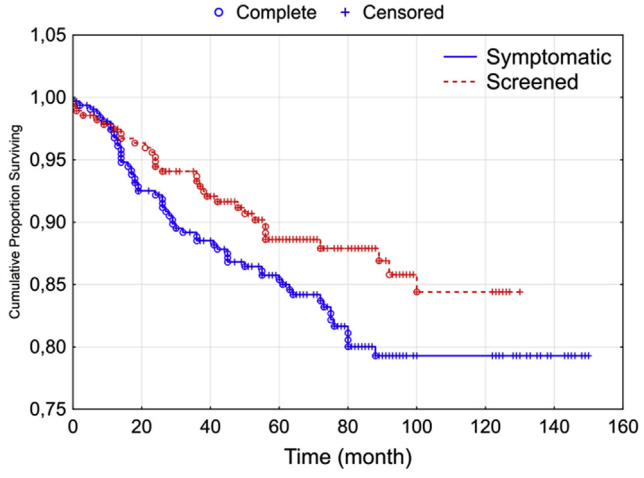

Figure 3. Kaplan–Meier curve for the DFS for the SCR and SYM groups.

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 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 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 responsible for reducing mortality in breast cancer. Modern multimodality cancer treatment 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.

A limitation of our study is the follow-up period. After 10 years of a national screening program, 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 may be too short to show the real advantages of the screening program. However, in RCTs, there was a reduction in mortality after 4 years, with an increasing effect up to 10 years.[7] 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.

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

Conclusion

Early tumour detection is very important in breast cancer treatment and clinical outcomes. Our results support the evidence that mammography screening reduces the rate of advanced breast cancers but do not support the evidence that patients with non-palpable early stage breast cancers diagnosed via population-based breast screening have better survival rates than those with symptomatic cancers. The reason why there were no differences in OS and DFS remains unclear, but it could be based on the efficiency of modern multimodality breast cancer treatment.

Authors do not suggest that mammography screening does not reduce breast cancer mortality. 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 treatment. However, the discovery of specific prognostic and predictive biomarkers that enable the application of more individualized comprehensive therapies to different molecular subgroups may indeed have reduced breast cancer mortality in symptomatic breast cancer patients. In our investigation, the OS and DFS were not worse in the SYM group, but this result may be

accompanied by a significant reduction in QOL due to the more aggressive treatments required. Further investigations are needed to answer these questions.

Conflict of interest

None.

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