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Association of symptoms and breast cancer in population-based mammography screening in Finland

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The study purpose was to assess association of symptoms at screening visits with detection of breast cancer among women aged 50–69 years during the period 2006–2010. Altogether 1.2 million screening visits were made and symptoms (lump, retraction, secretion etc.) were reported either by women or radiographer. Breast cancer risk was calculated for each symptom separately using logistic regression [odds ratio (OR)] and 95% confidence intervals (CIs). Of the 1,198,410 screening visits symptoms were reported in 298,220 (25%) visits. Breast cancer detection rate for women with and without symptoms was 7.8 per 1,000 and 4.7 per 1,000 screening visits, respectively, whereas lump detected 32 cancers per 1,000 screens. Women with lump or retraction had an increased risk of breast cancer, OR = 6.47, 95% CI 5.89−7.09 and OR = 2.19, 95% CI 1.92–2.49, respectively. The sensitivity of symptoms in detecting breast carcinoma was 35.5% overall. Individual symptoms sensitivity and specificity ranged from, 0.66 to 14.8% and 87.4 to 99.7%, respectively. Of 5,541 invasive breast cancers, 1,993 (36%) reported symptoms at screen. Breast cancer risk among women with lump or retraction was higher in large size tumors (OR = 9.20, 95% CI 8.08–10.5) with poorly differentiated grades (OR = 5.91, 95% CI 5.03–6.94) and regional lymph nodes involvement (OR = 6.47, 95% CI 5.67–7.38). This study was done in a setting where breast tumors size is generally small, and symptoms sensitivity and specificity in diagnosing breast tumors were limited. Importance of breast cancer symptoms in the cancer prevention and control strategy needs to be evaluated also in other settings.

Early Detection and Diagnosis

Early detection of breast cancer through organized screening in average risk women has reduced mortality from the disease.[1,2] In Finland, the national organized mammography screening program has been reported to reduce the incidence-based mortality from breast cancer by approximately 20–28% among those invited.[3] Many, even though not all, breast cancer screening programs include an examination of breasts done by the radiographer and/or reporting of symptoms by the woman at the screening visit.[1,4] Symptoms findings from such examination could convey to diagnostic work-up in the screening centers, as well as indicate a differential risk of breast cancer.

Over-diagnosis and unnecessary treatment of apparently healthy women in mammography screening raise the question about benefits versus harms of screening over clinical breast examination.[5] Many countries where mammography screening is not organized at population level but with the increasing awareness about breast cancer, patients may present with breast complaints.[6] Hence in such situation, detection of breast cancer cases mostly rely on breast complaints. Research on the possible symptoms can provide feedback for the clinicians and help in making decisions when reading screening films and in further investigations (recall or referral).[4] Few studies have highlighted the relevance of assessing symptoms at screening diagnostic mammography.[4,7–9]

So far, no studies till date have studied the association of symptom and breast cancer risk at population level. There is a possibility to learn about benefits of assessing symptoms during screening as well as to improve the procedures by reducing unnecessary diagnostics and false positive findings. Moreover, for developing countries, where high technology for detecting early cancer is not feasible, symptoms can be used as an indication for early diagnostics. Provided that adequate resources are available for confirmation and treatment, this could prevent late stage presentation of cancer.[7]

The aim of the study was to assess the association of symptoms with the occurrence of breast cancer and to

Key words: breast cancer symptoms, screening, clinical breast examination, lump, scar

Abbreviations: MSR: mass screening registry; OR: odds ratio; CI: confidence interval; CBE: clinical breast examination; BSW: Breast Test Wales; PPV: positive predictive value

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What's new?
A key component of breast cancer screening programs is the collection of data on symptoms at the time of screening visit. In many cases, however, the data are not subsequently analyzed for relationships between symptoms and breast cancer diagnosis. Based on analysis of data from 1.2 million screening visits recorded in the Finnish Cancer Registry, the present report describes a significant association between breast cancer risk and symptoms either self-reported by patients or detected by radiographers. Risk was highest for breast lumps reported at screening. Importantly, the findings also highlight limitations regarding the clinical significance of symptoms.

analyse the cross-sectional clinical validity of symptoms among screened women under the organized breast cancer-screening program.

Materials and Methods

This study is based on breast cancer screening data provided by the Mass Screening Registry (MSR) of the Finnish Cancer Registry (http://www.cancer.fi/syoparekisteri/en/). The MSR receives information on the breast cancer screening program through the population files and the screening centers.[10] Registration is based on the law of personal data in the health-care and the Government Decree on Screenings, 1,339/2,011, and the respective recommendations published by the National Research and Development Centre for Welfare and Health.[11]

The Finnish breast cancer-screening program targets women aged 50–69 years every 2 years. A personal invitation letter is sent by mail with a prefixed time and place of screening. All women in the target age are invited with no exclusions. At the screening clinic woman may present with symptoms or no symptoms. Women are asked (or to fill in the form) whether they had any symptoms during the past 2 months. The nurse then examines the breast. Symptoms are recorded in the mammography screening form. After then, breasts are examined by mammography. After interpretation of the results those with mammography positives are recalled for further examination. Women who are mammography negative are sent home and invited after 2 years for the next biennial screening round. Physician examines the breast of the recalled women. Women may be healthy or referred for diagnostic workup at hospital. Those with cancers are followed up until death (mortality).[10]

For the current study, information on women aged 50–69 years who had breast cancer screening during the years 2006–2010 were retrieved. The first round of screening starts at the age of 50–51 years. The study is based on tabular information and originates from data recorded on the mammography screening form (http://www.cancer.fi/syoparekisteri/joukkotarkastusrekisteri/) for every woman who was screened during that period of time. Altogether 1,454,143 invitations were made during the period, of which 1,241,486 screening visits were made (attendance 85.4%). In all, 38,647 visits (3.11%) were excluded because of incomplete information on either the clinical examination or on self-reported symptoms. Furthermore, 4,429 (0.36%) visits were excluded because of not complying with the age range. The final data set contains 1,198,410 screening visits from all over Finland. Symptoms that were reported include lump, retraction, scar, secretion and mole. Outcome variables were histologically confirmed breast cancers (both invasive and in situ) and benign findings. Some tumor characteristics (tumors size and grade) were also available.

In the current analysis, women who had a given symptom at screen in either or both breasts were considered as symptomatic. Information on breast symptoms was dichotomized for any as well as for each individual symptom separately. The outcome was categorized as malignant (in-situ and invasive breast cancers) and benign finding (other histology). The age of screened women was categorized into four groups as "50–54," "55–59," "60–64" and "65–69." To do the homogeneity test of symptoms with age, age-groups were made as continuous variables where age-group 50–54 years indicate "0," 55–59 years indicate "1," 60–64 years indicate "2" and 65–69 years indicate "3." In classifying histologically confirmed tumors two categories of tumor size were made: "less than 20 mm" and "20–150 mm." Tumor grades were classified as "well-differentiated," "moderately differentiated" and "poorly differentiated." Tumor spreading was classified according to the TNM classification of tumors published by International Union Against Cancer (UICC) in 2002.[12]

Statistical analysis

Breast cancer detection rate (number of cancer cases detected divided by number of screening visits) was calculated for individual symptoms as well as for all possible pairwise combination of symptoms. Logistic regression model was used to calculate the crude and adjusted odds ratios (ORs) with 95% confidence interval (CI) using Wald statistics for individual terms. The univariate logistic regression model was used to estimate the age-adjusted association of symptom with the occurrence of breast cancer. For calculating the joint exposure effects and homogeneity analysis likelihood ratio statistics was used. Effects by individual and combined symptoms (self-reported and radiographer reported) as well as pairwise analysis of symptoms with all possible combinations were also estimated. All the statistical analyses were two-sided, and a p value ≤ 0.05 was considered to be statistically significant. The statistical analyses were carried out using STATA software release 11.0.

To analyze the cross-sectional validity of the symptoms, sensitivity and specificity were estimated. True positives are here those with a "positive" symptom and with breast cancer and vice-versa for true negatives. Breast cancer included invasive and in situ carcinoma of the breast, and analyses were done also separately for these two diagnosis categories when relevant. False positives are here those with a positive symptom but no breast cancer whereas false negatives are those with no symptom but had breast cancer. Sensitivity was here defined as the number of visits with screen-detected malignant cancers in those who had symptoms (true positives for symptoms) divided by the total number of visits with breast cancer. Specificity was the number of visits with no symptoms and no malignant finding (true negatives for symptoms), divided by the total number of visits with no malignant findings. CIs for sensitivity and specificity were produced with the Wilson score method.[13] The positive predictive value (PPV) is the likelihood of cancer detected among those who had symptoms. CI for PPV was calculated using the method described by Simel et al.[14] We considered lump or retraction as clinically relevant symptoms while reporting and analyzing symptoms information on histological confirmed tumors.

Results

A total of 1,198,410 screening visits were made in 2006–2010 and out of these, a histologically confirmed breast cancer (including in-situ cases) was diagnosed in 6,009 (0.5%) women at screen. In this period, the national decree of screening was given and women aged 60–69 years were also included into the target population if they were born in 1947 or later. Thus, the number of screened women increased year by year clearly between 2006 and 2010, *i.e.*, 192,892 and 264,678, respectively. Altogether 298,220 visits with at least one symptom out of 1,198,410 visits (24.9%) were reported in this period (Table 1). Lump was reported in 15,587 (1.30%) screening visits and retraction was reported in 20,880 (1.74%) visits. The percentage of women who reported symptoms (out of total screened) increased clearly by age of the women, 21.8% in age-group 50–54 years and 30% in age group 65–69 years, respectively. Screen positive women (who were recalled) were 30,392 (2.5%) out of which 9,659 (32%) reported any of the symptoms. The percentage of women out of total screening visits that were referred for further assessment was 0.75%.

Breast cancer detection rate of lump was 31.9 per 1,000 screening visits whereas detection rate of retraction and secretion was 11.6 per 1,000 and 10.8 per 1,000 screening visits, respectively. The age-adjusted risk of breast cancer in women who reported a lump was 6.61 (95% CI 6.03–7.26) times higher compared to those with no symptoms (Table 2). Similarly, the risk in women who reported retraction or secretion was more than twofold, OR = 2.11, 95% CI 1.86–2.41 and OR = 2.14, 95% CI 1.58–2.89, respectively, compared to women who reported no symptoms. Reporting a scar or mole indicated a small increase in the risk of breast cancer compared to those with no symptoms, *i.e.*, OR = 1.26, 95% CI 1.17–1.35 and OR = 1.16, 95% CI 1.09–1.25, respectively.

The risk of breast cancer in women who reported lump was higher in all age groups compared to women with other symptoms. Women who reported lump and/or retraction had a significant increase in breast cancer risk across age groups. Women who reported secretion had an increase in trend of breast cancer risk with age (Fig. 1). The joint effect of symptoms with two possible combinations was measured simultaneously. The cancer detection rate of lump and retraction combined was 102 per 1,000 screening visit whereas combined lump and secretion was 26 per 1,000 screening visits. Similarly, the combined cancer detection rate of retraction and scar was 12 per 1,000 screening visits. The combined effect of lump and retraction showed a 23-fold (OR = 22.6, 95% CI 16.5–30.8) increase in the risk of breast cancer compared to women with no lump or retraction. Similarly, the joint effect of lump and scar showed a sixfold (OR = 5.37, 95% CI 4.31–6.69) increase in the risk of breast cancer compared to women with no lump or scar (Table 3).

Overall, 2,314 women who had any of the symptoms were diagnosed with breast cancer at screen. The sensitivity to detect cancer for women with any of the symptoms was 35.5% (95% CI 34.3–36.6%) whereas specificity was 75.2% (95% CI 75.1–75.3%; Table 4). The sensitivity to detect cancer was 8% in women who had a lump whereas in case of retraction the sensitivity was 4%. However, the specificity was high for lump and retraction, 98.7 and 98.3%, respectively. Scar and mole both had a sensitivity of 15% each whereas specificity was low for these symptoms, 88.3 and 87.4%, respectively.

Altogether 5,541 invasive breast cancers were detected at screen out of which 1,993 (36%) were reported with symptoms at the time of screening and 652 (32.7%) reported lump or retraction only. In all, 70% of the invasive cancers were less than 20 mm in diameter. The presence of lump or retraction increased from 8% in tumors less than 20 mm of size to 22% in tumors of 20–150 mm in size (Table 5). The probability of having age-adjusted invasive breast cancer was significantly higher (OR = 4.31, 95% CI 3.96–4.69) in those who reported lump or retraction compared to those with no lump or retraction. Women with lump or retraction had a significantly higher age-adjusted risk for big tumors than nonsymptomatic women, OR = 2.84 (95% CI 2.53–3.19) in tumors less than 20 mm and OR = 9.20 (95% CI 8.08–10.5) in 20–150 mm size tumors. The probability of having poorly differentiated tumors was significantly higher (OR = 5.91, 95% CI 5.03–6.94) in women who reported symptoms than in those without symptoms. The probability of having tumors in regional lymph nodes was significantly greater in women with symptoms compared to those with no symptoms, OR = 6.47, 95% CI 5.67–7.38.

Discussion

The purpose of the study was to examine the association between symptoms at the screening visit and detection of breast cancer at screen. In addition, we described the size

Table 1. Symptoms[2] reported during the screening visits at different time-periods and by age, recall, or referral due to screening results

	Total screening visits	Lump (%)	Retraction (%)	Scar (%)	Mole (%)	Secretion (%)	Any of the symptoms (%)[1]
Year							
2006	192,892	2,570 (1.3)	3,425 (1.8)	22,239 (11.5)	27,411 (14.2)	726 (0.4)	50,402 (26.1)
2007	235,304	3,044 (1.3)	3,858 (1.6)	27,819 (11.8)	31,239 (13.3)	879 (0.4)	60,106 (25.5)
2008	237,389	3,011 (1.3)	4,297 (1.8)	27,821 (11.7)	30,937 (13.0)	797 (0.3)	60,117 (25.3)
2009	268,147	3,346 (1.2)	4,542 (1.7)	31,492 (11.7)	30,327 (11.3)	722 (0.3)	63,462 (23.7)
2010	264,678	3,616 (1.5)	4,758 (1.8)	30,766 (11.6)	31,115 (11.8)	841 (0.3)	64,133 (24.2)
Age							
50–54	469,594	6,932 (1.5)	6,794 (1.4)	44,587 (9.5)	52,734 (11.2)	2,081 (0.4)	102,538 (21.8)
55–59	339,635	4,095 (1.2)	6,368 (1.9)	41,029 (12.1)	42,885 (12.6)	943 (0.3)	85,715 (25.2)
60–64	306,227	3,622 (1.2)	6,012 (1.9)	42,552 (13.9)	42,343 (13.8)	721 (0.2)	85,177 (28.8)
65–69	82,954	938 (1.1)	1,706 (2.1)	11,969 (14.4)	13,067 (15.7)	220 (0.3)	24,790 (29.8)
Recall							
Yes	30,392	2,205 (7.2)	724 (2.4)	4,210 (13.8)	3,976 (13.1)	310 (1.0)	9,659 (31.7)
No	1,168,018	13,382 (1.1)	20,156 (1.7)	135,927 (11.6)	147,053 (12.6)	3,655 (0.3)	288,561 (24.7)
Referral							
Yes	8,093	613 (7.6)	278 (3.4)	1,248 (15.4)	1,169 (14.4)	87 (1.1)	2,876 (35.5)
No	1,073,462	13,979 (1.3)	19,429 (1.8)	129,050 (12.0)	141,470 (13.2)	3,559 (0.3)	276,507 (25.7)
Total	1,198,410	15,587 (1.3)	20,880 (1.7)	140,137 (11.7)	151,029 (12.6)	3,965 (0.3)	298,220 (24.9)

[1]Percentage (%) in the bracket means any of the symptoms out of total screening visits.
[2]Symptoms include women, radiographer reported or both.

Table 2. Age-adjusted odds ratios (OR) of breast cancer (including *in situ* and benign tumors) with 95% confidence intervals (CI) among women with symptoms[1] compared to women with no symptoms

	Cases (%)	Total (%)	Detection rate (per 1,000)	OR (95% CI)* adjusted with age
Lump				
Yes	497 (3.19)	15,587 (1.30)	31.9	6.61 (6.03–7.26)
No	6,027 (0.51)	1,189,601 (98.7)	5.07	Ref.
Retraction				
Yes	242 (1.16)	20,880 (1.74)	11.6	2.11 (1.86–2.41)
No	6,282 (0.53)	1,177,530 (98.3)	5.33	Ref.
Scar				
Yes	966 (0.69)	1,40,137 (11.7)	6.89	1.26 (1.17–1.35)
No	5,558 (0.53)	1,058,273 (88.3)	5.25	Ref.
Secretion				
Yes	43 (1.08)	3,965 (0.33)	10.8	2.14 (1.58–2.89)
No	6,481 (0.54)	1,194,364 (99.7)	5.43	Ref.
Mole				
Yes	963 (0.64)	1,51,029 (12.6)	6.38	1.16 (1.09–1.25)
No	5,561 (0.53)	1,047,299 (87.4)	5.31	Ref.
Total	6,524 (0.54)	1,198,410 (100.0)		

[1]Symptoms include women, radiographer reported or both.
Abbreviations: OR: odds ratio; CI: confidence interval; ref.: reference.

and grade of tumor in relation to symptoms at screen in women who attended screening and were diagnosed with a breast tumor. The large dataset of about 1.2 million screening visits allows studying breast cancer risk at the population level among women who reported symptoms at screening. The study found a significant association between all reported

symptoms and the occurrence of breast cancer. A breast lump at screen indicated the highest breast cancer risk.

In this study symptoms were either self-reported or radiographers reported and the rate of breast cancer associated with symptoms were calculated. Symptoms were reported in 25% of the screening exams. This is higher than previously reported in a study on postmenopausal women where the prevalence of symptoms was below 10%.[7] The explanation may be that in our study more symptoms were included and symptoms were considered valid whether reported by women or by the radiographer. In studies reporting symptoms at diagnostic mammography exams the prevalence has been more than 30%.[7,8,15] The reason for high prevalence of symptoms in diagnostic mammographic exams may be due to selection of women at increased risk of breast cancer[7,8,15] and premenopausal women in whom prevalence of symptom is higher.[6]

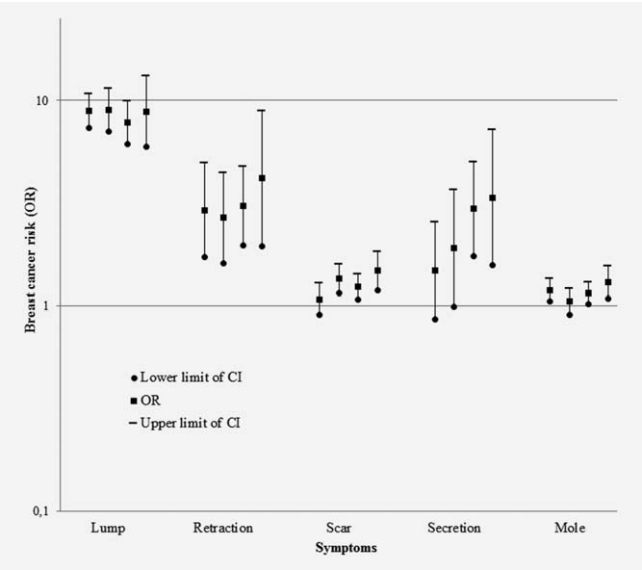

Figure 1. Breast cancer risk among women having symptoms reported by age groups.

The overall proportion of women with breast cancer among those reporting symptoms was 0.78% in our study. The recall rate (mammography positives) among women with symptoms was 3.24%, whereas only 1.73% of women with no symptoms were recalled. Similarly, the proportion of women who referred for further assessment was greater in those with symptoms compared to women with no symptoms, *i.e.*, 0.96 versus 0.44%, respectively. Aiello et al.[7] reported that 6.6% of women with symptoms at diagnostic examination and 1.3% of women at screening examination were diagnosed with breast cancer. Williams et al.[4] study on women who had mammography screening found the breast cancer rate of 0.5% in women with symptoms which is lower than in our study (0.8%). However, they evaluated only those women with "significant" breast symptoms as defined by Breast Test Wales (BSW) guidelines.[16] The Seltzer[9] study reported higher proportion (16%) of breast cancer diagnosed among women with symptoms or prior abnormal mammography that were referred for diagnostic examination. This study found the cancer rate of 7.6, 3.7 and 14.9% in patient with breast lump, retraction and scar, respectively, which is little lower than the study by Lumachi et al.[17] That study found a cancer rate of 3.2, 16.4 and 12.0%, respectively, in patient with breast pain, lump and nipple discharge.[17] In another study by Sterns,[18] breast cancer rate was 37, 11 and 3% in patients with breast mass, nipple discharge and lump, respectively. One reason for the differences may

Table 3. Odds ratios (ORs) of breast cancer with 95% confidence intervals (CI) for joint exposure to symptoms[1]

Symptoms	Screened women	Cancer cases (%)	Detection rate (per 1,000)	OR	95% CI
Lump#retraction	36,036	695 (1.93)	19.3		
0 0	1,162,374	5,829 (0.50)	5.01	Ref.	Ref.
0 1	20,449	198 (0.97)	9.68	1.94	1.68–2.24
1 0	15,156	453 (2.99)	28.9	6.15	5.55–6.74
1 1	431	44 (10.2)	102	22.6	16.5–30.8
Lump#scar	152,515	1,380 (0.90)	9.05		
0 0	1,045,895	5,144 (0.49)	4.92	Ref.	Ref.
0 1	136,928	883 (0.64)	6.45	1.31	1.22–1.41
1 0	12,378	414 (3.34)	33.4	7.0	6.32–7.75
1 1	3,209	83 (2.59)	25.9	5.37	4.31–6.69
Retraction#scar	157,121	1,162 (0.74)	7.4		
0 0	1,041,289	5,362 (0.51)	5.15	Ref.	Ref.
0 1	136,241	920 (0.68)	6.75	1.31	1.22–1.41
1 0	16,984	196 (1.15)	11.5	2.26	1.95–2.60
1 1	3,896	46 (1.18)	11.8	2.31	1.72–3.09

[1]Symptoms include women, radiographer reported or both.
Abbreviations: 0: absence of symptom; 1: presence of symptom; OR: odds ratio; CI: confidence interval; ref.: reference.

Table 4. Clinical validity of symptoms[1] in terms of sensitivity, specificity and positive predictive value (PPV)

Clinical validity	Lump	Retraction	Scar	Secretion	Mole	Any of the symptoms
True positives	497	242	966	43	963	2,314
True negatives	1,176,796	1,171,248	1,052,715	1,187,883	1,041,738	895,980
False positives	15,090	20,638	139,171	3,922	150,066	295,906
False negatives	6,027	6,282	5,558	6,481	5,561	4,210
Sensitivity %	7.62 (7.04–8.32)	3.71 (3.27–4.20)	14.8 (14.0–15.7)	0.66 (0.48–0.89)	14.8 (13.9–15.7)	35.5 (34.3–36.6)
Specificity %	98.7 (98.7–98.8)	98.3 (98.2–98.3)	88.3 (88.3–88.4)	99.7 (99.7–99.7)	87.4 (87.3–87.5)	75.2 (75.1–75.3)
Positive predictive value %	3.19 (2.92–3.48)	1.16 (1.02–1.32)	0.69 (0.65–0.73)	1.08 (0.79–1.47)	0.64 (0.60–0.68)	0.78 (0.74–0.81)

[1]Symptoms include women, radiographer reported or both.

be that our study was done among the general population and most women come for screening on a regular basis (once in every 2 years). Moreover, in our study women reported only symptoms that occurred in the past 2 months and radiographer reported those symptoms detected at the time of screening visit. The reason for higher rates in other studies[17,18] was that both studies were done among symptomatic women who had higher risk of developing cancer. However, due to variation in early detection program and collected symptoms information as well as varying age of the women at either screen or diagnostic examination than our study, results are not directly comparable with the current study.

In this study, the risk of breast cancer was found to be significantly associated with the occurrence of symptoms. The risk of developing breast cancer was sevenfold in women having a lump and the risk was almost similar across the age group. Aiello et al.[7] reported a risk of more than threefold in women who had a lump in the screening exam or diagnostic exam but no significant association between nipple discharge, breast pain and breast cancer risk. Moreover, our study showed a threefold increase in risk in women who had retraction in their breast and a small increase in risk in those who reported scar and mole. We are unaware of other epidemiological studies that would have examined the association between retraction, scar and the breast cancer risk. Two-way joint effects of symptoms showed a significant 23-fold breast cancer risk in women who reported lump and retraction and a 6-fold risk in women who reported lump and scar. The higher risk of breast cancer in our study may be due to the information about breast symptoms systematically collected. A study by Sarkeala et al.[3] in Finland found a 1.56 (95% CI = 1.25–1.91) times higher death rate in women who had no screening visits. The interval cancers, since screening visits are made once in every 2 years, can be more aggressive than screen-detected cancers. Hence, the risk might be even higher in women who had symptoms and are not screened.

In our study breast cancer rate among women with any of the given symptoms was 0.66% in age-group 50–59 years and 0.99% in age-group 60–69 years. Sterns'[18] study in symptomatic patients found the cancer rate to be significantly age-related, being 0.8% in women younger than 40 years and 5% in those between 41 and 55 years. Kerin et al.[19] evaluated the 585 symptomatic patients found breast cancer rate of 2.2% in patient aged 40–49 years, 4.5% in patient aged 50–59 years and 3.1% in patient aged more than 60 years of age. In our study women who reported a lump or retraction showed significantly higher risk of breast cancer in all age-groups compared to non-symptomatic women. Women with other symptoms had a nonsignificantly higher breast cancer risk across age groups. The p value test for homogeneity showed no age related breast cancer risk with an exception of secretion (p value <0.05).

The sensitivity of reporting any symptom in detection of invasive carcinoma was 35.5% in the present study, which is lower than that reported by others.[20–22] However, Harvey et al.[20] and Kerlikwoske et al.[21] measured sensitivity based on the mammography findings and Bobo et al.[22] based the sensitivity calculation on clinical breast examination. A community based study among asymptomatic women in United States reported lower sensitivity than found in our study, between 18.1 and 21.6% based on clinical breast examination.[23] Findings from a randomized controlled trial of breast cancer screening by clinical breast examination in India showed a moderate sensitivity and high specificity, 51.7 and 94.3%, respectively, but PPV was lower than found in our study.[24] In our study, the sensitivity of lump, retraction, scar and mole was 7.7, 3.7, 14.8 and 14.8%, respectively, while high specificity of 99% was reported by lump and retraction. We are not aware of any other studies that measured the clinical validity of symptoms at screen and hence our study findings are not directly comparable to other studies. The low sensitivity of any specific symptom in our study may be explained by the magnitude of diagnostic activities, several rounds of screening in the program, and access to mammography services outside the screening program. Thus, both the population and the tumors found by screening are different from those in the trial from India.[24]

Another purpose of our study was to assess tumor characteristics (size and grade) in relation with breast cancer symptoms. We found that close to 70% of invasive breast cancers detected by screening were less than 20 mm of size. Sankaranarayanan et al.[24] study reported a significantly lower percentage of tumors

Table 5. Characteristics of and probability (odds ratios, OR, with 95% confidence intervals, CI) of invasive breast cancer in women with symptoms[1] (lump or retraction only) compared to women with no symptoms at screen

Tumor characteristics	Total	Symptoms (lump or retraction)	OR (95% CI)* adjusted with age
Size in histology			
Less than 20 mm	3,841	311 (8.1 %)	2.84 (2.53–3.19)
20–150 mm	1,340	294 (21.9 %)	9.20 (8.08–10.5)
Missing[2]	360	47 (13.6 %)	
Total	5,541	652 (11.8%)	4.31 (3.96–4.69)
Grade			
Well differentiated	1,570	142 (9.05%)	3.18 (2.68–3.78)
Moderately differentiated	2,520	302 (12.0%)	4.39 (3.89–4.95)
Poorly differentiated	1,140	177 (15.5%)	5.91 (5.03–6.94)
Missing[2]	311	31 (10.0%)	
Total	5,541	652 (11.8%)	4.37 (4.02–4.76)
pN			
pN0	3,533	340 (9.6%)	3.42 (3.06–3.83)
pN1+	1,601	267 (16.7%)	6.47 (5.67–7.38)
pNX	40	4 (10.0%)	3.56 (1.27–10.0)
Missing[2]	367	41 (11.2%)	
Total	5,541	652 (11.8%)	4.34 (3.99–4.73)
pM			
pM0	4,213	484 (11.5%)	4.20 (3.81–4.62)
pM1	32	7 (21.9%)	9.04 (3.91–20.9)
pMX	772	109 (14.1%)	5.29 (4.32–6.48)
Missing[2]	5,24	52 (9.9%)	
Total	5,541	652 (11.8%)	4.41 (4.04–4.80)

[1]Symptoms include women, radiographer reported or both.
[2]Missing cases here are those referred for further assessment but with missing histological confirmation.
Abbreviations: pN: regional lymph nodes; pN0: no regional lymph node metastasis; pN1+: metastasis with ipsilateral lymph nodes; pNX: regional lymph nodes cannot be assessed; pM: distant metastases; pM0: no distant metastases; pM1: distant metastases; pMX: distant metastases cannot be assessed.

less than 20 mm in size compared to our study, 18.8% versus 69.3%, respectively. The high proportion of invasive cancers of small size highlights the importance of organized screening program where tumors can be detected at early stage of disease. Similarly, other studies have found quite significant difference in tumors characteristics between screen detected and clinical breast cancer cases.[25–29] A study by Miller et al.[5] among women with annual screening in age 40–59 found that 68% of the palpable cancers had a mean tumor size of 21 mm, which is significantly higher than in our study. The probability of detecting invasive tumors with poor differentiation (high grade) was significantly higher in those who reported symptom at screen compared to those with no symptom.

To the best of our knowledge, our study is the largest study done on breast cancer symptoms, either self-reported or radiographer reported, and breast cancer risk at screen. Our findings reinforce the importance of evaluating symptoms as a predictor of breast cancer and warrant extra consideration while evaluating mammograms of women with symptoms. Also, continual maintaining of the information about symptoms at screening visits is useful for the clinician as well as for epidemiological research.

This study was limited to those women who attended screening and the size of breast tumors was generally small. Thus, the sensitivity and specificity of diagnosing breast tumors based on symptoms were limited. Also, breast cancer cases detected outside screening were not included. It may be that women with symptoms also had other risk factors (like dense breasts or positive family history) which might confound the observed effect. A potential limitation of this cross-sectional study is the lack of descriptive information other than age so no adjustment for confounders such as breast density, family history of breast cancer or number of previous screens was possible in the multivariate analysis. The study was cross-sectional and no follow-up or subsequent round of screening was included. There was a possibility that knowing the symptom status may have already influenced the radiology result. Given the low sensitivity of symptoms in our study it is likely that a prevention program based on clinical examination would not provide sufficient benefit for breast cancer control in Finland and the mammography screening program is still justified. The study provides limited evidence that reporting symptoms at screen was associated with aggressive tumors, *i.e.*, tumors with poor prognosis. This study cannot say about the impact in low resource setting with currently no breast cancer screening services. However, considering the higher risk of breast cancer in women with symptoms, clinical breast examination together with the availability of diagnostic services could help in detecting large size tumors. Importance of breast cancer symptoms in the cancer prevention and control strategy needs to be evaluated also in other settings.

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