Bodyweight and other correlates of symptom detected breast cancers in a population offered screening

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ABSTRACT

Objective To determine factors associated with symptom detected breast cancers in a population offered screening.

Methods We interviewed 1,459 Australian women aged 40–69, 946 with symptom detected and 513 with mammogram detected invasive breast cancers ≥1.1 cm in diameter, about their personal, mammogram and breast histories before diagnosis and reviewed medical records for tumour characteristics and mammogram dates, calculating ORs and 95% confidence intervals (CIs) for symptom- vs mammogram-detected cancers in logistic regression models.

Results Lack of regular mammograms (<2 mammograms in the 4.5 years before diagnosis) was the strongest correlate of symptom detected breast cancer (OR=3.04 for irregular or no mammograms). In women who had regular mammograms (≥2 mammograms in the 4.5 years before diagnosis), the independent correlates of symptom detected cancers were low BMI (OR <25kg/m^2 vs ≥30kg/m^2=2.18, 95% CI 1.23-3.84; p=0.008), increased breast density (available in 498 women) (OR highest quarter vs lowest =3.50, 95% CI 1.76-6.97; p_{trend}=0.004), high grade cancer and a larger cancer (each p<0.01). In women who did not have regular mammograms, the independent correlates were age <50 years, a first cancer and a ≥2cm cancer. Smoking appeared to modify the association of symptom detected cancer with low BMI (higher ORs for low BMI in current smokers) and estrogen receptor (ER) status (higher ORs for low BMI in ER− cancers).

Conclusion Women with low BMI may benefit from a tailored approach to breast cancer detection, particularly if they smoke.

INTRODUCTION

Most breast cancers are detected following the appearance of symptoms or signs [1,2] despite the ability of organised mammography screening to detect breast cancers when they are small [3]. Organised screening programs target women at highest risk for breast cancer and, typically, more than half the women in targeted age groups accept screening. In 2002-2003, 56.1% of Australian women aged 50-69 years participated in an organised screening program, BreastScreen Australia [4]. However, many breast cancers diagnosed in women who are screened regularly are not screen detected [5,6]. We estimated from BreastScreen Australia data for 1997 [7] and 2000-2004 data from the New South Wales and Queensland Cancer Registries (personal communication) that symptom detected breast cancers made up some 46-50% of all breast cancers of any size in Australian women 50-69 years in 2002-2003.

Symptom detected breast cancers are under-researched despite their common occurrence in populations offered mammographic screening. Interval cancers in screened women are usually characterised as larger and having less favourable pathology characteristics than screen-detected breast cancers [8], but little is otherwise known about symptom detected breast cancers. We sought, therefore, to identify characteristics of women, their cancers and their health services that distinguished between symptom detected breast cancers and mammogram detected cancers in a population offered screening [3]. Our study includes a population-based sample of women who were diagnosed with breast cancer in 2002-2003 in Australia where biennial screening mammography is offered free of charge to women 50-69 years of age.

MATERIALS AND METHODS

Study population

Eligible women were 20-69 years of age and newly notified to cancer registries in three Australian states (New South Wales, Victoria and Queensland) with a first primary invasive breast cancer 1.1cm or larger diagnosed between March 2002 and December 2003. The study was designed principally to identify factors other than lack of mammographic screening that might contribute to diagnosis with a large breast cancer [9]. It excluded tumors <1.1cm, which we estimated to be about 20% of breast cancers diagnosed in Australia and 60% of breast cancers detected in women 50-69 years by the national, publicly-funded screening program, BreastScreen Australia, in 1997 [7]. We have already reported on correlates of diagnosis with a larger breast cancer, by comparing breast cancers ≥2cm with those 1.1-1.9cm in diameter [9].

BreastScreen Australia offers biennial mammograms as the sole screening modality to women aged 50-69; women aged 40-49 or 70+ years are also able to attend. Private radiology practices also provide screening mammograms, the cost of which is usually reimbursed by the national health insurance scheme (Medicare). This analysis was limited to 1,459 women aged 40-69 years of age.

Women were recruited by state cancer registries asking doctors for their agreement to us inviting women to participate. Women participated by completing a self-administered questionnaire and a computer-assisted telephone interview (CATI), and by giving written consent for the study to obtain basic information and pathology characteristics of their breast cancers from cancer registry records and mammogram dates from medical records. The study was approved by the cancer registries' ethics committees and those of the investigators' host institutions. Most participating women (90%) were interviewed within 12 months of diagnosis; on average, interviews were completed 7.5 months after diagnosis (range 2.1 to 20.4 months). The study procedures have been described in detail elsewhere [9].

Data collection

Breast cancer size and diagnosis date were extracted from cancer registry records and verified in pathology reports. Reproductive history (birth years of children, menopause status), use of oral contraceptives (OCs) and hormone replacement therapy (HRT), and history of all mammograms in the 5 years before diagnosis (including date, place and provider) were collected in the self-administered questionnaire. We sought to confirm dates of mammograms in BreastScreen Australia records from 1990 and in Medicare records from 1996 and used this information to construct a mammogram history for each woman. Based on the observed pattern of mammograms before surgical treatment of breast cancer, we defined the *diagnosis mammogram* as the earliest mammogram, in the 84 days before histopathological diagnosis of the breast cancer, that detected the cancer or contributed to its diagnosis. All preceding mammograms were classified as *pre-diagnosis* mammograms. Under a biennial screening policy, two screening mammograms should have been done in the 4.5 years before diagnosis of breast cancer. Thus two or more mammograms in this period were considered to indicate that a woman was having *regular mammograms*, fewer than this were considered to indicate *no regular mammograms*. Percent mammographic density was measured in a subset of 665 women who attended BreastScreen Australia and had a mammogram before the diagnosis mammogram. Mammograms were randomised into reading sets of approximately 100 and measured by a single reader (JS) using a computer-thresholding technique [10] and blinded to all identifying information. A 10% random sample of mammograms was repeated in each set and between every third set to test reliability of the measurement.

The CATI began with the question "*How was your breast cancer first discovered?"* in response to which women identified one of two methods of detection: a breast change (symptom), including presence of a breast lump, was noticed by the woman, her partner, or a doctor (a *symptom detected* breast cancer), or the cancer was detected by screening mammography (a *mammogram detected* breast cancer).

The CATI also asked for weight, height, history of breast changes before diagnosis, family history of breast cancer, personal history of other cancers, residence at diagnosis, education, employment, marital status, health insurance, use of health care, breast checks by self or a doctor in the 2 years before the events that led to diagnosis, and smoking and alcohol use. All women were considered to be postmenopausal if they had undergone natural menopause (menstruation cessation) or had ovaries removed. Natural and surgical menopause were combined for analysis. Age at menopause was imputed for women who reported a hysterectomy, based on predictor variables of age at natural menopause [11] in women in our study. HRT use was assigned as current for women who said they were taking HRT at the time of diagnosis and past if they had stopped. We used WHO categories for body mass index (BMI): <25 (underweight, normal), 25-29 (overweight) and $\geq 30 kg/m^2$ (obese) [12]. Pathology characteristics (cancer type, size, grade, estrogen receptor (ER) status, cancer in lymph nodes) were abstracted from pathology reports and are included in these analyses as possible indicators of the behavior of breast cancers in the pre-detection phase. Categories used for variables are given in the relevant results tables.

Statistical analysis

We examined the association of characteristics of the women and characteristics of the cancer with detection as a result of symptoms (*symptom detection*), relative to *mammogram detection*, and calculated odds ratios (ORs) and 95% confidence intervals (CIs) in logistic regression models adjusted for age at diagnosis in 5 year age groups and state of residence (New South Wales, Victoria, Queensland). Women who had regular mammograms before diagnosis and those who did not were analysed separately. Variables with p for heterogeneity <0.1 in single variable analyses in either group of women were selected as candidate variables for inclusion in multivariable analyses. Age, state of residence and menopausal status were included in all models regardless of p value. HRT use was analysed only in postmenopausal women.

The final multivariable model in each group of women was also used to examine ORs relating BMI to detection method in additional analyses stratified by smoking and cancer characteristics: size, grade, and ER status. We also did analyses of the associations of BMI and age with detection method stratified by ER status. To assist in evaluating the presence of effect modification in each of these instances, a cross product term was added to the logistic regression model and a *p* value for interaction calculated using the Wald test to compare the model with main effects only with a model with main effects and the cross product term. SAS software version 9.1 was used for the statistical analyses.

RESULTS

The women included in these analyses were aged 40-69 years (1,459 women); 460 were 40-49 (32%) and 999 were 50-69 years of age (68%). For a more detailed description of participants, see Kricker et al [9]. The initial study included 1,602 women with breast cancer (79% of 2,024 ascertained) who were 22–69 years of age and residents of NSW (38%), Victoria (34%), and Queensland (28%). By design, all women had breast cancers that were 1.1 cm or larger.

Most breast cancers were symptom detected (65%, 946/1459), more commonly in women 40-49 (86%) than 50-69 (55%) years of age, and most symptom detected cancers (61%, 574 of 946) were in women who did not have regular mammograms. The frequency of symptom detected cancers was higher in women with no regular mammograms (82%) than regular mammograms (49%) (OR=3.04, 95% CI 2.33-3.98; p value <0.001, associated with no regular mammograms); thus lack of regular mammograms before diagnosis was the strongest risk factor for a symptom detected cancer. Given the dominance of this risk factor, our analyses examine the correlates of symptom detected breast cancers separately in women who had regular mammograms and women who had irregular or no mammograms before their diagnosis of breast cancer.

We first analysed the correlates of symptom detected cancers in 748 women 40-69 years who had regular mammograms before diagnosis. Almost all of the symptom-detected breast cancers (92%) were diagnosed within two years of the last screening mammogram. Being 40-49 years of age was the strongest correlate of symptom detected breast cancers in these women: the

ORs fell with age from OR=2.51 at 40-49 to OR=0.71 at 65-69 years (Table 1). Postmenopausal women had a somewhat lower odds for symptom detection than premenopausal women (OR=0.69; p=0.21). The OR for symptom detected breast cancer was also increased with a low BMI (OR for <25 kg/m^2=2.00), any history of breast changes in the years before diagnosis (OR=1.54), and with cancers that were larger (OR for 3+cm=7.88, relative to 1-1.9cm; 73% of the mammogram detected cancers were 1.1-1.9cm), high grade (OR=3.89), node positive (OR for 3+ nodes=4.38) and ER− (OR=2.45) (all p<0.001). In 619 postmenopausal women, the OR for symptom detection with current HRT use was 1.81 (p value 0.004; Table 1). Models for each variable in these analyses were adjusted for age and state.

We constructed a multivariable model in women who had had regular mammograms before diagnosis to include all variables with p<0.1 in these women (see Table 1) and in women who had irregular or no mammograms before diagnosis(Table 3). The variables examined were age, BMI, whether a first cancer, regular breast examination by a doctor, reporting a breast change in the years before diagnosis, smoking, cancer size and grade, nodal status and ER status, and menopause status and state of residence as potential confounders. BMI <25kg/m^2, any history of breast changes, higher grade, larger size, positive lymph nodes, and HRT use in postmenopausal women were each independently associated with symptom detected cancers (Table 1; p≤0.05 in each case). Age was inconsistently associated with symptom detection in this model (p=0.51) and the positive association with ER− status was substantially attenuated, mainly because of confounding with cancer grade. Postmenopausal women's current use of HRT increased the odds of symptom detection for smaller cancers, OR for 1.1-1.9cm=3.77 (95% CI 2.02-7.03), but not larger cancers, OR for ≥2cm=0.52 (95% CI 0.24-1.11) (p for interaction=0.002).

We fitted the same multivariable model in 665 women who were aged 50-69 years, the target age for women invited to attend BreastScreen Australia, and had regular mammograms before diagnosis. The ORs for all variables were very similar to those in all women.

Mammographic density was available for 698 women 40-69 years of age. Increasing density increased the odds of symptom detection in all women when modeled with age, personal and cancer characteristics. Relative to the lowest quarter (Q1), the ORs were: Q2=1.4, 95% CI 0.89-2.42, Q3=1.87, 95% CI 1.11-3.16, Q4=2.52 95% CI 1.47-4.32 (p=0.008). In the 498 women who had regular mammograms, low BMI, a history of any breast change (each OR ~2.0), current smoking, greater breast density, larger cancer size, higher grade (each OR 3.0 or greater) were independently associated with symptom detection (Table 2). In a similar model limited to postmenopausal women who had regular mammograms, current HRT use increased the OR for symptom detected cancers (OR=1.67, 95% CI 0.93-2.99; p value 0.22).

We next analysed the correlates of symptom detected cancers in the 696 women who did not have regular mammograms before diagnosis; 68% of these women had one mammogram in the 4.5 years before diagnosis and the others had none. In a multivariable model similar to that described above, fully adjusted ORs for a symptom detected breast cancer in women who had no regular mammograms were increased only for being 40-49 years of age (OR=2.96 at 40-44 and 2.10 at 45-49 years), having a first cancer (OR=2.23), larger cancer size (OR=2.26 for 2.0-2.9 and OR=2.22 for 3+ cm) and high cancer grade (OR=2.08) (Table 3; $p \leq 0.05$ in each case). There were too few women with mammographic density measurements (193) to include density in a fully adjusted model. However, there was only weak evidence that density was associated with symptom detected cancer in these women when adjusted only for age and state of residence: OR for Q2=1.11, 95% CI 0.44-2.79, Q3=1.91, 95% CI 0.75-4.83, Q4=1.85, 95% CI 0.76-4.52; p_{trend}=0.11.

We also fitted the fully adjusted model separately in women aged 40-49 and 50-69 years who had irregular or no mammograms before diagnosis. In 321 women 50-69 years, only cancer size and estrogen receptor status were independently associated with symptom detected cancers: the OR was OR=3.42 (95% CI 1.38-8.45) for 3cm+ cancers (*p* value for model <0.001) and OR=2.50 (95% CI 1.11-5.66) for ER− cancers (*p* value for model=0.03). The OR for high grade fell to OR=1.54 (95% CI 0.65-3.62; *p* value for model=0.67) and the association with being a first cancer weakened (OR=1.75, *p*=0.31). To examine these same factors in women 40-49 years, who had only 35 mammogram-detected cancers, we re-categorised most as dichotomous variables. The ORs were increased for high grade (OR=3.45, 95% CI 1.29-9.22; *p*=0.01) relative to low or intermediate grade cancers, and for being a first cancer (OR=4.20, 95% CI 1.20-14.67; p=0.02). The OR in women aged 40-44 was OR=1.96 (95% CI 0.88-4.34), relative to 45-59 years, but the *p* value was 0.10.

Other personal (SES, marital status, education, country of birth, cancer type), and health or behavioral characteristics examined (employment, urban or rural residence, parity, OC use, breast cancer in 1^{st} degree relative, health insurance status, alcohol use) had ORs for a symptom detected cancer of between 0.62 and 1.36 and *p* values >0.1. Each variable was examined separately in each group of women, those who had regular mammograms and those who did not, in a model adjusted for age and state of residence (results not shown).

Smoking appeared to modify the association of BMI with symptom detected cancers in all 1,459 women 40-69 years. The fully adjusted OR for a symptom detected cancer with BMI $<25kg/m^2$ relative to $25+kg/m^2$ was 5.86 (95% CI 1.68-20.48) in current smokers and OR=1.68 (95% CI 1.27-2.22) in former or non-smokers (*p* for interaction=0.04). This observation was similar in women who did not have regular mammograms (*p* for interaction=0.07). There were only 45 current smokers in women who had regular mammograms, and so the OR for a symptom detected cancer with BMI $<25kg/m^2$ in current smokers was estimated with adjustment for age and state only, OR=44.44 (95% CI 4.33-456.54). The fully adjusted OR for a symptom detected cancer with BMI <25kg/m^2 in non- or former smokers was 2.48 (95% CI 1.73-3.57). The association of symptom detected breast cancers with BMI did not vary across categories of cancer size or grade or HRT use in postmenopausal women.

The average cancer size in our study tended to be smaller in low BMI women, 1.99cm in those with regular mammograms before diagnosis and 2.25cm with irregular or no mammograms, than in those with higher BMI, 2.17cm with regular mammograms and 2.62cm with irregular or no mammograms (p <0.05 in each case). The proportions with high grade lesions, cancer in the nodes, and ER− cancers, however, did not vary by BMI.

Although the association of estrogen receptor status with symptom detected cancers was weakened in the fully adjusted models due to confounding with cancer grade, we explored its relationship with BMI because of evidence elsewhere that estrogen receptor status modifies the association of BMI with breast cancer risk [13]. In women who had regular mammograms the OR was higher for symptom detected cancers with BMI <25 kg/m^2 in ER− cancers (OR=6.60, 95% CI 2.45-17.79) than in ER+ cancers (OR=2.00, 95% CI 1.33-3.01; p for interaction=0.01) (Table 4). In women who had irregular or no mammograms, it was also higher in ER− cancers (OR=4.18, 95% CI 1.12-15.61) than in ER+ cancers (OR=0.83, 95% CI 0.50-1.38) (p for interaction 0.11).

DISCUSSION

As would reasonably be expected, not having regular mammograms was the strongest predictor of a symptom detected breast cancer in women 40-69 years of age. In women who were diagnosed with breast cancer and had regular mammograms before diagnosis, the breast cancer was more likely to have been detected following symptoms than a screening mammogram when there was a low BMI, greater breast density, current HRT use, a history of breast changes, a ≥2cm or higher grade breast cancer and nodal metastases at diagnosis.

However, HRT was not associated with symptom detection when breast density was included in the statistical model in a subset of women with density measurements. Only younger age, being a first cancer, and a ≥2cm breast cancer were independently associated with a symptom detected breast cancer in women who did not have regular mammograms. Smoking and estrogen receptor status appeared to modify the association of a low BMI with symptom detected breast cancers in both groups of women, the association being stronger in current smokers than former or non-smokers and in women with ER− cancers than ER+ cancers.

In women who had regular mammograms, almost all of the symptom-detected breast cancers were diagnosed within two years of the last screening mammogram, that is, they were interval cancers. This was probably due, in part at least, to the fact they were high grade and therefore faster growing cancers [14]. It is also contributed to by BreastScreen Australia's comparatively low program sensitivity (71.7% for second or later screening rounds in 2000-2002 [15]) and the possibility that the sensitivity of private screening mammography is less than in organised screening [16].

The association of symptom detected breast cancers with low BMI that we observed in women who had regular mammograms is consistent with more ready mammographic detection of breast cancer in heavier women [17,18], probably because fatty breasts are more radiolucent [18-20]. Reduced mammographic sensitivity may be part of the explanation, although only small differences in mammographic sensitivity have been reported between BMI categories (85.7% for BMI $<25 kg/m^2$, 91.0% for BMI $\geq 25 kg/m^2$[21]). Greater symptom detection of breast cancer in women with low BMI might also reflect easier palpability of breast lumps in lean women [22], which is consistent with the greater frequency of interval cancers in normal weight than overweight postmenopausal women [23-25] and as breast density increases [25]. Mammographic density was inversely correlated with BMI in our study, an association consistently reported by others [26-28], especially in women with breast cancer [29]. The smaller average size of symptom detected cancers in women with a low BMI may also indicate easier and earlier diagnosis of breast cancer in lean women, as Willett et al have suggested [30].

Having low estrogen activity is more probable for a woman with low BMI than high BMI [31], and could be part of the reason that women with low BMI were more likely to have ER− cancers than ER+ cancers detected symptomatically. Rather than greater detectability of ER− cancers in thinner women though, this association probably reflects more rapid growth of ER+ cancers in overweight or obese women. As de Waard put it: “ER+ cancer cells thrive and multiply in fat women” and “find no stimulus for multiplication” in lean postmenopausal women [23]. The stronger association of low BMI with symptom detected ER– than ER + cancers may also be due to less effective mammogram detection of ER– breast cancers [32-34].

A low BMI was more strongly associated with symptom detection in current smokers (OR=5.02) than in non- or former smokers (OR=1.60). Current smokers have been reported to have less dense breasts than former or non-smokers (absolute mammographic density percentages around 3-7% lower) [35-37], although we did not observe this in our study. Current smokers have also been recently reported to have higher levels of sex hormone binding globulin (SHBG) and free estradiol than former or non-smokers, with the former greater in lean women and the latter in overweight women [38]. The combination of high SHBG levels due to smoking with the high levels already present in lean women [39] would be expected to further reduce estrogen activity in lean women. If anything this might be expected to reduce the likelihood of symptom detected breast cancer in lean women rather than increase it. Thus we cannot readily explain the apparently strong modification by smoking of the association of low BMI with symptom detected breast cancer.

That current HRT users who had regular mammograms were more likely to have symptom detected cancers was consistent with HRT reducing both the sensitivity and specificity of mammography [21,40]. The increased likelihood that smaller breast cancers were symptom detected in current HRT users is consistent with reduced effectiveness of mammography in denser breast tissue. Current HRT use was much more common in low (46%) than high BMI postmenopausal women (32%; $p < 0.001$), and could have further increased breast density in low BMI women.

A history of a breast change, 73% of which were breast lumps, was more common in women 50-59 years (57%) than 40-49 (50%) or 60-69 (46%) (p=0.02) and in women who had regular mammograms (54%) than women who did not (49%) (p=0.07). These observations suggest that women having regular mammograms may be more breast aware than women who do not, that they know the normal look and feel of their breasts. Breast awareness is recommended by cancer organisations (see, eg, http://canceraustralia.nbocc.org.au/view-document-details/cwwb-breast-cancer-won-t-wait; http://www.cancerscreening.nhs.uk/breastscreen/breastawareness.html), even when women are having regular mammograms. Breast awareness may increase the detection of benign breast changes and of symptoms of breast cancer, thus making symptom detected breast cancer more likely and explaining the link we observed between previous breast changes and symptom detection in women having regular mammograms.

Mammographic density was another factor independently associated with symptom detected breast cancers in women who had regular mammograms in our study, consistent with greater density reducing mammographic sensitivity [25,41,42]. Increasing density is also associated with increasing cancer size [41] and inversely with grade in interval cancers (ie, detected symptomatically) [43,44]. There was, however, no such correlation between grade and density in symptom detected cancers in our study. The ORs for mammographic density in our study changed only minimally when adjusted for BMI, age, cancer size and grade (see Table 2) and all except age remained independently associated with symptom detected breast cancers. Density, BMI and cancer size and grade appear to influence symptom detection of breast cancer independently of one another.

The higher frequency of symptom detected cancers in women in their forties in our study is likely to be a consequence of the primary targeting of screening in BreastScreen Australia to women 50-69 years of age. In 2002-2003, BreastScreen Australia detected 15% of all breast cancers in women 40–49 years (675 of 4453), who are not in the target age range but may attend, and 44% of all breast cancers in women 50-69 (5227 of 11760) [4,45]. Interestingly, the relatively greater OR for symptom detection in women 40-49 years who had regular mammograms was limited to ER+ cancers (OR=2.86 in ER+ vs OR=1.73 in ER− cancers); this was also evident in women who had irregular or no mammograms (OR=4.62 in ER+ vs OR=0.52 in ER− cancers) (Table 3). These observations suggest that higher estrogen levels in younger women increase the probability of symptom detected breast cancers.

Our finding that symptom detected breast cancers in women with regular mammograms were more commonly high grade is consistent with previous observations [8,32,46,47]. That low grade cancers were more often mammogram-detected, as we and others have found [8,32,46,47], is consistent with the presumed longer mean sojourn time for low grade cancers.

The strengths of this study are its population base and the rigor with which we sought to document the antecedents of and pathway to diagnosis of breast cancer. Women told us whether a routine mammogram or noticing a breast change led to detection of their breast cancer: 10% of women declare breast symptoms at a screening visit [48]. We had comprehensive information on dates of mammograms and confirmed the dates for all but 6% of women. Women’s recall of the number and calendar period of mammograms in the past 2 years agreed well with breast screening records. In addition, we had data on personal characteristics, risk factors for breast cancer and breast symptoms to analyse as covariates; all were self-reported.

Lack of regular screening mammograms was the strongest correlate of symptom detected breast cancers. Of several other potentially important correlates of these cancers, low BMI was arguably the strongest in women who had regular mammograms and its association with symptom detection did not appear to be explained by any of the other variables measured. Tailored approaches to increase cancer detection could be considered in women of low BMI and women who smoke, for whom the likelihood of symptom detection is increased. It has been suggested that the likelihood of symptom detection in women with regular mammograms might be reduced if women more likely to have poor screening outcomes, such as women with high breast density, were identified (see, for example Kavanagh et al [41] and Schousboe [49]). In addition, given our findings, a tailored approach to increasing cancer detection might be considered in women of low BMI and women who smoke. It is possible, for example, that women of low BMI would benefit from receiving expert breast examination in addition to mammography screening, particularly if they also smoke. The apparent lack of effectiveness of addition of mammography to clinical breast examination in one Canadian screening trial has been taken to suggest that clinical breast examination is a useful alternative screening modality [3].

No ready intervention is available to address greater estrogen activity in younger women if it contributes to their higher frequency of symptom detected breast cancers. Regular screening for women 40-49 years is increasingly recommended. The US Preventive Services Task Force, however, did not recommend universal screening of women 40-49 years on the basis that the reduction in breast cancer mortality by starting screening mammography at age 40 may be only about 15% [50] and that earlier screening involves important harms [51].

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Table 1. Associations of personal, health and cancer characteristics with symptom detection of breast cancer relative to mammogram detection in 748 women aged 40-69 years who had regular mammograms

			Odds ratios for symptom detected cancers	
			Adjusted for age and state	Fully adjusted
Characteristic	Mammogram detected *n*=382	Symptom detected *n*=366	OR[a] (95% CI) *p* value	OR[b] (95% CI) *p* value
Age				
40-44	6	13	2.51 (0.92-6.88)	1.81 (0.48-6.81)
45-49	21	43	2.49 (1.37-4.50)	1.61 (0.68-3.81)
50-54	68	76	1.28 (0.83-1.96)	0.84 (0.49-1.44)
55-59	112	99	1.0	1.0
60-64	96	84	0.99 (0.66-1.47)	1.15 (0.72-1.83)
65-69	79	51	0.71 (0.46-1.11)	0.94 (0.56-1.58)
			p=0.002	p=0.51
BMI				
30+ kg/m^2	116	78	1.0	1.0
25-29 kg/m^2	133	95	1.01 (0.68-1.50)	1.17 (0.74-1.86)
<25 kg kg/m^2	130	193	2.00 (1.39-2.90)	2.96 (1.90-4.61)
			p_{trend}<0.001	p <0.001
Menopausal status				
premenopausal	45	81	1.0	1.0
postmenopausal	337	285	0.69 (0.38-1.23)	0.60 (0.31-1.17)
			p=0.21	p=0.13
1st cancer of any kind				
no	43	33	1.0	1.0
yes	336	333	1.15 (0.71-1.87)	1.23 (0.71-2.14)
			p=0.57	p=0.46
Regular breast exam by Dr				
yes	238	233	1.0	1.0
no	144	133	1.03 (0.76-1.40)	1.01 (0.71-1.44)
			p=0.83	p=0.95
Breast change (any time)				
none	195	147	1.0	1.0
any	187	219	1.54 (1.14-2.07)	1.73 (1.23-2.44)
			p=0.005	p=0.002
Smoking				
never	226	203	1.0	1.0
former	138	136	1.04 (0.77-1.42)	1.14 (0.80-1.63)
current	18	27	1.73 (0.91-3.26)	2.02 (0.98-4.16)
			p=0.24	p=0.15
Cancer characteristic				
Cancer size				
1.1-1.4cm	158	73	1.0	1.0
1.5-1.9cm	133	89	1.52 (1.02-2.26)	1.52 (0.99-2.34)
2.0-2.9cm	65	112	3.81 (2.50-5.81)	3.13 (1.96-5.01)

			Odds ratios for symptom detected cancers	
			Adjusted for age and state	Fully adjusted
Characteristic	Mammogram detected n=382	Symptom detected n=366	OR[a] (95% CI) *p* value	OR[b] (95% CI) *p* value
3.0+cm	26	92	7.88 (4.66-13.33) <0.001	6.55 (3.58-11.96) <0.001
Grade				
low	100	50	1.0	1.0
moderate	183	139	1.49 (0.99-2.25)	0.95 (0.60-1.50)
high	86	172	3.89 (2.52-6.00)	2.41 (1.41-4.10)
not reported	13	5	0.69 (0.22-2.12)	0.58 (0.17-1.95)
			p_{trend}<0.001	*p*<0.001
Lymph nodes positive				
none	226	158	1.0	1.0
1-2	76	91	1.65 (1.13-2.39)	1.23 (0.81-1.88)
3 or more	29	85	4.38 (2.72-7.05)	2.40 (1.39-4.16)
not reported	51	32	0.95 (0.57-1.56)	1.05 (0.61-1.83)
			p_{trend} <0.001	*p*=0.02
ER status				
positive	311	250	1.0	1.0
negative	52	102	2.45 (1.68-3.58)	1.17 (0.72-1.90)
not reported	19	14	0.82 (0.40-1.71)	0.77 (0.33-1.78)
			p<0.001	*p*=0.65
Postmenopausal women only				
HRT use[c]				
never	118	79	1.0	1.0
former	93	66	1.11 (0.72-1.71)	0.96 (0.57-1.60)
current	123	140	1.81 (1.24-2.66)	1.80 (1.15-2.83)
			p=0.004	*p*=0.008

Regular mammograms were defined as two at intervals of 2 years or three at intervals of 1 year in the 4.5 years before diagnosis.

[a] Adjusted for age and state of residence; *p* for trend calculated on categories excluding 'not reported'.

[b] Adjusted for age, state of residence and all other variables in the Table except HRT

[c] Estimates calculated in 619 postmenopausal women (N= 334 mammogram detected, N=285 symptom detected); fully adjusted model includes all other variables in the Table.

Table 2. Associations of personal, health and cancer characteristics with symptom detection of breast cancer relative to mammogram detection in 497 women with breast density who had regular mammograms.

			Odds ratios for symptom detected cancers	
			Adjusted for age and state	Fully adjusted
Characteristic	Mammogram detected *n*=257	Symptom detected *n*=240	OR[a] (95% CI) *p* value	OR[b] (95% CI) *p* value
Age				
40-44	3	5	1.52 (0.20-11.35)	1.16 (0.15-9.00)
45-49	12	22	1.28 (0.40-4.03)	1.14 (0.36-3.65)
50-54	45	48	0.68 (0.34-1.34)	0.67 (0.33-1.34)
55-59	80	72	1.0	1.0
60-64	63	56	1.11 (0.63-1.95)	1.33 (0.74-2.39)
65-69	54	37	0.90 (0.48-1.68)	1.15 (0.60-2.19)
			p=0.65	p=0.53
BMI				
30+ kg/m^2	75	54	1.0	1.0
25-29 kg/m^2	91	60	1.23 (0.69-2.18)	1.04 (0.57-1.87)
<25 kg kg/m^2	91	126	3.03 (1.75-5.26)	2.25 (1.27-4.00)
			p<0.001	p=0.003
Menopausal status				
Pre	28	45	1.0	1.0
Post	229	195	0.55 (0.23-1.30)	0.57 (0.24-1.38)
			p=0.17	p=0.21
1[st] cancer of any kind				
no	30	16	1.0	1.0
yes	227	224	1.68 (0.81-3.49)	1.58 (0.75-3.35)
			p=0.17	p=0.23
Regular breast exam by Dr				
	152	146	1.0	1.0
yes	105	94	0.93 (0.61-1.42)	0.97 (0.62-1.50)
no			p=0.72	p=0.88
Breast change (any time)				
none	144	107	1.0	1.0
any	113	133	2.05 (1.34-3.14)	1.92 (1.24-2.98)
			p<0.001	p=0.004
Smoking				
never	152	132	1.0	1.0
former	94	87	1.19 (0.77-1.86)	1.24 (0.79-1.96)
current	11	21	3.09 (1.27-7.50)	3.39 (1.35-8.51)
			p=0.04	p=0.03
Breast density				
Quartile 1	88	35	-	1.0
Quartile 2	71	61	-	1.94 (1.05-3.59)
Quartile 3	60	65	-	2.47 (1.30-4.68)

			Odds ratios for symptom detected cancers	
			Adjusted for age and state	Fully adjusted
Characteristic	Mammogram detected n=257	Symptom detected n=240	OR[a] (95% CI) p value	OR[b] (95% CI) p value
Quartile 4	38	79	-	3.90 (1.97-7.71)
				p=0.001
Cancer characteristic				
Cancer size				
1.1-1.4cm	100	43	1.0	1.0
1.5-1.9cm	87	61	1.63 (0.95-2.79)	1.59 (0.92-2.75)
2.0-2.9cm	51	78	3.10 (1.73-5.54)	2.82 (1.55-5.11)
3.0+cm	19	58	6.93 (3.30-14.55)	6.35 (2.97-13.57)
			p<0.001	p<0.001
Grade				
low	67	33	1.0	1.0
moderate	116	88	1.00 (0.57-1.77)	1.01 (0.57-1.80)
high	64	116	2.74 (1.42-5.28)	2.91 (1.49-5.70)
not reported	10	3	0.41 (0.09-1.91)	0.43 (0.09-2.11)
			p<0.001	p<0.001
Lymph nodes positive				
none	155	108	1.0	1.0
1-2	52	62	1.35 (0.81-2.27)	1.24 (0.73-2.11)
3 or more	19	52	2.72 (1.35-5.47)	2.62 (1.28-5.35)
not reported	31	18	1.10 (0.53-2.29)	1.06 (0.50-2.26)
			p=0.04	p=0.07
ER status				
positive	208	162	1.0	1.0
negative	38	69	1.08 (0.59-1.97)	1.11 (0.60-2.06)
not reported	11	9	1.13 (0.38-3.33)	1.26 (0.41-3.89)
			p=0.95	p=0.88

Regular mammograms were defined as two at intervals of 2 years or three at intervals of 1 year in the 4.5 years before diagnosis.

[a] Adjusted for age and state of residence; *p* for trend calculated on categories excluding 'not reported'.

[b] Adjusted for age, state of residence and all other variables in the Table

Table 3. Associations of personal, health and cancer characteristics with symptom detection of breast cancer relative to mammogram detection in 696 women aged 40-69 years who had no regular mammograms

			Odds ratios for symptom detected cancers	
			adjusted for age and state	fully adjusted
Characteristic	Mammogram detected n=126	Symptom detected n=570	OR[a] (95% CI) p value	OR[b] (95% CI) *p* value
Age				
40-44	14	164	3.37 (1.56-7.26)	2.96 (1.13-7.74)
45-49	24	173	1.99 (1.00-3.98)	2.10 (0.89-4.98)
50-54	41	109	0.73 (0.38-1.41)	0.76 (0.36-1.59)
55-59	17	59	1.0	1.0
60-64	17	38	0.67 (0.30-1.47)	0.69 (0.29-1.64)
65-69	13	27	0.63 (0.27-1.49)	0.52 (0.21-1.31)
			p<0.001	p=0.003
BMI				
30+ kg/m^2	27	124	1.0	1.0
25-29 kg/m^2	36	160	0.91 (0.51-1.60)	0.99 (0.54-1.81)
<25 kg kg/m^2	63	286	0.82 (0.49-1.39)	1.04 (0.59-1.81)
			p=0.75	p=0.98
Menopausal status				
premenopausal	48	333	1.0	1.0
postmenopausal	78	237	0.94 (0.53-1.64)	0.81 (0.44-1.49)
			p=0.81	p=0.50
1st cancer of any kind				
No	13	30	1.0	1.0
Yes	113	540	1.97 (0.96-4.04)	2.23 (1.03-4.84)
			p=0.06	p=0.04
Regular breast exam by Dr				
Yes	71	292	1.0	1.0
No	55	278	1.49 (0.99-2.24)	1.43 (0.92-2.22)
			p=0.06	p=0.11
Breast change (any time)				
none	67	286	1.0	1.0
any	59	284	1.11 (0.74-1.67)	1.15 (0.75-1.76)
			p=0.61	p=0.52
Smoking				
Never	62	294	1.0	1.0
Former	49	188	0.68 (0.44-1.05)	0.73 (0.46-1.16)
Current	15	88	1.26 (0.67-2.36)	1.20 (0.62-2.35)
			p=0.10	p=0.25
Cancer characteristic				
Cancer size				
1.1-1.4cm	36	98	1.0	1.0
1.5-1.9cm	45	128	1.00 (0.58-1.70)	0.92 (0.52-1.64)
2.0-2.9cm	27	196	2.67 (1.49-4.78)	2.26 (1.21-4.20)

			Odds ratios for symptom detected cancers	
			adjusted for age and state	fully adjusted
Characteristic	Mammogram detected n=126	Symptom detected n=570	OR[a] (95% CI) p value	OR[b] (95% CI) *p* value
3.0+cm	18	148	2.99 (1.57-5.69)	2.22 (1.08-4.55)
			p<0.001	*p*=0.003
Grade				
low	30	82	1.0	1.0
moderate	64	235	1.36 (0.81-2.29)	1.31 (0.75-2.27)
high	30	235	2.76 (1.54-4.96)	2.08 (1.08-4.02)
not reported	2	18	3.26 (0.68-15.62)	4.16 (0.79-21.83)
			p=0.003	*p*=0.08
Lymph nodes positive				
none	73	275	1.0	1.0
1-2	31	138	1.22 (0.75-1.98)	1.11 (0.66-1.87)
3 or more	12	118	2.28 (1.17-4.44)	1.53 (0.73-3.17)
not reported	10	39	1.32 (0.61-2.86)	1.58 (0.70-3.59)
			p=0.11	*p*=0.52
ER status				
positive	104	403	1.0	1.0
negative	19	134	1.99 (1.16-3.43)	1.50 (0.81-2.78)
not reported	3	33	2.90 (0.85-9.90)	2.51 (0.69-9.08)
			p=0.01	*p*=0.19
Postmenopausal women only				
HRT use[c]				
never	45	133	1.0	1.0
former	9	36	1.53 (0.67-3.47)	1.93 (0.77-4.83)
current	24	68	1.07 (0.59-1.93)	1.21 (0.61-2.39)
			p=0.60	*p*=0.36

Women in this table had 1 or no mammogram in the 4.5 years before diagnosis

[a] Adjusted for age and state of residence; *p*-trend calculated on categories excluding 'not reported'.

[b] Adjusted for age, state of residence and all other variables in the Table except HRT.

[c] Estimates calculated in 315 postmenopausal women (N= 78 mammogram detected, N=237 symptom detected); fully adjusted model includes all other variables in the Table

Table 4 Associations of BMI and age, with symptom detection of breast cancer, relative to mammogram detection, stratified by estrogen receptor status.

		regular mammograms *n*=714[a]			no regular mammograms *n*=661[a]		
ER status	factor	Mammogram detected	Symptom detected	OR[b] (95% CI)	Mammogram detected	Symptom detected	OR[b] (95% CI)
	BMI						
ER+	25+kg/m^2	197	123	1.0	48	198	1.0
	<25kg/m^2	112	127	2.00 (1.33-3.01)	56	205	0.83 (0.50-1.38)
ER−	25+kg/m^2	38	43	1.0	13	68	1.0
	<25kg/m^2	13	59	6.60 (2.45-17.79)	6	66	4.18 (1.12-15.61)
				p interaction 0.01			*p* interaction 0.11
	Age						
ER+	50-69	291	207	1.0	75	154	1.0
	40-49	18	43	2.75 (1.20-6.34)	29	249	3.95 (2.07-7.54)
ER−	50-69	45	92	1.0	11	63	1.0
	40-49	6	10	0.56 (0.09-3.58)	8	71	0.48 (0.10-2.38)
				p interaction 0.02			*p* interaction 0.12

Regular mammograms: two at intervals of 2 years or three at intervals of 1 year in the 4.5 years before diagnosis.
No regular mammograms: 1 or no mammogram in the 4.5 years before diagnosis
[a] numbers are: regular mammograms, ER+ 559, ER- 153; no regular mammograms, ER+ 507, ER- 153.
[b] Adjusted for all variables in the multivariate models of Tables 1 and 3.