

## Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study

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### Abstract

**Objectives** To examine how lifestyle, hormonal, and other factors influence the sensitivity and specificity of mammography.

**Methods** Women recruited into the Million Women Study completed a questionnaire about various personal factors before routine mammographic screening. A sample of 122 355 women aged 50-64 years were followed for outcome of screening and incident breast cancer in the next 12 months. Sensitivity and specificity were calculated by using standard definitions, with adjustment for potential confounding factors.

**Results** Breast cancer was diagnosed in 726 (0.6%) women, 629 in screen positive and 97 in screen negative women; 3885 (3.2%) were screen positive but had no subsequent diagnosis of breast cancer. Overall sensitivity was 86.6% and specificity was 96.8%. Three factors had an adverse effect on both measures: use of hormone replacement therapy (sensitivity: 83.0% (95% confidence interval 77.4% to 87.6%), 84.7% (73.9% to 91.6%), and 92.1% (87.6% to 95.0%); specificity: 96.8% (96.6% to 97.0%), 97.8% (97.5% to 98.0%), and 98.1% (98.0% to 98.2%), respectively, for current, past, and never use); previous breast surgery *v* no previous breast surgery (sensitivity: 83.5% (75.7% to 89.1%) *v* 89.4% (86.5% to 91.8%); specificity: 96.2% (95.8% to 96.5%) *v* 97.4% (97.3% to 97.5%), respectively); and body mass index < 25 *v* ≥ 25 (sensitivity: 85.7% (81.2% to 89.3%) *v* 91.0% (87.5% to 93.6%); specificity: 97.2% (97.0% to 97.3%) *v* 97.4% (97.3% to 97.6%), respectively). Neither sensitivity nor specificity varied significantly according to age, family history of breast cancer, parity, past oral contraceptive use, tubal ligation, physical activity, smoking, or alcohol consumption.

**Conclusions** The efficiency, and possibly the effectiveness, of mammographic screening is lower in users of hormone replacement therapy, in women with previous breast surgery, and in thin women compared with other women.

### Introduction

The effectiveness of mammographic screening for breast cancer depends on its ability to detect and to exclude the presence of breast cancer, measured as the sensitivity and specificity of mammography, respectively. Reliable data on how these measures vary between women are lacking. We examined how women's personal characteristics influence the sensitivity and specificity of mammography in a large cohort of women attending the UK NHS breast screening programme.<sup>1 2</sup>

### Methods

#### Recruitment and definitions

At the time of the study, all women aged 50 to 64 years in the United Kingdom who were registered with a general practitioner were invited to attend the NHS breast screening programme for routine mammography about once every three years. Women recruited into the Million Women Study (described in detail elsewhere<sup>3</sup>) who attended screening at 10 breast screening units in England from June 1996 to March 1998 were selected for a special study of the effect of hormone replacement therapy (HRT) on mammographic sensitivity and specificity. The women received a study questionnaire a few weeks before their screening appointment and returned the questionnaire at screening, also giving signed consent for follow up. The questionnaire contained items on lifestyle and sociodemographic factors, reproductive factors, past health, and use of HRT (see [www.millionwomenstudy.org](http://www.millionwomenstudy.org)).

Women were followed up for outcome of mammography (screen positive or screen negative) and for the diagnosis of incident breast cancer in the next 12 months through records from the screening centre and the NHS central register. Women were defined as having screen positive or screen negative results if they were recalled or not recalled for further investigation, respectively, after initial mammography,

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**Table 1** Overall outcome at mammographic screening

Outcome of mammography	Breast cancer*		Total
	Yes	No	
Screen positive	629	3 885	4 514
Screen negative	97	117 744	117 841
Total	726	121 629	122 355

\*Diagnosed at screening or in the 12 months after screening.

according to screening centre records. Women were defined as having breast cancer if they had a histologically confirmed breast cancer (invasive cancer or carcinoma in situ, ICD-10 (international classification of diseases, 10th revision) codes C50 or D05, respectively) at screening or in the 12 months after screening.

**Analysis**

We analysed data from 122 355 women aged 50-64 years who did not report a history of cancer (except non-melanoma skin cancer) at recruitment. We calculated sensitivity as the number of women who were screen positive and had breast cancer detected at screening divided by the total number of women with breast cancer (that is, with cancer detected at screening plus breast cancers not detected at screening but diagnosed in the first 12 months after screening). We calculated specificity as the number of women who were screen negative and did not have breast cancer divided by the total number of women with no breast cancer. We also calculated adjusted values for sensitivity and specificity with logistic regression, adjusting where appropriate for screening centre, age, whether they were likely to have attended screening through the programme before, use of HRT/menopausal status, previous breast surgery, and body mass index. The P values in the tables

refer to the significance of the variable examined in the adjusted model with the likelihood ratio test.

**Results**

Overall, among 122 355 women included in the analyses, 629 (0.51%) had cancer detected at screening, 97 (0.08%) were screen negative but had breast cancer diagnosed in the 12 months after screening, and 3885 (3.2%) were screen positive but did not have breast cancer (table 1). Overall sensitivity of mammography was 86.6% and specificity was 96.8%.

Among women who had never used HRT, we found no significant effect of menopausal status on sensitivity, although specificity was significantly lower in premenopausal and perimenopausal compared with postmenopausal women (see *bmj.com*).<sup>1</sup> We were able to examine screening outcome over a range of ages only among postmenopausal women; in these women neither sensitivity nor specificity was significantly related to age (see *bmj.com*).<sup>1</sup>

Among postmenopausal women, sensitivity varied significantly according to use of HRT (table 2). Sensitivity did not vary significantly between current users of oestrogen only HRT (84.5%, 74.2% to 91.1%) and current users of oestrogen-progestogen HRT (84.1%, 76.9% to 89.4%). Specificity was significantly lower in current and past users compared with never users of HRT (table 2). Specificity did not vary significantly between current users of oestrogen only HRT (96.9%, 96.6% to 97.2%) and current users of oestrogen-progestogen HRT (96.6%, 96.3% to 96.8%).

We examined sensitivity and specificity in relation to nine additional factors: previous breast surgery for con-

**Table 2** Sensitivity and specificity of breast cancer screening mammography according to various characteristics of women attending screening (results for nine other characteristics appear on *bmj.com*)

Characteristic and outcome at mammography	Breast cancer*		Sensitivity			Specificity		
	Yes	No	Crude	Adjusted† (95% CI)	P value‡	Crude	Adjusted† (95% CI)	P value‡
<b>Use of HRT (postmenopausal women only)</b>								
Current user:								
Screen positive	185	1 171	80.8	83.0 (77.4 to 87.6)		96.4	96.8 (96.6 to 97.0)	
Screen negative	44	30 990						
Past user:								
Screen positive	56	355	83.6	84.7 (73.9 to 91.6)	0.01	97.6	97.8 (97.5 to 98.0)	<0.0001
Screen negative	11	14 188						
Never used:								
Screen positive	207	931	91.2	92.1 (87.6 to 95.0)		97.9	98.1 (98.0 to 98.2)	
Screen negative	20	44 050						
<b>Previous breast operation</b>								
No:								
Screen positive	525	3 217	87.6	89.4 (86.5 to 91.8)		97.0	97.4 (97.3 to 97.5)	<0.0001
Screen negative	74	103 114						
Yes:								
Screen positive	100	627	81.3	83.5 (75.7 to 89.1)		95.6	96.2 (95.8 to 96.5)	
Screen negative	23	13 483						
<b>Body mass index</b>								
<25:								
Screen positive	279	1 916	83.8	85.7 (81.2 to 89.3)		96.6	97.2 (97.0 to 97.3)	
Screen negative	54	54 104						
≥25:								
Screen positive	316	1 739	89.8	91.0 (87.5 to 93.6)	0.03	97.0	97.4 (97.3 to 97.6)	0.003
Screen negative	36	57 149						

\*Diagnosed at screening or in the 12 months after screening.

†Adjusted for age, likelihood of previous NHS breast screening programme screening, screening centre, body mass index, previous breast surgery, menopausal status, and use of HRT, when appropriate.

‡For heterogeneity.

ditions other than cancer, family history of breast cancer, parity, use of oral contraceptives, tubal ligation, body mass index, exercise, smoking, and alcohol consumption. Two factors—previous breast surgery and low body mass index—seemed to have an adverse effect on both sensitivity and specificity. Women reporting previous breast surgery for a condition other than breast cancer had a lower sensitivity and specificity compared with women not reporting previous breast surgery (table 2). Women with a body mass index <25 also had a lower sensitivity and specificity compared with women with a body mass index  $\geq$ 25 (table 2). The seven other factors examined had no appreciable effect on either sensitivity or specificity (see bmj.com).

## Discussion

Our results support previous findings that use of HRT reduces both the sensitivity and the specificity of mammography.<sup>4-7</sup> Neither sensitivity nor specificity varied significantly between users of oestrogen only and oestrogen-progestogen HRT. Although previous studies have reported that mammographic sensitivity is lower among younger women,<sup>8-11</sup> confounding with use of HRT and other factors can occur. After accounting for screening history, menopausal status, and use of HRT, we found that age did not have an independent effect on the sensitivity and specificity of mammography.<sup>1</sup> The age range examined here—50 to 64 years—was, however, somewhat limited. Sensitivity did not vary significantly according to menopausal status, though specificity was significantly lower in premenopausal or perimenopausal compared with postmenopausal women. Our findings agree with previous results that showed no significant difference in mammographic sensitivity among women with and without a family history of breast cancer.<sup>8 12 13</sup> Previous studies have not reported on the effect of many other personal factors on overall mammographic effectiveness, and two of the nine factors examined here—previous breast surgery for conditions other than cancer and low body mass index—seemed to have an adverse effect on both sensitivity and specificity.

Women with a relatively high proportion of their mammograms occupied by radiologically dense tissue experience reduced sensitivity and specificity of mammographic screening for breast cancer compared with women with more radiolucent breasts.<sup>7 12-16</sup> Current use of HRT, having had a previous breast operation, and having a low body mass index are all associated with increased mammographic density, which is a plausible explanation for our findings.<sup>7 17 18</sup>

The ultimate aim of mammographic screening is to reduce mortality from breast cancer in a cost effective way, and sensitivity and specificity are proxy measures of its effectiveness and efficiency. Reduced mammographic sensitivity may lessen the benefit conferred by screening. Thus our results suggest that mammography may be less efficient, and possibly less effective at reducing mortality, in users of HRT, in women with previous breast surgery, and in thin women compared with other women.

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## What is already known on this topic

Evidence is limited on how the sensitivity and specificity of mammography vary between women

## What this study adds

Sensitivity and specificity of breast cancer screening were reduced in users of hormone replacement therapy, in women who had had previous breast surgery for conditions other than breast cancer, and in thin women compared with other women

Sensitivity and specificity did not vary significantly according to a woman's age, family history of breast cancer, parity, past oral contraceptive use, tubal ligation, physical activity, smoking, or alcohol consumption

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