Papers

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

Emily Banks, Gillian Reeves, Valerie Beral, Diana Bull, Barbara Crossley, Moya Simmonds, Elizabeth Hilton, Stephen Bailey, Nigel Barrett, Peter Briers, Ruth English, Alan Jackson, Elizabeth Kutt, Janet Lavelle, Linda Rockall, Matthew G Wallis, Mary Wilson, Julietta Patnick

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.[1 2]

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[3]) who attended screening at 10 breast screening units (Avon, Gloucestershire, Hereford-Worcester, Manchester, North Lancashire, Oxfordshire, Portsmouth, Warwickshire-Solihull-Coventry, West London, and West Sussex) 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).

We defined the variables for these analyses, including use of HRT, according to what was reported on the recruitment questionnaire. Women who reported not using HRT and menstruating regularly or irregularly at baseline were defined as premenopausal or perimenopausal, respectively. Women whose periods had ceased either naturally or as the result of a bilateral oophorectomy were defined as postmenopausal. As described previously,[4] we also defined women aged 53 and over who had had a hysterectomy without oophorectomy and women aged 53 and over who had begun use of HRT before their natural menopause as postmenopausal. All women were asked to give the date that they completed the questionnaire and the date of screening was taken to be seven days after this date. (In a sample of 3002 women for whom the date of screening was recorded, the mean time between the date of completing the questionnaire and being screened was 7.5 days, with an interquartile range of 0-12 days.)

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

Table 1 Overall outcome at mammographic screening

Outcome of mammography	Breast cancer*		Total
	Yes	No	
Screen positive	629	3885	4514
Screen negative	97	117 744	117 841
Total	726	121 629	122 355

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

defined as having screen positive or screen negative results if they were recalled or not recalled for further investigation, respectively, after initial mammography, according to screening centre records. Women for whom the films were technically inadequate and needed to be repeated were classified according to the results of their repeat mammogram. 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. Because they were no longer subject to routine surveillance we excluded from the analyses those women who were screen positive and did not have breast cancer diagnosed at the time but were asked to return for repeat screening earlier than the usual three year interval (n = 585).

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. Of these, 6203 (5.1%) were aged 49 or 65 when they underwent screening but were close to their 50th or 65th birthday, as women are invited to screening according to their year of birth, rather than their exact age.

We classified women into one of four groups: screen positive with breast cancer (that is, breast cancer was detected at screening); screen positive and no breast cancer; screen negative with breast cancer (that is, breast cancer was diagnosed in the 12 months after screening but was not detected at screening); and screen negative and no breast cancer. A total of 726 women were diagnosed with breast cancer either at screening or in the subsequent 12 months. Of these, 596 were recorded as having breast cancer detected at screening by the collaborating screening centres, and in 565 (95%) the cancer was histologically confirmed within three months of screening. The 130 remaining women were notified to us by the NHS central register as having breast cancer histologically confirmed within 12 months after screening. A detailed investigation of all available records for 88 of these women indicated that defining women with breast cancer histologically confirmed within three months after screening as having breast cancer detected at screening correctly classified around 99% of the study population. Hence, 33 women with breast cancer histologically confirmed within three months after screening notified only through the NHS central register were defined as having cancer detected at screening. Of the women we defined as having breast cancer not detected at screening, seven had been recalled and, at assessment, were not diagnosed with breast cancer at that screening episode; however, they subsequently had breast cancer diagnosed in the 12 months after mammography.

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 (50-54, 55-59, and 60-64 years), whether they were likely to have attended screening through the programme before,[1] use of HRT/menopausal status (premenopausal or perimenopausal; postmenopausal and never used HRT; postmenopausal and currently using HRT; postmenopausal and

Table 2 Sensitivity and specificity of breast cancer screening mammography by menopausal status and age among women who have never used hormone replacement therapy (HRT)

Characteristic and outcome at mammography	Breast cancer*		Sensitivity			Specificity		
	Yes	No	Crude	Adjusted† (95% CI)	P value‡	Crude	Adjusted† (95% CI)	P value‡
Menopausal status								
Premenopausal:								
Screen positive	39	356	90.7	81.0 (51.5 to 94.5)	0.6	94.6	96.9 (96.4 to 97.2)	<0.0001
Screen negative	4	6 228						
Perimenopausal:								
Screen positive	50	311	94.3	89.5 (66.6 to 97.3)		95.4	97.2 (96.8 to 97.6)	
Screen negative	3	6 521						
Postmenopausal:								
Screen positive	207	931	91.2	90.9 (83.7 to 95.1)		97.9	98.0 (97.8 to 98.1)	
Screen negative	20	44 050						
Age (years)								
50-54§:								
Screen positive	42	321	95.5	89.9 (64.3 to 97.8)	0.6	97.0	98.1 (97.7 to 98.3)	0.4
Screen negative	2	10 518						
55-59§:								
Screen positive	59	263	86.8	85.8 (72.9 to 93.1)		98.2	98.1 (97.9 to 98.4)	
Screen negative	9	14 003						
60-64§:								
Screen positive	106	327	92.2	91.3 (82.6 to 95.8)		98.3	98.3 (98.1 to 98.5)	
Screen negative	9	18 804						

*Diagnosed at screening or in the 12 months after screening.
†Adjusted for age, screening centre, likelihood of previous NHS breast screening programme screening, body mass index, and previous breast surgery, when appropriate
‡For heterogeneity.
§Postmenopausal women only

Table 3 Sensitivity and specificity of breast cancer screening mammography by use of hormone replacement therapy (HRT) among postmenopausal women

Use of HRT and outcome at mammography	Breast cancer*		Sensitivity			Specificity		
	Yes	No	Crude	Adjusted† (95% CI)	P value‡	Crude	Adjusted† (95% CI)	P value§
Current user:								
Screen positive	185	1 171	80.8	83.0 (77.4 to 87.6)	0.01	96.4	96.8 (96.6 to 97.0)	<0.0001
Screen negative	44	30 990						
Past user:								
Screen positive	56	355	83.6	84.7 (73.9 to 91.6)		97.6	97.8 (97.5 to 98.0)	
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						

*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, and previous breast surgery, when appropriate.
‡For heterogeneity.

previously used HRT; other or unknown), previous breast surgery (no, yes, unknown), and body mass index (<25, ≥25, unknown). 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%.

Age, menopausal status, and use of HRT

Among women who attend screening, age, menopausal status, use of HRT, and whether or not a woman has attended for screening before are closely related. Women are typically invited for their first routine screen between the age of 50 and 53 years, and they are more likely to be premenopausal at these ages than at older ages. Furthermore, the prevalence of use of HRT is higher in women in their early 50s, soon after the menopause, than at older ages.[5] To investigate the independent effects of age and menopausal status, we restricted analyses to women who had never used HRT and adjusted for screening history (table 2).[2] We found no significant effect of menopausal status on sensitivity (table 2), although specificity was significantly lower in premenopausal and perimenopausal compared with postmenopausal women (table 2).[1] 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 (table 2).[1]

Among postmenopausal women, sensitivity varied significantly according to use of HRT (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%), respectively, for current, past, and never users, test for heterogeneity P=0.01, table 3). 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 (96.8% (96.6% to 97.0%), 97.8% (97.5% to 98.0%), and 98.1% (98.0% to 98.2%), respectively, P<0.0001, table 3).[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%).

Other personal characteristics

We examined sensitivity and specificity in relation to nine additional factors: previous breast surgery for conditions 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 sensitivity of 83.5% (75.7% to 89.1%) compared with 89.4% (86.5% to 91.8%) for women not reporting previous breast surgery (table 4, P=0.06) and specificities of 96.2% (95.8% to 96.5%) *v* 97.4% (97.3% to 97.5%), respectively (table 4, P<0.0001). Women with a body mass index <25 had a sensitivity of 85.7% (81.2% to 89.3%) compared with 91.0% (87.5% to 93.6%) among women with a body mass index ≥25 (table 4, P=0.03) and specificities of 97.2% (97.0% to 97.3%) and 97.4% (97.3% to 97.6%), respectively (table 4, P=0.003). The seven other factors examined had no appreciable effect on either sensitivity or specificity (table 4).

Discussion

Joint consideration of the sensitivity and specificity

To evaluate the impact of a particular factor on the effectiveness and efficiency of mammographic screening for breast cancer, its effect on both the proportion of cancers detected at screening (measured as sensitivity) and the proportion of women who are screen positive but do not have breast cancer (measured as 100% – specificity) need to be considered together. About a tenth of the women recruited to the Million Women Study were selected for this special investigation of how characteristics of individual women influence mammographic sensitivity and specificity. The sample includes around 70% of the women screened at the 10 participating NHS breast screening centres during the recruitment period for this investigation (May 1996 to March 1998).[3] We prospectively gathered detailed data on sociodemographic, reproductive, lifestyle, and other factors immediately before screening, eliminating potential differential reporting of personal characteristics after the diagnosis of breast cancer. Questionnaire data on use of HRT have shown excellent agreement with data from general practice prescription records.[6]

Our results support previous findings that current use of HRT reduces both the sensitivity and the specificity of mammography.[7–10] The adjusted sensitivity among current users (83.0%) is substantially lower than the value among women who have never used HRT (92.1%). Mammographic sensitivity did not differ significantly between current users of oestrogen only

Table 4 Sensitivity and specificity of breast cancer screening mammography according to various characteristics of women attending screening

Characteristic and outcome of mammography	Breast cancer*		Sensitivity			Specificity		
	Yes	No	Crude	Adjusted† (95% CI)	P value‡	Crude	Adjusted† 95% CI)	P value‡
Previous breast operation								
No:								
Screen positive	525	3 217	87.6	89.4 (86.5 to 91.8)	0.06	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						
Mother or sister with breast cancer								
No:								
Screen positive	507	3 306	86.5	89.4 (86.3 to 91.9)	0.1	96.8	97.3 (97.2 to 97.4)	0.5
Screen negative	79	99 742						
Yes:								
Screen positive	81	348	83.5	83.8 (74.6 to 90.0)		96.8	97.2 (96.9 to 97.5)	
Screen negative	16	10 514						
Parity								
Nulliparous:								
Screen positive	91	499	89.2	91.5 (84.7 to 95.4)	0.3	96.5	97.1 (96.9 to 97.4)	0.2
Screen negative	11	13 858						
Parous:								
Screen positive	536	3 374	86.3	88.0 (84.9 to 90.5)		96.8	97.3 (97.2 to 97.4)	
Screen negative	85	103 358						
Previous use of oral contraceptives								
No:								
Screen positive	276	1 447	87.9	89.4 (85.3 to 92.5)	0.6	97.2	97.3 (97.1 to 97.4)	0.6
Screen negative	38	50 289						
Yes:								
Screen positive	345	2 396	85.4	88.2 (84.3 to 91.3)		96.5	97.3 (97.2 to 97.4)	
Screen negative	59	65 801						
Tubal ligation								
No:								
Screen positive	497	2 932	87.0	89.3 (86.2 to 91.8)	0.5	96.8	97.3 (97.2 to 97.4)	0.9
Screen negative	74	90 073						
Yes:								
Screen positive	114	847	84.4	87.3 (80.5 to 91.9)		96.5	97.3 (97.1 to 97.5)	
Screen negative	21	23 556						
Body mass index								
<25:								
Screen positive	279	1 916	83.8	85.7 (81.2 to 89.3)	0.03	96.6	97.2 (97.0 to 97.3)	0.003
Screen negative	54	54 104						
≥25:								
Screen positive	316	1 739	89.8	91.0 (87.5 to 93.6)		97.0	97.4 (97.3 to 97.6)	
Screen negative	36	57 149						
Regular strenuous exercise								
No:								
Screen positive	305	1 770	86.2	88.1 (83.9 to 91.2)	0.5	96.8	97.3 (97.1 to 97.4)	0.4
Screen negative	49	53 519						
Yes:								
Screen positive	302	2 001	87.0	89.6 (85.7 to 92.5)		96.8	97.3 (97.2 to 97.5)	
Screen negative	45	60 166						
Current smoker								
No:								
Screen positive	472	2 893	86.6	89.1 (85.8 to 91.6)	1.0	96.9	97.3 (97.2 to 97.4)	0.7
Screen negative	73	89 042						
Yes:								
Screen positive	119	789	86.9	89.1 (82.7 to 93.4)		96.5	97.3 (97.0 to 97.4)	
Screen negative	18	21 760						
Ever drinks alcohol								
No:								
Screen positive	152	886	86.9	88.0 (82.1 to 92.1)	0.7	96.9	97.3 (97.1 to 97.5)	1.0
Screen negative	23	28 101						
Yes:								
Screen positive	471	2 955	86.6	89.0 (85.8 to 91.6)		96.8	97.3 (97.2 to 97.4)	
Screen negative	73	88 383						

*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.

and of combined oestrogen-progestogen HRT. The specificity of mammography was also significantly lower among current users of HRT (and separately among current users of oestrogen only and of combined HRT) and among past users of HRT, compared with women who had never used HRT.

Although previous studies have reported that mammographic sensitivity is lower among younger women,[11–14] 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.[1] 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.[11 15 16] 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.[10 15–19] 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.[10 20 21] Women using HRT and those who have had previous breast surgery may perhaps be under greater surveillance between screens, resulting in higher rates of breast cancer not detected at screening and hence apparently reduced mammographic sensitivity compared with other women. The relative risk of breast cancer not detected at screening among current compared with never users of HRT, however, is greater in the first year after mammography than in subsequent years.[22] This suggests that the reduced sensitivity observed here and by others is probably due to tumours being missed at mammography rather than increased surveillance in users.

Implications

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. We measured sensitivity as the proportion of all breast cancers diagnosed either at screening or in the 12 months after screening that are detected by screening. This is a commonly used measure of mammographic sensitivity[7] and assumes that the breast cancers diagnosed in the first 12 months after a negative result at screening are present, but missed, at mammography, whereas some new breast cancers may well arise in the 12 months after mammography was performed. Nevertheless, it is generally thought that reduced mammographic sensitivity would lessen the benefit conferred by screening. Our results suggest that mammography may thus 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.

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

We thank the many women who completed questionnaires for this study. We are grateful to the staff at the collaborating breast screening units and at the Million Women Study coordinating centre for their valuable contribution to the study.

Contributors: EB, GR, VB, and JP had the original idea for the study, with important input on practical aspects of study design from DB, BC, EH, and MS. EB and DB analysed the data and EB, GR, VB, and JP interpreted the data. SB, NB, PB, RE, AJ, EK, JL, LR, MGW, and MW contributed to local study design and conduct. All the authors participated in drafting the paper and gave final approval of the version to be published. EB, GR, VB, and DB are guarantors for the study

Funding: The Million Women Study is supported by Cancer Research UK, the Medical Research Council, and the NHS breast screening programme.

Competing interests: None declared.

Ethical approval: The study was approved by the Anglia and Oxford multicentre research ethics committee.

1 Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, et al. Predictors of outcome of mammography in the National Health Service breast screening programme. *J Med Screen* 2002;9:74-82.
2 Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, et al. Impact of use of hormone replacement therapy on false positive recall in the Million Women Study. *BMJ* 2004;328:1291-2.
3 Million Women Study Collaborative Group. The Million Women Study: design and characteristics of the study population. *Breast Cancer Res* 1999;1:73-80.
4 Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-27.
5 Million Women Study Collaborators. Patterns of use of hormone replacement therapy in one million women in Britain, 1996-2000. *Br J Obstet Gynaecol* 2002;109:1319-30.
6 Banks E, Beral V, Cameron R, Hogg A, Langley N, Barnes, et al. Agreement between general practice prescription data and self-reported use of hormone replacement therapy and treatment for various illnesses. *J Epidemiol Biostatistics* 2001;6:357-63.
7 Banks E. Hormone replacement therapy and the sensitivity and specificity of breast cancer screening: a review. *J Med Screen* 2001;8:29-35.
8 Chlebowski R, Hendrix S, Langer R, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA* 2003;289:3243-53.
9 Crane CEB, Luke CG, Rogers JM, Playford PE, Roder DM. An analysis of factors associated with interval as opposed to screen-detected breast cancers, including hormone therapy and mammographic density. *Breast* 2002;11:131-6.
10 Carney P, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al. Individual and combined effects of age, breast density and hormone replacement therapy use on the accuracy of mammography. *Ann Intern Med* 2003;138:168-75.
11 Kerlikowske K, Carney P, Geller B, Mandelson MT, Taplin SH, Malvin K, et al. Performance of screening mammography among women with and without a first-degree relative with breast cancer. *Ann Intern Med* 2000;133:855-63.
12 Schouten LJ, de Rijke JM, Schlangen JT, Verbeek ALM. Incidence of interval cancer. *Lancet* 1997;349:1104.
13 Rosenberg RD, Hunt WC, Williamson MR, Gilliland FD, Wiest PW, Kelsey CA, et al. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183,134 screening mammograms in Albuquerque, New Mexico. *Radiology* 1998;209:511-8.
14 Porter P, El-Bastawissi A, Mandelson MT, Lin MG, Khalid N, Watney EA, et al. Breast cancer tumour characteristics as predictors of mammographic detection: comparison of interval and screen-detected cancers. *J Natl Cancer Inst* 1999;91:2020-8.
15 Ma L, Fishell E, Wright B, Hanna W, Allan S, Boyd NF. Case-control study of factors associated with failure to detect breast cancer by mammography [see comments]. *J Natl Cancer Inst* 1992;84:781-5.
16 Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA* 1996;276:33-8.

17 Wang H, Bjurstam N, Bjorndal H, Braaten A, Eriksen L, Skanne P, et al. Interval cancers in the Norwegian breast cancer screening program: frequency, characteristics and use of HRT. *Int J Cancer* 2001;94:594-8.
18 Mandelson MT, Oestreicher N, Porter P, White D, Finder CA, Taplin SH, et al. Breast density as a predictor of mammographic detection: comparison of interval and screen-detected cancers. *J Natl Cancer Inst* 2000;92:1081-7.
19 Sala E, Warren R, McCann J, Duffy S, Day N, Lucas LL. Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme. *J Med Screen* 1998;5:207-12.
20 Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. *Ann Intern Med* 1999;130:262-9.
21 de Stavola BL, Gravelle IH, Wang DY, Allen DS, Bulbrook RD, Fentiman IS, et al. Relationship of mammographic parenchymal patterns with breast cancer risk factors and risk of breast cancer in a prospective study. *Int J Epidemiol* 1990;19:247-54.
22 Beral V, Banks E, Reeves G, Green J, Gathani T, Bull D, et al. The effect of hormone replacement therapy on breast and other cancers. In: Critchley HOD, Beral V, Gebbie A, eds. *Menopause and hormone replacement, proceedings of the forty seventh study group of the Royal College of Obstetricians and Gynaecologists*. London: Royal College of Obstetricians and Gynaecologists (in press).

(Accepted 6 July 2004)

bmj.com 2004;329:477

Cancer Research UK Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE
Emily Banks *deputy director*
Gillian Reeves *statistical epidemiologist*
Valerie Beral *director*
Diana Bull *senior statistician*
Barbara Crossley *chief data manager*
Moya Simmonds *clinical coordinator*
Elizabeth Hilton *clinical coordinator*

Breast Screening Service, Princess of Wales Community Hospital, Bromsgrove B61 0BB
Stephen Bailey *clinical director*

West of London Breast Screening Service, Charing Cross Hospital, London W6 8RF
Nigel Barrett *clinical director*

Gloucestershire Breast Screening Service, Linton House, Cheltenham GL53 7AS
Peter Briers *clinical director*

Breast Care Unit, Oxford Radcliffe Hospital NHS Trust, Churchill Hospital, Oxford OX3 7JH
Ruth English *clinical director*

Patricia Massey Breast Screening Unit, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY
Alan Jackson *consultant radiologist*

Avon Breast Screening, Central Health Clinic, Tower Hill, Bristol BS2 0JD
Elizabeth Kutt *clinical director*

North Lancashire Breast Screening Service, Royal Lancaster Infirmary, Ashton Court, Lancaster LA1 4GG
Janet Lavelle *clinical director*

West Sussex Breast Screening Service, Worthing Hospital, Worthing BN11 2DH
Linda Rockall *clinical director*

Breast Screening Unit, Coventry and Warwick Hospital, Coventry CV1 4FH
Matthew G Wallis *clinical director*

Greater Manchester Breast Screening Service, Nightingale Centre, Withington Hospital, Manchester M20 0PT
Mary Wilson *clinical director*

NHS Breast Screening Programme, Manor House, Sheffield S11 9PS
Julietta Patnick *national coordinator*

Correspondence to: E Banks emily.banks@anu.edu.au