

Hormone Replacement Therapy, Percent Mammographic Density, and Sensitivity of Mammography

Anne M. Kavanagh,¹ Jennifer Cawson,² Graham B. Byrnes,³ Graham G. Giles,⁴ Georgina Marr,⁴ Bin Tong,¹ Dorota M. Gertig,³ and John L. Hopper³

¹Australian Research Centre in Sex, Health and Society, La Trobe University; ²St. Vincent's BreastScreen, St. Vincent's Hospital and ³Centre for Genetic Epidemiology Centre, Department of Public Health, University of Melbourne, Melbourne, Victoria, Australia and ⁴Cancer Epidemiology Centre, the Cancer Council of Victoria, Carlton, Victoria, Australia

Abstract

Objective: We examine to what extent the lower mammographic sensitivity found in hormone replacement therapy (HRT) users can be explained by any association of HRT use with higher mammographic density and more difficult to detect cancers.

Methods: We used logistic regression to estimate the odds of a false-negative screen (a breast cancer diagnosed in the 24 months after a negative screening examination) for HRT users and to estimate, and adjust for, mammographic density (measured on a continuous scale, blinded, using a reliable, computer-assisted method), tumor characteristics (size, grade, and morphology), and potential confounders (age, symptom status, family history, and prior screening) among women ages ≥ 55 years who attended BreastScreen Victoria for first round screening mammography in 1994 and 1995 (1,086 breast cancers) and for subsequent round screening (471 breast cancers) in 1995 and 1996.

Results: After adjusting for confounders, HRT users were more likely to have a false-negative screen [first round: odds ratio (OR), 1.99; 95% confidence interval (95% CI), 1.4-2.9; subsequent round: OR, 2.29; 95% CI, 1.4-3.8]. This effect was modestly attenuated by adjusting for mammographic density (first round: OR, 1.54; 95% CI, 1.0-2.3; subsequent round: OR, 1.97; 95% CI, 1.2-3.3). Adjusting for tumor characteristics resulted in a modest increase in the odds of a false negative at first round but had no effect at subsequent round.

Conclusions: Mammographic density only partly explains the effect of HRT on sensitivity. Further research needs to clarify whether hyperemic breast tissue changes affect cancer detectability in HRT users as well as the possibility that the quality of mammography may be poor in some HRT users. (Cancer Epidemiol Biomarkers Prev 2005; 14(5):1060-4)

Introduction

Hormone replacement therapy (HRT) is associated with a reduction in the sensitivity of mammography (1-7) defined as the probability of having a cancer detected at screening. This is thought by some to be due the fact that up to a quarter of women who commence estrogen only or combined estrogen and progesterone hormone preparations have increases in mammographic density (the relative proportion of fibroglandular breast tissue, which appears radiodense on mammography; ref. 8). Higher mammographic density is associated with a reduction in the sensitivity of mammography (9-13).

To date, researchers have used qualitative methods to classify density and their findings suggest that the effect of HRT on sensitivity is mediated by breast density (14) and that sensitivity is reduced only in HRT users who have high mammographic density (5, 14). As HRT users have different tumor profiles than nonusers (15-19), it is possible the lower sensitivity in HRT users is due to poorer detectability of breast cancers in HRT users.

To our knowledge, no previous study has examined the effects of HRT on mammographic sensitivity after adjusting for both mammographic density and tumor characteristics. We have shown previously that HRT use is associated with a lower sensitivity of mammography at first round screening

(80% versus 65%) in 50- to 69-year-old women who attended BreastScreen Victoria (BSV) in 1994 (2). In this article, we expand that analysis to report on the effects of HRT use (and duration of use) on mammographic sensitivity in women ages ≥ 55 years who attended for first round screening in 1994 and 1995 and subsequent round screening in 1995 and 1996. We then examine the impact of mammographic density (measured on a continuous scale, blinded, using a reliable, computer-assisted method) and tumor characteristics on our estimates of the effects of HRT. The aim of our study was to determine to what extent the effect of HRT use in reducing mammographic sensitivity is explained by any association of HRT use with higher mammographic density.

Materials and Methods

Subjects. The study subjects are women ages ≥ 55 years who were diagnosed with invasive screen-detected or interval breast cancers and who attended BSV for first round screening between January 1, 1994 and December 31, 1995 or for subsequent (second or later rounds) screening between January 1, 1995 and December 31, 1996. The two samples (first round screening and subsequent round) screening were analyzed separately because the sensitivity of mammography is higher at first round when there is a higher proportion of larger (easier to detect) cancers. Once a woman is diagnosed with breast cancer, she is discharged from the screening program so the two samples are independent of each other.

We restricted our analysis to women ages ≥ 55 years because we did not have information on menopausal status, and a recent longitudinal study of a random sample of women found that the median age of menopause was 52.9 years and at least 83% of women living in Melbourne, Victoria, have

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Requests for reprints: Anne M. Kavanagh, Key Centre for Women's Health in Society, School of Population Health, University of Melbourne, Victoria 3010. Phone: 61-3-8344-7394; Fax: 61-3-9347-9824. E-mail: a.kavanagh@unimelb.edu.au

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had menopause by age 55 years.⁴ Menopausal status is associated with both HRT use and mammographic density (20) and is likely to confound relationships between HRT use and mammographic sensitivity. We also excluded non-Victorian residents at the time of screening and women who reported a personal history of breast cancer or a breast lump and/or a blood-stained or watery nipple discharge (classified as significant symptoms at BSV) at the time of screening.

Details of the Program. BSV provides free biennial mammography to all women ages ≥ 40 years. Women aged between 50 and 69 years who are listed on the electoral roll and who have never attended the BreastScreen program are sent an invitation (registration for voting is compulsory for Australian citizens). Women can attend for rescreening from as early as 21 months after their previous screen. Participation among women in the target age group of 50 to 69 years was 48.3%, 57.5%, and 57.8% in 1994/1995, 1996/1997, and 1998/1999, respectively. Participation rates are lower for women from non-English-speaking background women and Aboriginal and Torres Strait Islander women and are higher among rural women. Participation rates do not vary by socioeconomic status (21).

Screening consists of two-view mammography with films being read independently by two radiologists. If there is disagreement regarding recall, either the films are reviewed by the two radiologists and a consensus is reached or a third reader makes the decision. Women are then recommended for routine re-screen or are referred for assessment. Assessment may include clinical examination, further X-rays, ultrasound, or biopsy (fine needle aspiration, core biopsy, or open biopsy). After assessment, women may have a cancer diagnosed, be recommended for routine rescreening, or be recommended for further assessment (early review).

Classification of Subjects. Subjects were classified into two categories: true positive and false negative. True positives were cases of invasive breast cancer diagnosed as a result of screening. False negatives were women who developed invasive breast cancer during the interval between attending for screening and the next recommended screening attendance (usually 24 months). Interval cancers are identified by yearly matching of the BSV registry database with the Victorian cancer registry. Hospital and pathology laboratories are required by law to report all cases of cancer (except non-melanomatous skin cancer) to the Victorian Cancer Registry. BSV and cancer registry records are matched on name, street address, country of birth, and date of birth using the Automatch program. Given that cancer registry is population based and that the BSV and cancer registry collect detailed individual information, it is anticipated that matching process enables almost complete ascertainment of interval cancers (22).

Self-Reported Questionnaire Data. At attendance for screening, women return a self-completed questionnaire that asks about family history of breast cancer, current use of HRT (yes/no), duration of HRT use (< 1 or ≥ 1 year; if ≥ 1 year, specify the number of years), and symptom status.

A strong family history was defined as having one or more first-degree relative with breast cancer before age 50 years. "Other family history" was defined as breast cancer in a first-degree relative ages ≥ 50 years. "Other" symptoms were defined as any breast symptom other than a breast lump and/or blood or watery nipple. Age was taken to be the age at time of screening. At first round screening, women reported whether they had had a previous mammogram outside the program (yes/no).

Measurement of Mammographic Density. Mammographic density was measured by digitizing the mammograms of the study subjects. The images were displayed on a computer monitor, and thresholds were then set by an observer to define the margin of the breast (skin line) and the margin of fibroglandular breast tissue. The areas defined by these margins enabled us to measure the percentage of dense tissue in the breast (mammographic density). Details of the technique have been described previously (23). Craniocaudal views of both breasts were digitized (i.e., both ipsilateral cancer-affected breast and contralateral breast).

We used four observers: a radiologist (trained in this technique by Norman Boyd, Toronto, Ontario, Canada), a radiology registrar, and two research assistants (trained by the radiologist). All observers were blinded to whether the case was a true positive or a false negative and to all other clinical and demographic variables, including HRT use. Over 19,000 films were digitized and measured as part of a larger study on mammographic density. One in 10 films were repeated to assess intrarater reliability at any one measurement session. After every 750 films, each observer remeasured a random selection of 50 films from their previous measurement sessions. This assessed intrarater reliability over time. To assess interrater reliability, after every 750 films were measured, each observer read 51 films that were a random sample of films measured by the three other observers and four repeat films from within that batch.

Reliability of Mammographic Density Measures. To assess reliability only, percent mammographic density measures were ranked and then transformed to follow a normal distribution. Two four-level variance-component models were fitted using the MIWin statistical package (24). In the first model, measurements were first grouped by woman, then mammography episode, then film, then by reader of the film. This was used to assess the interrater variability of measurements. The second model differed only at the lowest level, which grouped measurements by date of reading to assess variability over time.

In both models, 80% of the variation were estimated to be explained by differences between women. Interrater variation explained 11.4% of variation corresponding to an intraclass correlation coefficient of 88.6% [95% confidence interval (95% CI), 88.2-89.0%]. Similar estimates were found for intrarater variation over time. Correlation between the ipsilateral and the contralateral breasts was also high, with an intraclass correlation coefficient of 94% (95% CI, 92.4-95.6%). On average, density measures of the ipsilateral breast were larger by a small but statistically significant margin of 0.11 (95% CI, 0.08-0.14) of a SD.

For the following analyses, ipsilateral breast density measures were used; for the 9% of cases where this measure was missing, measures from the contralateral breast were used. If there was more than one estimate for the ipsilateral breast (i.e., where the mammogram was used to assess observer reliability), then one measure was randomly selected. Similar results for the effect of percent mammographic density on sensitivity were obtained if the contralateral breast or the mean of the percent mammographic density of both breasts were used.

Tumor Characteristics. Tumor histology, histologic size (cross-sectional), and grade (well differentiated, moderately differentiated, and poorly differentiated) were recorded by the pathologists on a standardized form. For cancers coded as microinvasive, we assigned a minimal size (0.1 mm) consistent with national protocols (25).

Statistical Analysis. To examine the association between HRT use and percent mammographic density (measured continuously), we used multiple linear regression adjusting for age.

⁴ Janet Guthrie, personal communication.

Sensitivity of mammography was defined as the number of women with screen-detected invasive cancer (true positive) divided by the sum of the screen-detected (true positive) and interval (false negative) invasive cases. We estimated the sensitivities for 65-year-old women by current duration of HRT use (no current use, ≤1, 1-2, 2-3, 4-5, 6-10, and 11-30 years) for first round screening and mammographic density (≥0% and <10%, ≥10% and <25%, ≥25% and <50%, and ≥50%) and current use of HRT (yes/no) for both first and subsequent round screenings using unconditional logistic regression. We tested for trend by coding the categories of density from 1 to 4 and the categories of duration of HRT use as 1 to 8 and fitting these terms as continuous variables. For duration of HRT use, we fitted continuous terms with a dichotomous variable for use of HRT (yes/no). (There were insufficient cases at subsequent round screening to examine duration of HRT use).

Unconditional multiple linear logistic regression modeling of the odds of a false-negative mammogram was used to estimate mammographic sensitivity, to adjust for and estimate the effects of potential confounders (age, family history, and symptom status), and to assess to what extent mammographic density or tumor characteristics might explain the effects of HRT on the risk of a false-negative mammogram. At first round screening, we also adjusted for self-reported history of previous mammography (yes/no), and at subsequent round screening, we adjusted for the time since previous screen (in days). At first round and subsequent round screenings, we examined the effects of current use of HRT (yes/no). Percent mammographic density and age were fitted as continuous variables and family history (no family history, other family history, and strong family history) and symptom status (no symptoms and "other symptoms") were fitted as categorical variables. Size was modeled as a continuous variable, tumor grade as a categorical variable (well differentiated, moderately differentiated, and poorly differentiated), and morphology as a categorical variable (ductal, lobular, mixed ductal and lobular, and other). We tested for interactions between mammographic density (fitted as a continuous variable) and HRT status (yes/no). A two-tailed 5% significance level was used for all statistical tests. Analysis was conducted using Intercooled Stata 7.

There were 1,086 breast cancer cases at first round and 471 cases at subsequent round. Complete data were available for age, symptom status, family history, and morphology at both rounds and for HRT use and time since screen at subsequent round. For the multiple logistic regression analysis, we excluded cases where there was missing information on current use of HRT (5 at first round), mammographic density (81 at first round and 33 at subsequent round), size (12 at first round and 24 at subsequent round), and grade (5 at first round and 3 at subsequent round); at first round, we also excluded

1 case that had missing data on self-reported previous mammography and 27 cases that had missing data on duration of HRT use. In the multivariable analysis, there were 983 cases at first round and 416 cases at subsequent round.

The study was approved by the Anti-Cancer Council of Victoria Institutional Ethics Committee and did not involve contact with individual women.

Results

Table 1 shows the relationships among age, mammographic density, and HRT use. The proportion of HRT users decreased with age from 44% in 55- to 59-year-old women to 6% in women aged ≥70 years. After adjusting for age, HRT use was associated with a 3.22% mean increase in percent mammography density (95% CI, 2.1-4.3; *P* < 0.001).

In bivariate analyses, there was no evidence for differences between HRT users and nonusers in terms of tumor characteristics (grade and size), family history, symptom status, and, for subsequent round attendees, time since previous screen. At first round, HRT users were more likely to report having had a previous mammogram outside the program (57% versus 26%; *P* < 0.001) and were slightly more likely to have mixed tumors (5% versus 3%; *P* = 0.05).

Table 2 shows the predicted sensitivities by HRT use and percent density for 65-year-old women. With increasing categories of density, there was a marked reduction in the sensitivity of mammography at both rounds. Current use of HRT use was associated with a reduction in sensitivity (first round: 66.1% versus 82.2%; *P* < 0.001; subsequent round: 56.2% versus 73.2%; *P* = 0.001). As there was no apparent trend in the sensitivity of mammography with duration of HRT use at first round (*P* = 0.7), duration of use was not examined further.

After adjusting for age, a 5% increase in percent density was associated with an increase in the odds of a false negative [first round: odds ratio (OR), 1.22; 95% CI, 1.2-1.3; subsequent round: OR, 1.16; 95% CI, 1.1-1.3]. This effect was unchanged after adjusting for HRT use (first round: OR, 1.20; 95% CI, 1.1-1.3; subsequent round OR, 1.14; 95% CI, 1.1-1.2).

Table 3 shows that, after adjusting for age, family history and symptom status, previous mammography (at first round), and time since screen (at subsequent round), current HRT use was associated with an raised odds of a false negative (first round: OR, 1.99; 95% CI, 1.4-2.9; subsequent round: OR, 2.29; 95% CI, 1.4-3.8). This was modestly attenuated, but not obliterated, by adjusting for percent density (first round: OR, 1.54; 95% CI, 1.0-2.3; subsequent round: OR, 1.97; 95% CI, 1.2-3.3). No further appreciable changes in the OR estimates for current use of HRT were found after adjusting for size, grade, and tumor morphology at subsequent round, whereas a moderate increase in the

Table 1. Percent density by age and HRT status

Percent density	55-59 y				60-64 y				65-69 y				≥70 y			
	<10	10-<25	25-<50	≥50	<10	10-<25	25-<50	≥50	<10	10-<25	25-<50	≥50	<10	10-<25	25-<50	≥50
First round																
Nonuser,	65	55	21	3	100	58	24	1	119	71	25	6	149	58	21	1
n (%)	(45.1)	(38.2)	(14.6)	(2.1)	(54.4)	(31.7)	(13.1)	(0.6)	(53.9)	(32.1)	(11.3)	(2.7)	(65.1)	(25.3)	(9.2)	(0.4)
User,	22	35	41	5	25	20	14	0	17	13	12	3	5	8	4	0
n (%)	(21.4)	(34.0)	(39.8)	(4.9)	(42.4)	(33.9)	(23.7)	(0.0)	(37.8)	(28.9)	(26.7)	(6.7)	(29.4)	(47.1)	(23.5)	(0.0)
Second round																
Nonuser,	36	27	10	2	44	26	8	1	65	14	14	0	47	16	9	1
n (%)	(48.0)	(36.0)	(13.3)	(2.7)	(55.7)	(32.9)	(10.1)	(1.3)	(69.9)	(15.1)	(15.1)	(0.0)	(64.4)	(21.9)	(12.3)	(1.4)
User,	20	26	20	4	6	10	12	1	10	4	2	0	1	1	0	1
n (%)	(28.6)	(37.1)	(28.6)	(5.7)	(20.7)	(34.5)	(41.4)	(3.5)	(62.5)	(25.0)	(12.5)	(0.0)	(33.3)	(33.3)	(0.0)	(33.3)

Table 2. Predicted sensitivity by round, percent density, and HRT status for 65-year-old women

	First round, sensitivity (95% CI)	Subsequent round, sensitivity (95% CI)
Percent density		
≥10 and <10	85.4 (82.0-88.3)	77.8 (71.9-82.8)
≥10 and <25	80.2 (75.4-84.2)	70.1 (61.1-77.8)
≥25 and <50	60.7 (52.9-68.0)	60.5 (48.7-71.2)
≥50	54.8 (32.9-75.0)	35.3 (12.1-68.5)
<i>P</i> for trend	<0.001	<0.001
Percent density (continuous)		
5	85.1 (82.2-87.6)	77.4 (72.3-81.9)
15	79.7 (76.9-82.2)	71.8 (66.9-76.2)
35	64.8 (58.8-70.4)	58.4 (49.0-67.2)
75	29.0 (17.2-44.4)	29.9 (14.4-51.8)
HRT use		
No	82.2 (79.4-84.7)	73.0 (68.0-77.5)
Yes	66.1 (59.6-72.1)	56.3 (46.7-65.4)
Duration of HRT use (y)		
None	82.2 (79.4-84.7)	
≤1	71.4 (55.7-83.3)	
2-5	66.4 (54.0-76.9)	
6-10	67.8 (56.8-77.1)	
>10	66.3 (47.9-80.8)	
<i>P</i> for trend	0.71	

odds of a false negative with HRT use was found at first round. Interactions between mammographic density and HRT use were not statistically significant (first round: $P = 0.3$; subsequent round: $P = 0.8$).

Discussion

This study confirms and extends the findings of previous studies—that current use of HRT is associated with a reduction in mammographic sensitivity (1-7); if the 371 HRT users in our sample (24% of subjects) had the same sensitivity as nonusers, then an additional 76 cancers would have been detected at screening. We found, however, that the effect of HRT on mammographic sensitivity is only partly explained by the effect of HRT on mammographic density; we found a reduction in the odds of a false-negative screen associated with HRT use (45% at first round and 32% at subsequent rounds) after adjusting for mammographic density. Although adjusting for mammographic density does modestly attenuate the effect of HRT, there is still a strong, statistically significant residual effect of current HRT use on having a false-negative mammogram (first round: OR, 1.54; subsequent round: OR, 1.97). In addition, the observation by us and others that HRT users tend to have different tumor profiles than nonusers does not explain the lower sensitivity found in HRT users. We found that adjusting for tumor characteristics in fact strengthened the effect of HRT on having a false-negative mammogram, particularly at first round screening.

Earlier studies found lower sensitivity in HRT users but only in those women who also had high mammographic density (5, 14). In contrast, we found no evidence that mammographic density modifies the effect of HRT on sensitivity; interactions between HRT and mammographic density were not statistically significant, but it is possible that we had insufficient power to detect effect modification.

Previous researchers have used qualitative subjective methods for measuring mammographic density using many observers from multiple sites who were not necessarily blinded to clinical information, such as HRT use. These studies have also typically had a substantial amount of missing data on HRT and mammographic density (5, 14).

Our study has several strengths: it was based on a large cohort of asymptomatic women who attended a population-based screening program, observers were blinded to the HRT

status and diagnosis of the women, mammographic assessment was based on 93% of mammograms, and there was high reliability in measuring mammographic density. The fact that we found a graded increase in the effect of density on mammographic sensitivity (Table 2) also suggests that our measurements were accurate. The lack of attenuation of the effect of HRT use after adjusting for density is unlikely to be explained by measurement error.

There were some potential weaknesses in our study that we attempted to minimize. Although menopausal status is likely to be associated with HRT use and mammographic density (26), BSV does not routinely collect information about menopause. By restricting our analysis to women ages >55 years, the great majority would have been postmenopausal. In a prospective Australian study of the menopausal transition, 83% of subjects had reached menopause by age 55 years, even though the study had excluded women who had menopause before 45 years.⁴ A further possible limitation of this study is that we did not have details on preparations, or past use, of HRT. Over 80% of Australian HRT users are taking combined preparations of estrogen and progesterone (27). If past users continued to experience a reduction in sensitivity of mammography, then combining past HRT users with women who have never used HRT would have attenuated our estimates of the effects of current use on sensitivity.

There are several possible explanations for our finding that sensitivity is lower in HRT users after adjustment for mammographic density. These include more frequent screening outside the program, subtle breast tissue changes, and breast pain or tenderness. HRT users may be more likely to have annual screens and have another screen outside BSV, increasing the probability that they have cancers detected outside the program that are counted as interval cancers. If this were the case, then we would expect that a large proportion of interval cancers in HRT users would be diagnosed close to 12 months after their BSV screen; however, in our study, there was no statistically significant difference in the proportion of cancers diagnosed between 9 and 15 months after their previous screen (HRT users: 20% versus nonusers: 25%; $P = 0.25$).

HRT use may be associated with subtle breast tissue changes, such as edema or vascular dilation (28), which could potentially obscure tumors without causing an increase in measurable mammographic density. Diffuse parenchymal enhancement, indicative of increased vascularity, has been documented in HRT users using contrast-enhanced magnetic resonance imaging (29). Small studies on premenopausal women, also using contrast-enhanced breast magnetic resonance imaging, have shown parenchymal enhancement during the secretory, menstrual, and proliferative phases of the menstrual cycle with the strongest enhancement occurring in the progesterogenic phases of the cycle (30, 31). It is possible that the hyperemic changes noted in premenopausal women in the progesterogenic phases of the menstrual cycle will also be

Table 3. Multivariable logistic regression analysis of risk of false negative by HRT use

	OR (95% CI)
First round	
Model 1	1.99 (1.38-2.86)
Model 2	1.54 (1.04-2.27)
Model 3	1.72 (1.15-2.58)
Subsequent round	
Model 1	2.29 (1.37-3.81)
Model 2	1.97 (1.16-3.34)
Model 3	2.03 (1.16-3.54)

NOTE: Model 1: adjusted by age, symptoms, family history, previous mammography (first round), and time since screen (subsequent round). Model 2: model 1 plus percent density (continuous). Model 3: model 2 plus morphology, size, and grade.

found in HRT users who take progesterone. These changes may obscure breast cancers and this would in part explain the lower sensitivity in HRT users. As >80% of Australian HRT users use oral progesterone either sequentially or continually, mostly in conjunction with oral estrogen (27), this adds weight to the plausibility of this as an explanation for our findings. Other HRT-associated changes include an increase in the prevalence of cystic lesions (32, 33) and fibroadenomas (33) as well as benign breast lesions, including sclerosing adenosis, intraductal papillomas, and epithelial hyperplasia (34). It seems that HRT has complex effects on breast tissue and further research is needed to clarify the radiological and histologic effects of HRT on the breast.

It is known that HRT use is associated with increased breast pain and tenderness (35) and this may affect the quality of the breast image because it is harder to achieve adequate breast compression. Good compression is needed to immobilize the breast to eliminate blurring due to movement. Compression also decreases the thickness of the breast and produces uniform breast thickness, which reduces scatter radiation and lessens the radiation dose. By minimizing the distance between breast structures and the film and spreading the tissues apart, the resolution and sharpness of the image are also optimized. Between 1994 and 2001 at BSV, HRT users had a slightly higher proportion of films repeated for technical reasons (8.4 per 1,000 in HRT users versus 7.1 per 1,000 in nonusers; $P < 0.001$) and a higher proportion of films classified as suboptimal (3.1 per 1,000 in HRT users versus 2.4 per 1,000 in nonusers; $P < 0.001$) at subsequent round screening. Therefore, it is possible that HRT reduces the quality of mammography in a way that reduces sensitivity, although this requires further examination.

It is not possible to make recommendations for women as to whether they should cease HRT before having mammography. It is possible that short-term cessation may reduce breast pain or tenderness and reverse some of its effects on mammographic density, but this may not be sufficient to reverse fully the deleterious effects of HRT on the sensitivity of mammography. It is important that further research elucidates whether short-term cessation of HRT before mammography improves sensitivity. Until further evidence regarding the effects of HRT on mammography is accumulated, we emphasize the importance of achieving adequate breast compression so that the highest quality mammographic images are obtained for HRT users.

Despite the reduced mammographic sensitivity in HRT users, we would conclude that HRT users should continue to attend for mammography because it is the most effective screening tool for breast cancer. It may be that additional screening modalities need to be considered for HRT users. It is essential that HRT users are told about the effects of HRT on mammography before they make decisions as to whether they should commence HRT.

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