Influence of Patterns of Hormone Replacement Therapy Use and Mammographic Density on Breast Cancer Detection

Anna M. Chiarelli,[1,2] Victoria A. Kirsh,[1,2] Neil S. Klar,[5] Rene Shumak,[1] Roberta Jong,[3] Eve Fishell,[3] Martin J. Yaffe,[3] and Norman F. Boyd[4]

[1]Division of Preventive Oncology, Cancer Care Ontario; [2]Department of Public Health Sciences, University of Toronto; [3]Department of Radiology and Imaging Research, Sunnybrook and Women's College Health Science Centre; [4]Campbell Family Institute for Breast Cancer Research, Ontario Cancer Institute, Toronto, Canada; and [5]Department of Epidemiology and Biostatistics, University of Western Ontario, London Canada

Abstract

Background: **There is evidence that factors such as current hormone replacement therapy (HRT) use and mammographic density may each lower the sensitivity of mammography and are associated with a greater risk of developing an interval cancer. This study explores this relationship further by examining the influence of patterns of HRT use and the percentage of mammographic density on the detection of breast cancer by classification of interval cancer.**

Methods: **This study uses a case-case design nested within a cohort of women screened by the Ontario Breast Screening Program between 1994 and 2002. Interval cancers, both those missed at screening but seen on retrospective review (n = 87) or true intervals without visible tumor signs at screening (n = 288) were matched to 450 screen-detected cancers. The association between the percentage of mammographic density, measured by radiologists and a computer-assisted method, and HRT use, ascertained from a mailed questionnaire, and the risk of being diagnosed with an interval cancer was estimated using conditional logistic regression.**

Results: **A monotonic gradient of increasing risk for interval cancers was found for each 25% increase in mammographic density [odds ratio (OR), 1.77; 95% confidence intervals (95% CI), 1.07-2.95 for missed intervals and OR, 2.16; 95% CI, 1.59-2.94 for true intervals]. After adjusting for mammographic density, a significantly increased risk for true-interval cancers remained for women taking estrogen alone (OR, 1.75; 95% CI, 1.11-2.83) as well as for missed- (OR, 2.84; 95% CI, 1.32-6.13) and true-interval cancers (OR, 1.79; 95% CI, 1.10-2.90) for women taking combined HRT.**

Conclusions: **Information on mammographic density and HRT use should routinely be collected at the time of screening. Women at risk should be made aware of the lower sensitivity of mammography and offered alternative procedures for screening.** (Cancer Epidemiol Biomarkers Prev 2006;15(10):1856–62)

Introduction

Although there is evidence from several randomized controlled trials that screening mammography reduces the breast cancer mortality rate, not all breast cancers can be detected by mammography (1, 2). Interval breast cancers are those detected between screening examinations, following a normal screening mammogram, and are more likely than screen-detected cancers to have an unfavorable prognosis (3-5). Approximately 10% to 20% of breast cancers are not detected at screening; therefore, it is important to determine which factors increase the risk of interval cancers to maximize the effectiveness of screening in reducing the rate of mortality from breast cancer (3, 6, 7).

Interval cancers are a heterogeneous group comprised of those in which recognizable signs of tumor existed at the time of screening but were ''missed'' for technical or interpretive reasons and those that were not mammographically detectable at screening (8). Missed intervals caused by interpretive errors result from oversight on the part of the radiologist or misinterpretation of nonspecific mammographic signs of malignancy (3, 6, 9). True intervals are those without visible tumor signs at screening and account for 65% to 75% of all intervals (6, 8). These cancers could have existed at the time of screening but were ''masked'' from detection as result of a lobular histology, an absence of calcifications, or an increased breast density, or these cancers could be incident tumors with a high tumor growth rate (8, 10, 11).

Several studies have shown that current use of hormone replacement therapy (HRT) substantially lowered the sensitivity of screening compared with nonuse by 7% to 25% and resulted in a significant increase in interval cancers (7, 12-16). However, many of these studies did not collect data on potentially important aspects of HRT use such as type of HRT preparation taken, duration of use, and time since last use (17).

A few of the studies examining use of HRT on sensitivity also observed that a greater proportion of current HRT users had mammographically dense breasts (the relative proportion of connective and epithelial tissues to fatty tissue in the breast) (7, 14). In recent studies, the increase in mammographic density associated with HRT use has been shown to be more common in women taking combined estrogen and progesterone preparations compared with women taking estrogen alone (18-23). High mammographic density has been found to decrease the accuracy of screening mammography, and accordingly, has been associated more often with interval breast cancers as compared with screen-detected tumors (24-27). Women with extremely dense breasts were found to have a 6- to 9-fold increased risk of an interval cancer (11, 27).

A few studies have examined the combined effects of HRT use and breast density on sensitivity (7, 28, 29). Two of the

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Requests for reprints: Anna M. Chiarelli, Division of Preventive Oncology, Cancer Care Ontario, 620 University Avenue, Toronto, Ontario, Canada M5G 2L7. Phone: 416-971-9800; Fax: 416-971-6888. E-mail: anna_chiarelli@cancercare.on.ca

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studies that measured breast density on a categorical scale by radiologists found that HRT only lowered screening sensitivity in women with mammographically dense breasts (7, 28). A recent study that measured mammographic density on a continuous scale concluded that the effect of HRT on sensitivity remained significantly lowered even after adjusting for mammographic density (29). However, these previous studies did not examine the HRT preparation used or the effect of past use. To our knowledge, no study has evaluated the association between the HRT preparation used or the effect of past use and breast density on the detection of breast cancer, nor has any study examined these relationships by classification of interval cancer.

The purpose of this study was to examine the relationship between patterns of HRT use and the percentage of mammographic density at the last screening prior to diagnosis with the detection of interval and screen-detected breast cancer within a breast screening program. In addition, associations were examined separately by classification of interval cancer (missed or true) adjusted by potential confounders.

Materials and Methods

Description of the Ontario Breast Screening Program. The Ontario Breast Screening Program (OBSP), under the auspices of Cancer Care Ontario, has operated since 1990 to deliver a population-based breast screening program. The OBSP offers eligible women biennial screening consisting of two-view mammography and clinical breast examination by a nurse examiner. Women are not eligible if they have had a prior history of breast cancer or augmentation mammoplasty or if they currently have symptoms of breast disease. Although most women are screened every 2 years at OBSP, women considered at high risk of breast cancer are recalled annually. A complete description of the details of the operation of OBSP has been recently published (30).

Follow-up, identification, and classification of interval and screen-detected breast cancers are identical for all women screened by OBSP. Information on women diagnosed with breast cancers is obtained by regional staff (before or during the recall process) or through linkage with the Ontario Cancer Registry. As part of OBSP quality assurance, screening mammograms prior to diagnosis of all women with interval cancers are routinely reviewed and classified in a blinded fashion by OBSP radiologists.

Selection of Interval and Screen-Detected Breast Cancers. This study uses a case-case design nested within a cohort of women screened by the OBSP (31). All women eligible for this study were screened at the OBSP between 1994 and 2002, 50 years of age or older, diagnosed with a histologically confirmed invasive breast cancer, and alive at the time of the study. Cases comprised women with an interval breast cancer diagnosed before the next recommended screening visit of 12 or 24 months after a negative (mammographic) examination. Two case groups of interval cancers were identified. The first case group included women who had an abnormality seen retrospectively as a result of the review process on the screening mammogram (missed intervals) and the second case group included women who did not have an abnormality seen retrospectively on the screening mammogram (true intervals). The comparison group comprised women with a screen-detected breast cancer after a positive mammographic examination (with or without an abnormal clinical breast examination). Two screen-detected cancers were matched to each missed interval case and one screen-detected cancer was matched to each true interval case by region of screening center and within 5 years of age and year of last screen. The study was approved by the Health Sciences Research Ethics Board at the University of Toronto.

Questionnaire and Screening Data. All subjects recruited for this study were sent a letter of invitation, a self-administered questionnaire and a consent form for access to their mammograms. The questionnaire focused on the woman's history of HRT use up until their last screening mammogram prior to diagnosis. Information on type of HRT taken (estrogen alone or in combination with progesterone), method of taking combination HRT preparations (cyclical or continuous), and duration of use was collected. Women were defined as current HRT users if they had taken this medication for 2 months or more at the time of their last OBSP mammogram. Current HRT users were further classified by type of HRT taken and, for combination users, by the progesterone regimen. Pictures of different types of HRT preparations (pills and patches) were included in the questionnaire to assist women in remembering the name of the medication taken. Women who had stopped taking HRT 1 year before their last mammogram were considered to be former users. Information on menopausal status was ascertained by asking questions on date or age of last menstrual period, reasons for menstrual period stopping, and age and dates of any surgeries to remove ovaries. Women were defined as perimenopausal or postmenopausal if their periods had stopped for 1 year or more and/or both ovaries had been removed prior to their last screening mammogram. Additional questions were asked about highest level of education, height, weight at last mammogram, smoking and alcohol use at last mammogram, first-degree relatives with breast and/or ovarian cancer, age at first menstrual period, number of pregnancies and age and length of each pregnancy, and diagnosis of benign breast disease by a surgical breast biopsy.

Information on screening history was obtained from the OBSP screening report which included dates and outcomes for each screening examination. The number of screens indicates how many OBSP screening mammograms the women had prior to diagnosis. Prior screening mammogram was defined as first screen for women with one OBSP screen prior to diagnosis and as the time period (less than or equal to 18 months or greater than 18 months) between the two screening mammograms prior to diagnosis for women with more than one OBSP screen.

Mammographic Density Measurements. The screening mammogram prior to diagnosis was obtained from the OBSP screening centers for all women who participated in the study. The percentage of mammographic density of the cranial-caudal view of the mammogram from the breast contralateral to the cancer was assessed quantitatively by radiologists and by a computer-assisted method. Those classifying the mammograms were ''blinded'' to the identity of the cases or controls or any information about the women. Three experienced radiologists (R. Shumak, R. Jong, and E. Fishell) independently read a third of all study mammograms. The selected images were read in sets of about 100 images for each subject in matched pairs, in random order, with sequence of order unknown to the reader. The radiologists classified mammographic density on a six-category scale (0%, >0% to <10%, 10% to <25%, 25% to <50%, 50% to <75%, ≥75%) by visual estimation of the proportion of the breast area occupied by radiologically dense tissue (32). The interrater agreement of mammographic breast density was assessed in a subsample of 50, and found to be strong [0.86; 95% confidence intervals (95% CI), 0.78-0.91] between the three radiologists, as measured by the intraclass correlation coefficient.

For the computer-assisted method, the same cranio-caudal view was digitized using a Lumisys 85 digitizer at a pixel size of 260 μm and 12-bit precision and measured by one observer (N. Boyd) using a previously described interactive thresholding technique (33). The observer establishes thresholds for the edge of the breast and the edge of dense tissue. A computer then records the number of pixels in the digitized image that

lie within the defined areas. The percentage of mammographic density is the area of dense tissue divided by the entire projected area of the breast and multiplied by 100. Films were read in sets of about 150 images for each subject in matched pairs as described above. The intraclass correlation coefficient measuring agreement between the computer-assisted and the radiologist's categorized density reading was 0.72 (95% CI, 0.68-0.75).

Statistical Analysis. The association between the percentage of mammographic density and HRT use was estimated for each case group compared with their set of matched screen-detected cancers as well as to the set of pooled screen-detected cancers using both unconditional logistic regression adjusting by matching variables and conditional logistic regression. As results did not differ significantly and the case groups had similar distributions for the matching variables, to increase study power and efficiency, final analyses are presented for each case group compared with the pooled set of screen-detected cancers using conditional logistic regression (31). Odds ratios (OR) and their 95% CI were calculated separately for true- and missed-interval cancers. Multivariable analyses were adjusted for time since prior OBSP screening mammogram (first screen, ≤18 months ago, >18 months ago), benign breast disease (yes, no), body mass index (kg/m^2; continuous), smoking status (yes, no), family history of breast and/or ovarian cancer [none, moderate (first-degree relative with breast cancer age 50 or older; first-degree relative with ovarian cancer at any age), strong (two or more first-degree relatives with breast cancer and/or ovarian cancer at any age; first-degree relative with breast cancer <age 50)], parity (parous if one or more pregnancies >6 months, nulliparous), education (<high school, high school, >high school), age at menarche (continuous), menopausal status (premenopausal, perimenopausal, or postmenopausal), use of HRT (never, current estrogen, current estrogen and progesterone, former use; where applicable), and mammographic density [computer-assisted categorized density reading (continuous); where applicable]. Tests for trends in radiologist-determined mammographic density (≥0% to <10%, 10% to <25%, 25% to <50%, 50% to <75%, ≥75%) and duration of HRT use (none, ≤5, >5 to 10, >10 years) were conducted by testing the significance of the ordinal term in the logistic model; tests for trend in the computer-assisted mammographic density reading were conducted by testing the significance of the continuous variable, using a Wald χ^2 statistic. Interrater reliability was measured by intraclass correlation coefficients (34). A two-tailed 5% significance level was used for all statistical tests.

Results

Among the 431,480 women screened through OBSP between 1994 and 2002, there were 4,478 women who had an invasive breast cancer diagnosis, were alive at the start of the study, had consented to be contacted for research studies, and were classified as having a screen-detected or interval breast cancer. All of the 616 women with interval breast cancers were selected for the study as well as 798 women who had a screen-detected cancer and matched the interval breast cancers by region of screening center and within 5 years of age and year of last screen. Of the 1,414 eligible women for this study, 1,150 were contacted and 825 were interviewed and provided consent (overall response rate, 72%; missed interval, 76%; true interval, 77%; and screen-detected cases, 68%). The analytic series was comprised of 87 missed interval cases, 288 true interval cases, and 450 screen-detected cases.

The individual-matched sampling design accounted for similar distributions by age and year of last screen (Table 1). The total number of screening examinations and the likelihood of having had a recent prior screening mammogram did not differ appreciably between the groups. The average number of screening exams prior to diagnosis was 2.2 and the average age at last screening exam was 60.2 years of age. In addition, the matching resulted in similar average lengths of time between the last screen and completion of the questionnaire between the groups. However, as expected, the case groups did differ significantly by time to diagnosis and percentage of mammographic density. Women diagnosed with an interval cancer had a significantly longer median waiting time to breast cancer diagnosis (missed intervals, 393 days; true-intervals, 442 days) compared with women diagnosed with a screen-detected cancer (40 days). The average percentage of mammographic density at last screen was significantly greater by 5.5% among women diagnosed with a missed-interval cancer or by 8.2% among women with a true-interval cancer compared with women diagnosed at screening.

The distribution of characteristics of the mammogram at the time of last screening was generally similar across groups (Table 2). Previous diagnosis of benign breast disease was more common among the interval cases than among the

Table 1. Characteristics among women with interval cancer and with screen-detected cancer

Characteristic	Screen detected (N = 450)	Missed interval (N = 87)	True interval (N = 288)
Age at last screen (y), n (%)			
50-59	236 (52.4)	41 (47.1)	154 (53.5)
60-69	157 (34.9)	32 (36.8)	99 (34.4)
≥70	57 (12.7)	14 (16.1)	35 (12.2)
Year of last screen, n (%)			
1994-1997	173 (38.4)	28 (32.2)	118 (41.0)
1998-2002	277 (61.6)	59 (67.8)	170 (59.0)
No. of screens, n (%)			
One screen	181 (40.2)	35 (40.2)	89 (30.1)
Two screens	104 (23.1)	21 (24.1)	90 (31.3)
Three screens	75 (16.7)	11 (12.6)	64 (22.2)
Four screens	62 (13.8)	11 (12.6)	31 (10.8)
≥Five screens	28 (6.22)	9 (10.3)	14 (4.9)
Prior screening mammogram, n (%)			
First screen	181 (40.2)	35 (40.2)	89 (30.1)
≤18 months ago	37 (8.2)	11 (12.6)	38 (13.2)
>18 months ago	232 (51.6)	41 (47.1)	161 (55.9)
Last screen to questionnaire, mean year (SD)	4.8 (1.9)	4.1 (1.7)	4.4 (1.8)
Percentage of mammographic density, mean (SD)*	22.2 (15.9)	27.7 (15.7)	30.4 (17.2)

*P < 0.0001.

Table 2. Risk of missed- or true-interval breast cancer associated with various characteristics

Characteristic	Screen detected, *N* (%)	Missed interval		True interval	
		N (%)	OR (95% CI)	*N* (%)	OR (95% CI)
Menopause					
Premenopausal	41 (9.2)	6 (7.0)	1.00	22 (7.8)	1.00
Peri/Postmenopausal	403 (90.8)	80 (93.0)	1.13 (0.44-2.91)	261 (92.2)	1.23 (0.70-2.17)
Parity					
Nulliparous	59 (13.1)	13 (14.9)	1.00	45 (15.6)	1.00
Parous	391 (86.9)	74 (85.1)	1.00 (0.51-1.96)	243 (84.4)	0.72 (0.47-1.11)
Age at first birth (y)					
Nulliparous	59 (13.3)	13 (14.9)	1.00	45 (15.6)	1.00
<30	352 (79.1)	62 (71.3)	0.92 (0.46-1.82)	217 (75.6)	0.72 (0.46-1.11)
≥30	34 (7.6)	12 (13.8)	1.73 (0.68-4.44)	25 (8.7)	0.90 (0.47-1.73)
Age at menarche (y)					
≤11	77 (17.5)	13 (14.9)	1.00	71 (24.7)	1.00
>11	364 (82.5)	74 (85.1)	1.11 (0.58-2.12)	216 (75.3)	0.65 (0.45-0.94)
Education level					
>High school	233 (52.0)	49 (57.0)	1.00	157 (54.9)	1.00
High school	101 (22.5)	13 (15.1)	0.60 (0.30-1.18)	58 (20.3)	0.84 (0.57-1.24)
<High school	114 (25.5)	24 (27.9)	1.11 (0.62-2.00)	71 (24.8)	0.91 (0.62-1.33)
Body mass index					
<25	163 (37.8)	41 (48.2)	1.00	121 (43.2)	1.00
25-29.9	174 (40.4)	26 (30.6)	0.60 (0.34-1.06)	110 (39.3)	0.90 (0.65-1.27)
30-34.9	60 (13.9)	12 (14.1)	0.86 (0.41-1.78)	34 (12.1)	0.74 (0.46-1.21)
≥35	34 (7.9)	6 (7.1)	0.84 (0.33-2.18)	15 (5.4)	0.67 (0.35-1.29)
Family history					
None	365 (81.1)	68 (78.2)	1.00	217 (75.9)	1.00
Moderate	46 (12.4)	14 (16.1)	1.54 (0.79-2.99)	49 (17.1)	1.41 (0.92-2.15)
Strong	29 (6.4)	5 (5.8)	1.11 (0.40-3.09)	20 (7.0)	1.13 (0.62-2.06)
Benign breast disease					
No	376 (85.3)	63 (73.3)	1.00	227 (79.7)	1.00
Yes	65 (14.7)	23 (26.7)	2.28 (1.29-4.03)	58 (20.4)	1.50 (1.01-2.24)
Alcohol use					
No	286 (66.1)	55 (65.5)	1.00	183 (66.1)	1.00
Yes	147 (34.0)	29 (34.5)	1.05 (0.63-1.75)	94 (33.9)	1.08 (0.78-1.50)
Smoking					
No	381 (85.8)	77 (88.5)	1.00	265 (92.7)	1.00
Yes	63 (14.2)	10 (11.5)	0.81 (0.39-1.70)	21 (7.3)	0.49 (0.29-0.83)

NOTE: Numbers may not add to total due to missing values.

screen-detected cases (missed interval OR, 2.28; 95% CI, 1.29-4.03; true interval OR, 1.50; 95% CI, 1.01-2.24). Smokers were less likely than nonsmokers to be diagnosed with a true-interval cancer (OR, 0.49; 95% CI, 0.29-0.83).

A monotonic increasing gradient of risk for interval cancers was found with increasing categories of mammographic density percentage adjusted for HRT use. Compared with women with <10% density, those with 50% to <75% density, as determined by radiologists, were more likely to present with interval cancers than screen-detected cancers (missed interval OR, 3.51; 95% CI, 1.19-10.42; true interval OR, 3.73; 95% CI, 1.96-7.11; Table 3). This compared with lower point estimates associated with 50% to <75% mammographic density based on the computer-assisted method for missed-interval cancers (OR, 1.35; 95% CI, 0.35-5.21) and slightly higher estimates for true-interval cancers (OR, 4.17; 95% CI, 1.96-8.88). The trend was significant for both the categorical measures of mammographic density generated by the radiologists (P trend = 0.01 and

Table 3. Risk of missed- or true-interval breast cancer associated with percentage of mammographic density

Mammographic density	Screen detected, *N* (%)	Missed interval		True interval	
		N (%)	OR (95% CI)*	*N* (%)	OR (95% CI)*
Radiologist-determined					
<10%	78 (18.2)	9 (11.1)	1.00	24 (8.7)	1.00
10% to <25%	98 (22.8)	11 (13.6)	1.51 (0.52-4.58)	49 (17.7)	1.63 (0.86-3.01)
25% to <50%	149 (34.7)	31 (38.3)	2.89 (1.03-8.15)	78 (28.2)	1.65 (0.90-3.03)
50% to <75%	96 (22.4)	28 (34.6)	3.51 (1.19-10.42)	106 (38.3)	3.73 (1.96-7.11)
≥75%	8 (1.9)	2 (2.5)	4.06 (0.49-33.45)	20 (7.2)	7.76 (2.28-26.48)
			P trend = 0.01		P trend < 0.0001
Computer assisted					
<10%	115 (27.1)	13 (16.3)	1.00	36 (13.1)	1.00
10% to <25%	134 (31.5)	22 (27.5)	1.62 (0.67-3.91)	71 (25.9)	1.44 (0.86-2.42)
25% to <50%	150 (35.3)	40 (50.0)	2.57 (1.09-6.02)	126 (46.0)	2.45 (1.44-4.17)
50% to <75%	26 (6.1)	6 (6.3)	1.35 (0.35-5.21)	41 (15.0)	4.17 (1.96-8.88)
≥75%	—	—	—	—	—
			P trend = 0.03		P trend < 0.0001
per 25% increase			1.77 (1.07-2.95)		2.16 (1.59-2.94)

*ORs adjusted for time since prior screening examination, history of benign breast disease, smoking status, body mass index, family history of breast/ovarian cancer, parity, education, age at menarche, menopausal status, and use of hormone replacement therapy.

<0.0001 for missed- and true-interval cancers, respectively) and the continuous measure generated by the computer-assisted method (OR per 25% increase = 1.77 and 2.16 for missed- and true-interval cancers, respectively).

Average mammographic density was higher among current HRT users compared with nonusers (combined estrogen and progesterone use, 30.2% mean; estrogen use, 28.3% mean; nonuse, 23.1% mean). Therefore, additional adjustment by mammographic density was necessary to examine the association between HRT use and risk of developing an interval cancer. After adjusting for mammographic density, current use of estrogen alone was associated with an increased risk for true-interval cancer (OR, 1.75; 95% CI, 1.11-2.83) and current use of combined estrogen and progesterone therapy was associated with a significantly increased risk for both types of interval cases (missed interval OR, 2.84; 95% CI, 1.32-6.13; true interval OR, 1.79; 95% CI, 1.10-2.90; Table 4). There was no overall difference in risk for former users compared with never-users. Similar estimates of risk were found in analyses unadjusted for percentage of mammographic density, with the estimates for current estrogen and combination HRT use remaining within ~10% or less of the fully adjusted estimates.

Although based on small numbers, the risk for true-interval cancers among women taking cyclical-combined HRT was significantly greater compared with never users (OR, 5.04; 95% CI, 1.65-15.38). The opposite result was observed with missed intervals, with women taking continuous-combined HRT at a significantly higher risk compared with never users (OR, 2.50; 95% CI, 1.11-5.65). For current users, there was a significantly increased risk of interval cancers (missed and true) for women taking HRT for ≤5 years and a significantly increased risk of true-interval cancers for women taking HRT for >10 years. Additional adjustment of these estimates for type of HRT taken did not alter these results. For former users of HRT, there was no significant association with time since last use.

Discussion

This study found that the percentage of mammographic density and current use of HRT were both independently associated with an increased risk of being diagnosed with an interval cancer. Mammographic density was generally a stronger risk factor for interval cancers compared with HRT use. An increasing risk for missed and true-interval cancers was found for each 25% increase in mammographic density. The increased mammographic density associated with HRT use did not entirely explain the increased risk of interval cancers for women taking HRT. After adjusting for mammographic density, women taking estrogen alone had an almost 2-fold increased risk of being diagnosed with a true-interval cancer, whereas women taking combined HRT had a 2-fold increased risk of being diagnosed with a true-interval cancer or a 3-fold increased risk for a missed-interval cancer, compared with never users.

Higher mammographic density has been found to be associated more often with interval breast cancers as compared with screen-detected tumors (24-27). In this study, a significant trend of increasing risk of interval cancers (missed and true) was found with increasing mammographic breast density, measured either by radiologists or using the computer-assisted method. As would have been expected, the trend of increasing risk of interval cancers was more significant for true-interval cancers that were more likely masked from detection by the increased breast density than for missed-interval cancers which might have been slightly obscured, but were visible on retrospective review. This trend was similar to another study which found that when the analysis was limited to interval cancer patients identified as positive only in retrospective review (analogous to our ''missed intervals''), a smaller nonstatistically significant association with breast density was observed, whereas a stronger significant trend with breast density was observed for the true-interval cancer patients (27).

Table 4. Risk of missed- or true-interval breast cancer associated with HRT use

HRT	Screen detected *N* (%)	Missed interval			True interval		
		N (%)	OR (95% CI) Adjusted for covariates*	OR (95% CI) Additionally adjusted for mammographic density	N (%)	OR (95% CI) Adjusted for covariates*	OR (95% CI) Additionally adjusted for mammographic density
HRT use							
Never	238 (54.6)	35 (41.2)	1.00	1.00	115 (41.1)	1.00	1.00
Current estrogen alone	72 (16.5)	17 (20.0)	1.44 (0.68-3.04)	1.59 (0.73-3.50)	68 (24.3)	1.88 (1.15-2.85)	1.75 (1.11-2.83)
Current combination	71 (16.3)	27 (31.8)	3.21 (1.56-6.62)	2.84 (1.32-6.13)	66 (23.6)	1.77 (1.11-2.81)	1.79 (1.10-2.90)
Former †	55 (12.6)	6 (7.1)	1.04 (0.38-2.83)	1.07 (0.38-3.02)	31 (11.1)	1.11 (0.65-1.90)	1.11 (0.63-1.94)
Continuous/cyclical use ‡							
Never	238 (78.2)	35 (59.3)	1.00	1.00	115 (65.3)	1.00	1.00
Continuous	59 (19.4)	21 (35.6)	2.79 (1.30-5.97)	2.50 (1.11-5.65)	48 (27.3)	1.48 (0.89-2.45)	1.50 (0.88-2.54)
Cyclical	7 (2.3)	3 (5.1)	4.27 (0.86-21.11)	2.00 (0.28-14.15)	13 (7.4)	4.34 (1.53-12.31)	5.04 (1.65-15.38)
Duration (y) ‡							
Never	238 (62.5)	35 (44.3)	1.00	1.00	115 (46.2)	1.00	1.00
≤5	52 (13.6)	21 (26.6)	3.09 (1.42-6.69)	2.68 (1.19-6.05)	53 (21.3)	2.07 (1.25-3.44)	2.04 (1.20-3.46)
>5 to 10	44 (11.5)	13 (16.5)	1.95 (0.85-4.50)	2.18 (0.89-5.39)	31 (12.4)	1.22 (0.69-2.16)	1.24 (0.67-2.29)
>10	47 (12.3)	10 (12.7)	1.51 (0.62-3.69)	1.54 (0.60-3.93)	50 (20.1)	2.04 (1.21-3.46)	1.95 (1.13-3.36)
			P trend = 0.21	*P* trend = 0.23		*P* trend = 0.02	*P* trend = 0.04
Time since last use (y) §							
Never	238 (82.0)	35 (85.4)	1.00	1.00	115 (78.8)	1.00	1.00
>1 to <5	23 (7.9)	2 (4.9)	0.76 (0.15-3.77)	0.85 (0.15-4.58)	14 (9.6)	1.26 (0.58-2.72)	1.22 (0.54-2.42)
≥5	29 (10.0)	4 (9.8)	1.38 (0.41-4.66)	1.37 (0.39-4.78)	17 (11.6)	1.13 (0.57-2.24)	1.18 (0.57-2.38)

NOTE: Combination use indicates estrogen and progesterone therapy.

*ORs adjusted for time since prior screening examination, history of benign breast disease, body mass index, smoking status, family history of breast/ovarian cancer, parity, education, age at menarche, and menopausal status.

† Includes former estrogen alone and former combination users.

‡ Among current users.

§ Among former users.

Several studies have shown that current use of HRT reduces the effectiveness of screening by decreasing mammographic sensitivity and increases the risk of having an interval cancer by ~2- to 5-fold (12-16). Although, none of these studies recorded the type of HRT preparation used, these findings are consistent with the current study in which we noted a 2- to 3-fold increased risk of being diagnosed with an interval cancer for women currently using estrogen alone or combined estrogen and progesterone compared with never users.

Only a few studies have examined the combined effects of current use of HRT and breast density on sensitivity (7, 28, 29). Only one of these studies found a similar result to ours, concluding that adjustment for breast density did not attenuate the increased risk of interval cancers for HRT users (29). In contrast, the two other studies suggested that the effect of HRT on lowering sensitivity is a result of increasing breast density. This finding may be explained by the way in which these studies measured breast density: both evaluated screening mammography across different screening populations and had mammographic breast density assigned by radiologists using varied approaches which may account for the heterogeneity in risk estimates across studies (7, 28).

In examining the combined effects of HRT and mammographic density on sensitivity, none of the previous studies examined whether estrogen was taken alone or in combination. After adjusting for density, our study found that the risk of having a missed or true-interval cancer was significantly higher among women currently using combined estrogen and progesterone. Observational studies note that mammographic density may increase more markedly in response to estrogen and progesterone preparations (18-20), however, recent randomized clinical trials using continuous measurements have shown that the magnitude of this increase ranges from 3% to 6% on average for women taking estrogen plus progesterone (21, 23). In fact, we noted that relative to nonusers, the average difference in mammographic density was 7.1% greater among estrogen plus progesterone users. Therefore, it is not surprising that this modest increase in density did not entirely account for the increased risk of interval cancers among women taking combination HRT. Our results also showed a 5-fold increased risk for true-interval cancers for women taking combined HRT cyclically, which remained after adjusting for mammographic density, suggesting a possible alternative mechanism and does not seem to be explained by any resulting increase in breast density.

Although our study did find that women currently taking HRT for <5 years had a significant 3-fold increased risk of true- and missed-interval cancers, there was no consistent trend by duration of use. The increased risk for women taking HRT for <5 years may be explained by the formulation taken, as more recent use may suggest that women were more likely receiving combined preparations. However, the results remained unchanged after adjusting by type of HRT taken. Only one of the previous studies that examined the combined effects of HRT and mammographic density investigated the duration of current use and found no apparent trend in the sensitivity of mammography with duration of HRT use (29).

As our study, along with one other, has shown that the increased risk of interval cancers for women taking HRT is not entirely explained by any increase in mammographic density, it is important to explore the other possible reasons for this association (29). It has been suggested that the decrease in sensitivity among HRT users may be due to the increased surveillance of HRT users between screens resulting in higher rates of breast cancers not detected at screening. This explanation seems unlikely in our study as women were all part of a mammography screening program and were following uniform screening guidelines. More frequent screening mammograms among HRT users is, in theory, plausible, however, adjustment for time since previous screening examination had no effect on the observed associations in our study. Another reason may be that women using HRT may have faster-growing tumors that would result in interval cancers. However, most studies have shown that breast cancers among women taking HRT have a better prognosis compared with nonusers, and that prognosis is independent of detection mode (35, 36). The better prognosis among women taking HRT may also reflect the increased surveillance of this group.

We noted that current HRT use was associated with an increased risk of both types of interval cancers. If the increased risk attributed to HRT had been a result of masking due to increased breast density or rapid tumor proliferation during the interval between screening mammograms, we would have expected HRT use to have had a greater effect on increasing the risk of true-interval cancers, but this was not the case. Therefore, the effect of HRT on detection may have resulted from producing other breast changes such as enlarging cysts and fibroadenomas as well as increasing benign breast lesions that could have made it more difficult to immediately recognize signs of the tumor (37, 38). A future study will examine the histologic features of the breast cancers in this study, as well as other benign breast abnormalities present at the time of diagnosis by HRT use and detection.

Our study has several strengths, including the use of routine follow-up data collected on a population-based group of women who were all part of the same mammography screening program. Furthermore, information on breast density was collected and reviewed in a consistent way by experienced radiologists who were blinded to whether or not the cancer was screen-detected. In addition to assessing breast density by study radiologists, we used the computer-assisted method; it is reassuring to note that conclusions are similar regardless of the method of assessing breast density, results for the computer-assisted method were, however, slightly attenuated compared with the radiologist-determined assessment.

A potential limitation of the study was the insufficient power to explore the interactions between patterns of HRT use and the percentage of mammographic density on the risk of interval cancers. In addition, as per the screening protocol, few women in the study had a screening interval of less than or equal to 18 months prior to their diagnosis, thus, we were unable to examine if a shorter screening interval would reduce the effect of mammographic density or HRT use on increasing the risk of interval cancers. Although a few studies have found that even with shorter screening intervals of 1 year, sensitivity remained lower for women with dense breasts (25, 27); screening interval may have been important to examine in this study as the median time to diagnosis for both missed and true-interval cancers was just over 1 year by 28 to 77 days, respectively. Also, as HRT use was based on self-reported data, misclassification may have occurred. However, given that the average time between last screen and completion of the questionnaire was similar between groups, any misclassification may have been nondifferential and would have resulted in attenuating our estimates. In addition, pictures of the different types of HRT preparations were included in the study questionnaire to improve the accuracy of reporting.

This study confirmed previous findings that extensive mammographic density and current use of HRT were both independently associated with an increased risk of being diagnosed with an interval cancer. Our study further found that breast density and combination HRT use increased the risk of being diagnosed with either a missed or true-interval cancer and that there was no increased risk for former HRT users. In addition, for current HRT users, there was no consistent trend according to duration of use, and for former users, there was no increased risk according to time since last

use. However, given the small sample size of some of these subgroup analyses, certain findings may warrant further examination to substantiate the results.

In conclusion, the results of this study suggest that information on the percentage of mammographic density and current HRT use should be routinely collected at the time of mammographic screening. Although women at risk should continue to be screened by mammography, they must also be made aware of the effect of these factors on the sensitivity of mammography and perhaps offered complementary screening procedures such as additional mammographic views or digital mammography. In addition, women who have stopped taking HRT for more than a year with a normal screening mammogram can be reassured of the validity of their results.

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Anna M. Chiarelli, Victoria A. Kirsh, Neil S. Klar, et al.

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