Is a Dense Mammographic Parenchymal Pattern a Contraindication to Hormonal Replacement Therapy?

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The aim of the study was to find out whether the effect of hormonal replacement therapy (HRT) is modified by the mammographic parenchymal patterns on the risk of breast cancer. Subjects were 4163 Finnish women aged 40–47 years at entry who were invited to breast cancer screening every second year from 1982 to 1990. Mammographic parenchymal patterns (Wolfe's classification) were recorded at each screening round. The information, on use of HRT, was recorded from 1984. The follow-up ended in 1993 and up until that time 68 new breast cancers were diagnosed. A Poisson regression model was used in the analysis of the data. Use of HRT was not related to the risk of breast cancer (RR = 0.7, 95% CI 0.4–1.4), whereas mammographic parenchymal pattern was statistically significantly associated with risk of breast cancer. The age-adjusted relative risk of breast cancer among women with P2 versus N1 pattern was 2.5 (95% CI 1.3–4.8) and with DY versus N1 pattern 4.9 (95% CI 1.6–15.1). Women using HRT and with DY pattern were at substantially increased risk of breast cancer (RR = 11.6, 95% CI 2.5–53.6) compared with women not using HRT and with N1 pattern. There was an increased risk of breast cancer among women with DY mammographic parenchymal pattern who used HRT, which was consistent with a synergistic joint effect.

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In earlier studies it has been found that risk of breast cancer is increased among women using hormonal replacement therapy (HRT) (1–3) and that the risk increases with increasing duration of use (1). Although there has been some controversy during the past 20 years, most of the studies indicate that dense mammographic parenchymal patterns (according to Wolfe's classification P2 and DY patterns) are related to increased risk of breast cancer (4–9). Further, it has been reported that using HRT makes the breast more dense (10–13). On that basis we wanted to study whether there is a joint effect of HRT and mammographic parenchymal pattern on risk of breast cancer.

MATERIAL AND METHODS

The Cancer Society of Finland initiated a mammography-based pilot screening program in south-eastern Finland in 1982. The primary aim of the study was to gain experience for a nationwide population-based organized program and to predict the potential effectiveness of a public-health policy. Women residing in the city of Kotka and in 12 municipalities around it, and born in 1936, 1938, 1940 or 1942, were identified (n = 4 163) by the national population registry and they were invited to attend by a letter identifying the place and time of the screening. The invitation was repeated every other year. Compliance with screening during the study period was 86%. In 1990, this pilot program was merged with the national public-health policy, which gradually began in 1987. Details on the original material are reported elsewhere (14). The breast cancer cases not detected by screening were found by linkage to the Finnish Cancer Registry. The follow-up of this cohort was extended to the end of the year 1993. Cases diagnosed before or at the first screening or within 6 months of the first screening were excluded (n = 38). Later on, if cancer was diagnosed within 6 months from the screening, round *r*, the mammographic parenchymal pattern on the mammogram stemming from round *r*–1 was used. Three women had incomplete information on the status of their breasts and were excluded. A total of 4081 women were thus eligible for participation in the study.

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Table 1

Wolfe's classification of the breast (1)

Class	Description
N1	Parenchyma composed primarily of fat with, at most, small amounts of 'dysplasia'. No ducts visible.
P1	Parenchyma chiefly fat with prominent ducts in anterior portion up to one-quarter of volume of breast. Also, may be a thin band of ducts extending into a quadrant.
P2	Severe involvement with prominent duct pattern occupying more than one-quarter of volume of breast.
DY	Severe involvement with 'dysplasia'. Often obscures an underlying prominent duct pattern.

Those 4081 women attended from one to five screening rounds, which resulted in 16322 screening visits altogether. The information of mammographic parenchymal pattern was missing for 133 screens. Each screening visit consisted of one observational unit. The person years for exposure were calculated respectively as the time between two screening visits, or the time between screening visit and diagnosis of breast cancer or screening visit and the end of follow-up date.

The mammographic parenchymal patterns were defined by the one and same radiologist throughout the study according to Wolfe's classification and recorded at every screening round. The radiologist had access to the earlier mammograms and other information recorded at previous screening rounds. Wolfe's classification is based on the relative amounts of fat, epithelial and connective tissue densities and prominent ducts observed in the mammogram, and consists of four different classes N1, P1, P2, DY in ascending order of indication for density (1). Those classes are briefly described in Table 1. The mammographic parenchymal pattern of both breasts was taken into account by taking the average of right and left breast and rounding it to a more dense category if necessary. At every screening round age, body mass index [BMI; calculated using the formula weight (kg)/height $(m)^2$] and number of pregnancies were also recorded. The use of HRT was recorded systematically at each screening from 1984 by asking whether the women were using HRT at the time of screening.

In multivariate analysis with the Poisson regression model (15), the possible confounding effects of such breast cancer risk factors as age, BMI and number of pregnancies, which were found to be related to mammographic parenchymal patterns in our previous studies (16, 17), were controlled for. The expected relative risk of joint effect was estimated by multiplying the relative risks caused by solitary effects.

RESULTS

During the follow-up period 68 new breast cancer cases were diagnosed and the breast cancer incidence was 1.6 per 1000 person years. The percentage of women using HRT increased from 13.5% in 1984–1985 (second screening round) to 36.0% in 1990–1991 (fifth screening round). Also the mammographic parenchymal pattern of women changed to be more radiolucent. At the first screening round the prevalence of normal breast pattern (N1) was 13% and the prevalence of DY pattern was ~4%. At the last screening round, 8 years later, the prevalences of N1 and DY patterns were, respectively 46% and under 1% (Table 2).

The incidence of breast cancer increased with age. The risk of breast cancer among women aged 50–55 was three times higher than among women aged 40–44 (95% CI 1.4–6.7). Use of HRT was not a significant risk factor of breast cancer (RR = 0.7, 95% CI 0.4–1.4). Mammographic parenchymal pattern was statistically significantly associated with risk of breast cancer. The age-adjusted risk of breast cancer among women with P2 pattern was 2.5 (95% CI 1.3–4.8) and with pattern of DY 4.9 (95% CI 1.6–15.1) in terms of unit risk among women with N1 pattern (Table 3).

Table 2

Mammographic parenchymal patterns at first and last screening rounds for women screened at least twice in the Kotka Screening Project 1982–1990

Last round	First round				
	N1 (%)	P1 (%)	P2 (%)	DY (%)	Total (%)
N1	470 (97.9)	983 (69.7)	325 (18.1)	2 (1.3)	1780 (46.4)
P1	9 (1.9)	379 (26.9)	853 (47.5)	29 (19.3)	1273 (33.2)
P2	1 (0.2)	48 (3.4)	607 (33.8)	97 (64.7)	753 (19.6)
DY	0 (0)	0 (0)	12 (0.7)	22 (14.7)	34 (0.9)
Total	480 (100)	1 410 (100)	1 797 (100)	150 (100)	3 840 (100)
Only 1 round	53	90	73	6	222
Total	533	1 500	1 870	156	4 062[1]

[1] For 19 women, data on mammographic parenchymal patterns were unknown in one or several screening rounds.

Table 3

Number of breast cancer cases, woman years, incidence per 1 000 woman years (wy) and age-adjusted relative risk (RR) with 95% confidence intervals (CIs) of breast cancer by HRT and mammographic parenchymal patterns

Breast cancer risk factor	No.	Woman years	Incidence (per 1 000 wy)	Age-adjusted RR (95% CI)
Use of HRT				
No	44	25 328.7	1.7	1
Yes	14	8 707.0	1.6	0.7 (0.4–1.4)
Mammographic parenchymal pattern				
N1	16	12 430.1	1.3	1
P1	18	14 834.8	1.2	1.2 (0.6–2.4)
P2	29	13 708.4	2.1	2.5 (1.3–4.8)
DY	4	1 042.2	3.8	4.9 (1.6–15.1)

Compared with a reference group of women not using HRT and with a N1 pattern, the observed joint relative risk of HRT and N1, P1 or P2 was close to unity and not significant. In contrast, women using HRT and with DY mammographic parenchymal pattern were at increased risk of breast cancer (RR = 11.6, 95% CI 2.5–53.6), which was statistically significant (Table 4). The association could not be accounted for by the potential confounders of age, BMI and number of pregnancies, i.e. those known risk factors of breast cancer, which in our material, were also related to changes in mammographic parenchymal patterns. The expected relative risks (assuming multiplicative joint effect) were very close to the observed ones among women using HRT and either with P1 or P2 pattern. Among women using HRT and with a DY pattern the observed relative risk was 11.6 and the expected relative risk was only 1.5 (0.6∗2.5) assuming a multiplicative joint effect. The difference between the observed RR (11.6) and the expected (1.5) is an indication of synergism.

Table 4

Adjusted relative risks with 95% confidence intervals (in parentheses) of breast cancer by HRT and mammographic parenchymal pattern and expected relative risk of breast cancer assuming multiplicative joint effect of HRT and mammographic parenchymal pattern. Adjusted for age, BMI and number of pregnancies

Mammographic parenchymal pattern	HRT		
	No	Yes Observed	Expected
N1	1	0.6 (0.2–2.0)	0.6
P1	1.3 (0.6–2.9)	1.1 (0.4–3.1)	0.8
P2	2.4 (1.1–5.4)	1.3 (0.4–4.3)	1.4
DY	2.5 (0.3–20.2)	11.6 (2.5–53.6)	1.5

DISCUSSION

Dense mammographic parenchymal patterns (P2, DY) are associated with increased risk of breast cancer (4–8), which was also confirmed in our study (9). During a woman's lifetime the mammographic parenchymal patterns of breast may change (18, 19). HRT has been found to be a factor that changes the mammographic parenchymal patterns to be more dense (10–13). In our previous study, based on an longitudinal analysis, we found that the use of HRT increased the incidence of unfavourable changes (from N1, P1 to P2, DY) (16) but did not have any effect on incidence of favourable changes (from P2, DY to N1, P1) (17).

HRT itself has been found to be a risk factor of breast cancer (1–3). There is also a biologically plausible mechanism for association between HRT and breast cancer (20, 21). Oestrogen and combined treatment by oestrogen and progesterone increase the cell division rate of breast tissue and there is some evidence that cell proliferation is the underlying process by which DNA damage accumulates and the risk of breast cancer increases (21). HRT can also make the detection of breast cancer more difficult by reducing the sensitivity of mammography to detect small tumours and by reducing the quality of mammography by increasing breast tenderness and making the adequate compression of the breast difficult (22, 23).

In this study, information on the use of HRT was not asked for at the first screening round, which weakens the exposure information. Furthermore, there was no reliable information available on the duration of HRT use or on the type of used hormones. Because of memory bias we elected not to use the data on duration of HRT use.

In Finland, the use of HRT started to increase in the mid-1970s and in 1989 the current use of HRT was more common in Finland than in several other countries with a prevalence of 22% (among women aged 45–64) (24). However, women mainly used hormones for short periods around the menopause (25). Based on the sales information of hormones until the mid-1980s oestrogens and their combinations were sold more than a combination of oestrogens and progestins. By 1987, equal amount of both types of hormones were sold. (26) In our material the prevalence of use of HRT increased from 13.5% at second screening round to 36.0% at fifth screening round and was thus somewhat higher than on average in Finland. This was expected because our material stems from the southern urban area.

In our material there was no statistically significant overall effect of HRT on the risk of breast cancer. Time of actual hormone exposure (use) was probably short as indicated by Finnish data (24) and there were only a few users in our study at the beginning of follow-up. The short exposure time may partly explain the lack of a strong association between the use of HRT and breast cancer in our study. However, HRT among women with DY mam-

our study. However, HRT among women with DY mammographic parenchymal patterns affected the risk of breast cancer. There was a statistically significant over 11-fold risk of breast cancer among women undergoing HRT with DY patterns, whereas the expected relative risk was 1.5 assuming a multiplicative joint effect. Therefore, our results are consistent with a synergistic interaction between HRT and mammographic parenchymal patterns. However, our number of data is small and the difference between observed and expected joint effect (11.6 vs. 1.5) is subjected to substantial random variation. The association cannot account for possible confounders, i.e. age, BMI and number of pregnancies, which were found in our previous studies (16, 17) to be associated with incidence of mammographic parenchymal patterns. To be a confounder, the variable has to correlate both with outcome and exposure. On that basis we adjusted for the above three factors.

Among those using HRT, only women with unfavourable DY mammographic parenchymal pattern were at significantly increased risk of breast cancer, whereas among women with N1, P1 or P2 pattern the relative risk of breast cancer was close to unity and not statistically significant. This observation is consistent with a synergistic joint effect of HRT and DY mammographic parenchymal pattern on risk of breast cancer. However, our sample was small and the overall pattern of HRT use and other risk factors of breast cancer among Finnish women may be different from that in other countries. Therefore our finding should be confirmed by other studies before concluding whether the DY mammographic parenchymal pattern can be considered as a contraindication of HRT.

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