Risk of Breast Cancer and Changes in Mammographic Parenchymal Patterns Over Time

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The relationship between sequential mammographic parenchymal patterns and breast cancer was estimated and the results were applied to selective screening. In a pilot screening program 4163 Finnish women aged 40–47 years at entry were invited to be screened every second year from 1982 to 1990. Mammographic parenchymal patterns (Wolfe's classification) were recorded at each screening round. The follow-up ended in 1993 and up until that time 68 new breast cancers were diagnosed. The age-adjusted relative risk of breast cancer was 2.5 (95% CI 1.5–4.0) among women with high-risk mammographic parenchymal patterns (P2,DY) at the screenings preceding cancer diagnosis compared with those with low-risk patterns (N1,P1). After further adjustment for body mass index, number of pregnancies and size of the breast, the relative risk increased to 2.8 (95% CI 1.7–4.9). The mammographic parenchymal pattern is an independent risk factor of breast cancer but not strong enough to be used as a criterion for selective screening.

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A relationship between risk of breast cancer and specific mammographic parenchymal patterns was first proposed by Wolfe (1, 2). Since then several studies reported weaker associations (e.g. (3–5)) resulting in somewhat inconsistent conclusions about the usefulness of mammographic parenchymal patterns to identify a high-risk group for selective screening or to indicate the interval length between screening for breast cancer (e.g. (6, 7)).

The purpose of this study was to estimate the relationship between the mammographic parenchymal patterns and breast cancer and to evaluate the feasibility of applying the patterns in selective screening for breast cancer.

MATERIAL AND METHODS

In 1982 the Cancer Society of Finland initiated a mammography-based pilot screening program in southeastern Finland. 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 neighbouring municipalities and born in 1936, 1938, 1940 or 1942 were identified (n = 4163) by the national population registry and invited to attend by a letter identifying the place and time of the screening. The invitation was repeated every other year. Compliance with screening in the study period was 86%. In 1990, this pilot program was merged with the national public health policy which began in 1987. Details on the original material are reported elsewhere (8). 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 after the first screening were excluded (n = 38). Three women had incomplete information on the status of their breasts and were excluded; 4081 women were thus eligible for participation in the study. Those 4081 women attended from 1 to 5 screening rounds which resulted in a total of 16322 screening visits. For 133 screenings the information on mammographic parenchymal pattern was missing. Each screening visit consisted of one observational unit. The person years for each screening visit were calculated separately, being 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 one and the 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

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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.

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 includes four different classes N1, P1, P2, DY, in ascending order of indication for density (1). These classes are briefly described in Table 1. The mammographic parenchymal pattern of both breasts was taken into account by taking the average of the right and left breast and rounding it to a less favourable alternative if necessary. For most of the analyses the mammography patterns of N1,P1 and of P2,DY were combined. At every screening round age, size of the breast (measured as brassiere cup size), body mass index (BMI) (calculated using the formula weight (kg)/height $(m)^2$) and number of pregnancies were also recorded.

The association between mammographic parenchymal patterns and occurrence of breast cancer was assessed using the information from the first visit only and from the separate visits preceding cancer diagnosis. The effect of change in mammographic parenchymal pattern of the occurrence of breast cancer was also assessed. The analysis included women who had been screened at least twice and more than 6 months before the diagnoses of cancer if diseased (n = 3840). The follow-up started at the second screening round and ended either with the first diagnosis of breast cancer or with the end of follow-up, whichever was first.

In a previous analysis of this material we found that old age, a high BMI, large size of the breast and multiparity were associated with the incidence of favourable (N1,P1) (9) mammographic parenchymal patterns and young age, a low BMI and small size of the breast with the incidence of unfavourable (P2,DY) (Salminen et al. Unpublished study) patterns. The possible confounding effects of these breast cancer risk factors on the relationship between mammographic parenchymal patterns and breast cancer were adjusted for by multivariate analysis with the Cox proportional hazard model (10).

RESULTS

At the first screening round, the prevalence of normal mammographic parenchymal pattern (N1) was 13% and the prevalence of DY pattern was about 4%. There was a drift in the mammographic parenchymal patterns from the unfavourable P2,DY types to the favourable N1,P1 types between the first and the last screening rounds. At the last screening round the prevalence of N1 patterns was 46% and that of DY patterns under 1% (Table 2).

During the follow-up 68 new breast cancers were diagnosed. The age-adjusted relative risks (RR) of breast cancer among women with unfavourable parenchymal patterns of the breast at the first round were only marginally increased (RR varied from 1.5 to 1.3 among women with P2 to DY patterns). After taking into account the mammographic parenchymal pattern sequentially at the rounds preceding the diagnosis, the RRS varied from 2.6 to 4.7 and were statistically significant (Table 3). There was only a small and not statistically significant increase in

Table 2

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

	First round				
Last round	N1 (%)	P1 (%)	P2 (%)	DY (%)	Total (%)
N1	470 (97.9)	983 (69.7)	325 (18.1)	2 (1.3)	1 780 (46.4)
P1	9 (1.9)	379 (26.9)	853 (47.5)	29 (19.3)	1 273 (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*

* For 19 women, data on mammographic parenchymal pattern were unknown in one or several screening rounds.

Table 3

Number of breast cancer cases and person years, incidence of breast cancer per 100 person years and age-adjusted relative risk of breast cancer by mammographic parenchymal patterns defined at first screening round or at screening rounds preceding the breast cancer diagnosis

Mammographic parenchymal patterns	No. of cases	Person years	Incidence	Age-adjusted RR (95% CI)
First round				
N1	8	5 031.9	0.16	1
P1	18	15 606.8	0.12	0.9 (0.4–2.0)
P2	39	19 996.3	0.20	1.5 (0.7–3.4)
DY	3	1 653.5	0.18	1.3 (0.4–5.1)
N1,P1	26	20 638.6	0.13	1
P2,DY	42	21 649.7	0.19	1.7 (1.0–2.8)
At screening rounds preceding cancer*				
N1	16	12 430.1	0.13	1
P1	18	14 834.9	0.12	1.2 (0.6–2.4)
P2	29	13 708.2	0.21	2.6 (1.4–4.9)
DY	4	1 042.2	0.38	4.7 (1.5–14.4)
N1,P1	34	27 264.9	0.12	1
P2,DY	33	14 750.5	0.22	2.5 (1.5–4.0)
Change				
First and last N1,P1	25	18 213.6	0.14	1
First P2,DY, last N1,P1	6	4 027.4	0.15	1.2 (0.5–2.8)
First N1,P1, last P2,DY	1	734.2	0.14	1.3 (0.2–9.8)
First and last P2,DY	21	9 255.1	0.23	2.2 (1.2–3.9)

* One cancer case with unknown mammographic parenchymal pattern.

the risk of breast cancer among those women whose breast patterns changed either from favourable to unfavourable or from unfavourable to favourable compared with women whose patterns remained favourable but the numbers of cases were small. Persistence of P2,DY pattern was associated with an age-adjusted RR of 2.2 (95% CI 1.2–3.9) compared with women with a consistent mammographic parenchymal pattern of N1,P1 (Table 3).

The crude RR of breast cancer was 2.0 after any round among women with P2,DY parenchymal patterns. If the mammographic parenchymal patterns P2,DY were used for selective screening, this corresponds to a sensitivity of 49% (33/67) and specificity of 65% (27264.9/42015.4) (Table 3). The adjustment for age, BMI, number of pregnancies and size of the breast strengthened the association and the adjusted RR was 2.8 (95% CI 1.7–4.9) (Table 4).

DISCUSSION

Studies on the relationship between breast cancer risk and mammographic parenchymal patterns have varied according to whether the mammograms were taken before, at the time of, or after the diagnosis of breast cancer (11). Throughout this study, the mammograms were classified by one and the same radiologist as a routine part of the screening work. All the mammograms were interpreted at least 6 months before the diagnosis of cancer. Furthermore, the sequential mammograms enabled us to study the effect of change in mammographic parenchymal pattern as well as time between mammogram and diagnosis of breast cancer.

In their review, Saftlas & Szklo (11) and Boyd et al. (12) concluded that most carefully conducted epidemiological studies support a positive association between mammographic parenchymal pattern and the risk of breast cancer. Mammographic parenchymal patterns persisted as a risk indicator of breast cancer for 4 (13) to 10 years (14). Mammographic parenchymal patterns are associated with many known breast cancer risk factors (3, 9, 14, 15, and unpublished study). Therefore, the relationship between the patterns and breast cancer may be only secondary and the pattern only a link in the causal chain.

In our study, we found that a statistically significantly increased risk of breast cancer was conferred by an unfavourable mammographic parenchymal pattern. In our previous study (9 and unpublished study), we found that the mammographic parenchymal patterns were related to age, number of pregnancies, size of the breast and BMI, which are also risk factors of breast cancer. Therefore, these breast cancer risk factors were possible confounders and they were selected for multivariate analysis. It showed that the effect of mammographic parenchymal pattern on the risk of breast cancer could not be accounted for by these confounders. In fact, unfavourable change was inversely related and favourable change was directly related to the risk factors of breast cancer. Therefore, the relative risk of breast cancer related to mammographic parenchymal patterns increased after such an adjustment. Hence our results

Table 4

Crude and adjusted relative risk of breast cancer with 95% confidence intervals (CI) according to mammographic parenchymal patterns at the 16 322 screening visits

Mammographic parenchymal pattern	Crude risk (95% CI)	Adjustment for	
		Age (95% CI)	Possible confounders* (95% CI)
P2/DY vs. P1/N1	2.0 (1.2–3.2)	2.5 (1.5–4.0)	2.8 (1.7–4.9)

* Adjusted for age, number of pregnancies, body mass index (BMI) and breast size.

are consistent with those by Saftlas & Szklo (11), Saftlas et al. (13) and Carlile et al. (16) showing that mammographic parenchymal pattern is an independent risk indicator of breast cancer. Furthermore, we found that the shorter the lag between definition of breast pattern and diagnosis of breast cancer, the higher the relative risk. The mammographic parenchymal pattern changed in general to a more favourable one and the highest risk was found among women with persistent high-risk patterns. Therefore, the relationship between persistent parenchymal pattern and risk of breast cancer was diluted by the subsequent changes, when early measurement was used to describe the association. We conclude that sequential measurements give substantially improved information on the relationship between mammographic parenchymal pattern and breast cancer.

Subsequent to the original classification by Wolfe (1), other classifications with quantitative estimates of breast density have been developed and used (5, 15, 17). Warner et al. (4) in their meta-analysis found that the quantitative method led to higher odds ratios than Wolfe's original method. However, since our material stems from a time prior to the development of more refined quantitative methods measuring breast density, we were unable to evaluate these more recent classification measures.

The data on woman's reproductive characteristics, family history of breast cancer and use of hormones have been studied as criteria for selective screening. In those studies these variables defined a high-risk population with a size from 37 to 65% of the total population and the proportion of cancers estimated to be detected in such a high-risk subgroup varied from 63 to 84% which was regarded to imply poor validity, if applied for selective screening (18–20). So far, not even a combination of these risk factors is recommended to be used as a criterion for selective screening. A research issue of interest is the potential applicability of mammographic parenchymal patterns as high-risk markers for selective screening. However, according to McDermott (21) the risk factors which included the high-risk mammographic parenchymal pattern (P2,DY) were prevalent in only 25% of breast cancer patients. Therefore, the use of mammographic parenchymal patterns for selection of women for breast cancer screening has been criticized because breast cancer is also diagnosed among large numbers of women who do not have mammographic markers indicating increased risk (15, 22, 23), i.e. the sensitivity of the mammographic pattern as a screening test is low. Nor are the patterns of practical use because of a high prevalence of high-risk patterns (5), i.e. the specificity is also poor. In our material the potential use of parenchymal pattern as a criterion for screening (with a sensitivity of 49% and specificity of 65%) was far from the validity of mammography, which in the nationwide organized program in Finland has a sensitivity of 77% (24) and a specificity of 96% (25). Therefore, the relationship between breast cancer risk and mammographic parenchymal pattern on its own is not valid enough to be used as a screening test or as a criterion for selective screening.

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