

Effect of Baseline Breast Density on Breast Cancer Incidence, Stage, Mortality, and Screening Parameters: 25-Year Follow-up of a Swedish Mammographic Screening

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Abstract

Background: We aimed to quantitatively assess the effect of baseline breast density on the incidence, stage, and mortality, and also the natural course of the disease, considering the sensitivity of mammography to clarify its causal or masking effect.

Methods: In total, 15,658 women ages 45 to 59 years from the Kopparberg randomized controlled trial in Sweden were prospectively followed from 1977 until 2004 to ascertain breast cancer incidence and death. Dense breast tissue collected at the beginning of the study was defined as pattern IV or V by the Tabár classification. Conventional risk factors were also collected at baseline. The three-state Markov model was used to estimate the preclinical incidence rate and the mean sojourn time given the fixed sensitivity.

Results: Dense breast tissue was significantly associated with breast cancer incidence [relative risk (RR) = 1.57 (1.18-1.67)] and with breast cancer mortality [RR = 1.91 (1.26-2.91)] after adjusting for other risk factors. Cumulative incidence rates irrespective of nonadvanced and advanced breast cancer were higher in dense breast tissue compared with nondense tissue but no difference in survival was detected between dense and nondense breast tissue. Dense breast tissue had a higher preclinical incidence rate (causal effect) and shorter mean sojourn time (masking effect) compared with nondense breast tissue by controlling the sensitivity of mammography.

Conclusion: We corroborated the effect of baseline breast density with a higher incidence and mortality and also showed its contribution to a masking effect with long-term follow-up data.

Impact: Results suggest that the screening policy with a predominantly shorter screening interval and with alternative imaging techniques might be indicated in women with dense breast tissue. *Cancer Epidemiology Biomarkers Prev*; 19(5); 1219–28. ©2010 AACR.

Introduction

The positive association between breast density and breast cancer risk has been reported by a meta-analysis study (1) and several well-designed longitudinal studies in recent years (2-6). The underlying biological role is upheld by its associated factors including younger age (7), premenopausal status, exogenous hormone use (8, 9), conventional risk factors (10), and genetic influence (11, 12), possibly through mutagenesis and mitogenesis

mechanisms (13, 14). In addition to biological causal effects, dense breasts also have a masking effect that leads to a high rate of interval cancers due to a lower sensitivity, particularly in young women (5, 15).

In spite of these findings, very few studies have elucidated the effect of mammographic density measured at baseline (prediagnostic mammograms) on incidence, stage, mortality, and mammography screening sensitivity related to masking effects using very long follow-up data. Doing so is helpful for predicting incidence, stage, and

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hood function. L. Tabár contributed to the study design, data collection, and interpretation of results. R.A. Smith made a contribution to the interpretation of the findings and revision of the manuscript. H-H. Chen contributed to the overall framework of the manuscript, study design, statistical analysis, and revision of the manuscript. All authors have read and approved the manuscript.

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death associated with breast cancer among women with dense breasts even as their breast tissue composition changes with time. To separate biological factors from the masking effect, we proposed an alternative approach by constructing a three-state disease natural history model [true normal, preclinical screen-detectable phase (PCDP), and clinical phase; see Fig. 1] supported by the corresponding data with mammographically normal, mammographically detected, and symptomatic cancers such as interval cancer, respectively, to estimate the two parameters, preclinical incidence rate (the rate of entering into the PCDP), and the mean sojourn time (MST; average duration of staying at the PCDP phase) given the sensitivity of mammography.

The purpose of this study was first to assess the cumulative incidence of all breast cancer and advanced cancers (defined by node positive, tumor size >2 cm in diameter or histologic grade of ≥ 2), case fatality, and population mortality from breast cancer by the density of breast tissue. We then estimated the preclinical incidence rate, age-specific MST, and the average duration of the preclinical detectable period by breast density based on the three-state disease natural history model in a screened cohort of 15,658 women ages 45 to 59 years at entry. Using this information, we addressed the following two questions. Is the preclinical incidence rate higher in dense breast than nondense breast? Does dense breast tissue have a shorter MST than nondense breast tissue given a constant sensitivity?

The high preclinical incidence rate has been postulated to be a reflection of an increased risk of breast

cancer (causal effect) and the shorter MST makes the detection of breast cancer by mammography difficult (masking effect).

Subjects and Methods

Study subjects and methods of cancer detection. The study population was composed of women ages 45 to 59 years at entry in the Kopparberg randomized controlled trial, one of the Swedish Two-County Trials for mammography screening for breast cancer that began in 1977. The details of study design and main results were included in the first article published in 1985 (16). A series of successive follow-up results on the comparison of mortality between the invited and the uninvited groups have been described in full elsewhere (17-19). In brief, women ages 40 to 74 years were randomized into invitation for screening (active study population) or no invitation (passive study population) between 1977 and 1981. During the trial period, women in the active study population provided information on breast density while they underwent mammographic examination. Note that after the trial, women enrolled in this study were continuously invited to have periodic service screenings until 70 years of age. Breast cancer cases and deaths were therefore ascertained by prospectively following the enrolled women over time until 2004 with an average of 25 years of follow-up.

We restricted our analysis to the 16,703 women ages 45 to 59 years, as estimation was very unstable in the 40- to 44-years age group due to small numbers of

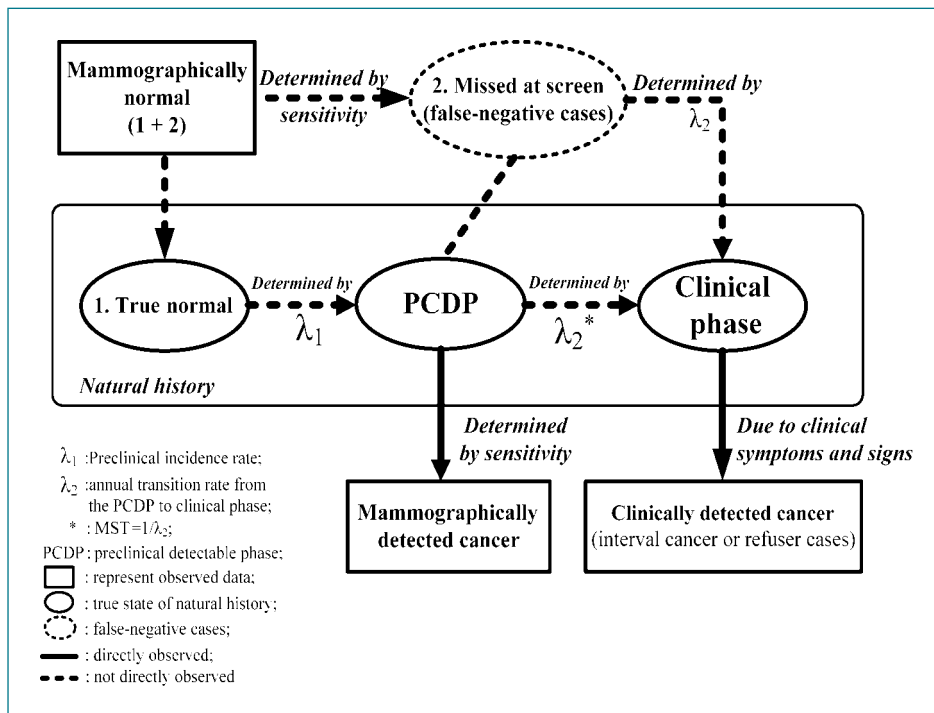


Figure 1. The three-state natural history model and the observed data from population-based screening with mammography for breast cancer.

cases; <4% of women ages 60 years and older were in the dense category. Of 16,703, 15,658 (80.6%) women, including 4,664, 5,181, and 5,813 for women ages 45 to 49, 50 to 54, and 55 to 59 years, respectively, had complete information on the classification of their first mammographic density pattern. This formed the data set for the following analysis. All breast cancer cases detected by different methods were classified as three detection modes, mammographically detected cancers, interval cancer, and refuser cases, all of which are regarded as clinically detected modes (Fig. 1). The first is defined as participants who had breast cancers detected with mammography upon invitation. This mode is further divided into first and subsequent screen-detected cases. The second is symptomatic cancers that occurred due to clinical symptoms or signs in between two regular screens among participants. The third is related to breast cancers diagnosed due to clinical symptoms and signs among nonparticipants.

Classification of breast density and conventional risk factors. At the inception of study, low-dose film-screen mammography with a mediolateral oblique view was applied to all participants in all of Kopparberg County (20, 21) by way of mobile units. Examinations were implemented by three technicians and read by the professional radiologist of the Department of Mammography at the Central Hospital in Falun, Sweden, pursuant to the standard procedure set up by Tabár (22). Breast density was collected at the beginning of the screening and classified as dense (Tabár patterns IV and V) or non-dense (Tabár patterns I-III; ref. 23). The Tabár patterns IV and V correspond to Wolfe patterns P2 and DY, excluding QDY (7). In addition, information on age at menarche, body mass index (BMI), age at first full-term pregnancy, and menopausal status was obtained from the active study population members with a questionnaire at the beginning of screening.

Natural history model, sensitivity of mammography, and observed data. By superimposing the findings of mammographies and different methods of detecting cancers into the temporal natural history of breast cancer, Fig. 1 shows the observed data (the square symbols) and three states of disease natural history (ovals) including "true normal," "PCDP," and "clinical phase." Three observed data sets correspond to three true states, including "mammographically normal," which was composed of "true normal" and "false-negative cases missed at screening," mammographically detected cases, and clinically detected cases (including interval cancers, false-negative cases, and newly incident cases, and the refuser cases). Mammographically detected cancers from the initial and subsequent screenings provide information about the preclinical incidence rate (λ_1), sensitivity of mammography, and MST of staying at the PCDP phase. Interval cancers provide information on the preclinical incidence rate, the transition rate from the PCDP to the clinical phase (λ_2), and the sensitivity of mammography. The refuser cases contribute to the preclinical

incidence rate and the transition rate from the PCDP to the clinical phase without being affected by the sensitivity of mammography.

Statistical analysis. All subjects in this study were followed over time until the end of 2004. Outcomes of breast cancer incidence and mortality were ascertained through the linkage of our main data set with the cancer registry and the trial committee report. Incidence of and mortality from breast cancer were analyzed by Poisson regression (24). Survival analysis was done using the Cox proportional hazards regression model (25). Regarding age adjustment in the multivariable regression model, due to our prospective study design with breast density classified at baseline, age at recruitment was used in the Poisson regression analysis whereas the age at diagnosis was used in the Cox proportional hazards regression model.

For the three-state natural history model delineated in Fig. 1, estimating the two parameters, the preclinical incidence rate (λ_1) and the MST ($1/\lambda_2$), is of great interest, along with the average duration of staying at PCDP, making allowances for sensitivity by making full use of data on mammographically detected cancer, interval cancers, and cancers from the refuser group based on the Chen et al. method (26). The former parameter was used to assess the effect of breast density on the increased risk of breast cancer (causal effect) and the latter was used to clarify whether dense breast tissue might make the detection of cancer by mammography difficult (masking effect), following the two hypotheses described above. The upshot for the link between the shorter MST and masking effect of dense breast is that because the MST represents the transition rate of progression from the PCDP to the clinical phase, it is not only determined by the underlying growth rate of breast tumors, but also can be affected by the sensitivity of the screening tool. Because sensitivity is correlated with MST (see Fig. 1), disentangling both parameters only on the basis of the directly observed data is very difficult, as underscored in Fig. 1. Given a specific growth rate of breast tumors, the higher the sensitivity of the screening tool (that is, advanced imaging technique), the longer the MST and the earlier the detection of breast cancer would be achieved and vice versa. On the other hand, given a specific screening tool, the more rapidly growing cancer in dense breast tissue, the shorter the estimated MST would be. This suggests that the variation in sensitivity and natural growth rate that leads to a masking effect related to breast density is shared with each other. Both variations can be reflected by the estimated MST when the sensitivity is controlled or by estimating sensitivity when the MST is fixed in either way. The technique for estimating one parameter by controlling other parameters has the advantage of reducing identifiable problems due to a correlation between MST and sensitivity. We estimated the preclinical incidence rate and the MST by age and density by adjusting sensitivity with the parameter that was estimated by applying the conventional proportional

incidence method to calculate 1 minus the ratio of the rate of interval cancer to the expected incidence rate in the absence of screening. The maximum likelihood estimation method was applied to estimating the two parameters and their 95% confidence intervals (CI).

Results

Table 1 shows breast tissue density by age group. Density declined with age and 19.9% of those ages 45 to 49 years had dense breast tissue compared with 6.6% of those ages 55 to 59 years. The overall prevalence of dense breast tissue was 12.7%. Table 1 also shows the number of cancers and the proportion of interval cancers among total breast cancers by age and density. Tumors in dense tissue were significantly more likely to be interval cancer ($P = 0.02$).

Table 2 shows the estimated effects of density and other factors on breast cancer incidence. In the multivariable model, the adjusted relative risk for dense versus nondense breast was 1.57 (95% CI, 1.23-2.01). Figure 2A shows the cumulative incidence of breast cancer by density. Figure 2B and C show the cumulative incidence stratified by age of entry, which revealed that the effect of dense breast was more remarkable in women ages 45 to 49 years compared with those ages 50 to 59 years due to the substantial change in breast density in the latter age group after long-term follow-up. Figure 3A to C show the cumulative incidence of tumors larger than 2 cm, of node-positive tumors, and histologic grade 2 or 3 tumors by breast density, with the adjusted relative risks, taking BMI and age into account. All were statistically significant at incidences of 1.79 (95% CI, 1.22-2.63) for tumors >20 mm in size, 2.46 (95% CI, 1.66-2.62) for cancer with lymph node involvement, and 1.80 (95% CI, 1.39-2.34) for histologic grade 2 or 3 tumors.

Figure 3D to F also show the cumulative incidence of the counterparts of three tumor attributes (<2 cm, node negative, and grade 1), respectively. The corresponding

adjusted relative risks were also statistically significant, 1.62 (95% CI, 1.27-2.06), 1.52 (95% CI, 1.18-1.96), and 1.37 (95% CI, 0.97-1.96), with tumors <20 mm in size, node negative, and histologic grade 1, respectively.

Density was suggestively, but not significantly, associated with survival ($P = 0.103$; Fig. 2D). The unadjusted Cox regression relative hazard ratio associated with dense tissue was 1.41 (95% CI, 0.92-2.14). Adjusting for age, tumor size, node status, grade, and BMI, the relative hazard was 1.75 (95% CI, 0.99-3.10). By stratification of three tumor attributes, the differences in the survival curves between dense and nondense breast tissue were not significant not only for tumors >20 mm in size [hazard ratio (HR), 1.14; 95% CI, 0.63-2.08], with node involvement (HR, 1.28; 95% CI, 0.75-2.17), and of histologic grade 2 or 3 (HR, 1.50; 95% CI, 0.96-2.35), but also for tumors <20 mm in size (HR, 1.69; 95% CI, 0.90-3.17), node-negative (HR, 1.19; 95% CI, 0.55-2.55), and histologic grade 1 (HR, 2.04; 95% CI, 0.53-7.79). We also examined the heterogeneity of the comparison between dense breasts and nondense breasts stratified by each tumor attribute and found a lack of statistical significance with respect to tumor size ($\chi^2_{(1)} = 0.05$; $P = 0.82$), node status ($\chi^2_{(1)} = 2.67$; $P = 0.10$), and histologic grade ($\chi^2_{(1)} = 0.35$, $P = 0.55$).

Figure 2E shows the cumulative mortality from breast cancer by density. The relative risk of breast cancer death (28 and 99 deaths for dense and nondense breast tissue, respectively) for dense versus nondense tissue was 1.91 (95% CI, 1.26-2.91). The increased mortality was, to a greater extent, due to the increased incidence and, to a lesser extent, due to the (nonsignificant) poorer survival with dense breasts in the light of findings from two components that determine mortality, incidence, and survival.

The overall sensitivity based on proportional incidence method was 79.5% (73.3-85.8%). Table 3 shows that dense breasts had lower sensitivity than nondense breasts [62.8% (95% CI, 47.2-78.3%) versus 82.0% (95%

Table 1. Prevalence of dense breast tissue and the proportion of interval cancer among total breast cancer by density and age

Age group (y)	Item	Density classification		Total (%)	% of density
		Nondense (%)	Dense (%)		
45-49	No. of participants	3,735	929	4,664	19.9
	Interval cancer/total BC cases	48/182 (26.4)	23/79 (29.1)	71/261 (27.2)	
50-54	No. of participants	4,508	673	5,181	13.0
	Interval cancer/total BC cases	38/261 (14.6)	8/42 (19.0)	46/303 (15.2)	
55-59	No. of participants	5,427	386	5,813	6.6
	Interval cancer/total BC cases	36/281 (12.8)	6/28 (21.4)	42/309 (13.6)	
Total	No. of participants	13,670	1,988	15,658	12.7
	Interval cancer/total BC cases	122/724 (16.9)	37/149 (24.8)	159/873 (18.2)	

Abbreviation: BC, breast cancer.

Table 2. Univariate and multivariate analysis of risk factors for breast cancer incidence

Variable	Group	Univariate	Multivariate
Age at recruitment, y	45-49	1.00	1.00
	50-54	1.05 (0.88-1.24)	1.25 (0.98-1.59)
	55-59	0.95 (0.80-1.12)	0.98 (0.74-1.30)
Age at menarche, y	≥14	1.00	1.00
	<14	1.20 (1.01-1.42)*	1.15 (0.95-1.39)
Pattern	Nondense	1.00	1.00
	Dense	1.45 (1.21-1.74) [†]	1.57 (1.23-2.01) [‡]
BMI	<25	1.00	1.00
	≥25	1.20 (1.03-1.40)*	1.23 (1.01-1.50)*
AFFTP, y	<20	1.00	1.00
	21-25	0.97 (0.80-1.17)	0.96 (0.74-1.24)
	26-30	1.12 (0.90-1.17)	0.96 (0.71-1.31)
	≥31	1.32 (1.02-1.71)*	1.16 (0.81-1.67)
	Never	1.00 (0.78-1.29)	0.87 (0.61-1.24)
Menopausal	Yes	1.00	1.00
	No	1.15 (1.00-1.32)*	1.10 (0.88-1.38)

Abbreviation: AFFTP: age at first full-term pregnancy.

* $0.01 \leq P < 0.05$.

[†] $P < 0.0001$.

[‡] $0.0001 \leq P < 0.01$.

CI, 75.2-88.8%]. The results also show a lower sensitivity of dense breast tissue compared with nondense breast tissue regardless of age. Table 3 shows the results of assessing the two hypotheses related to the preclinical incidence rate (λ_1) and MST ($1/\lambda_2$) between dense and nondense breast tissue by age, given a sensitivity of 79.5% obtained from the proportional incidence method. The preclinical incidence rates were higher in dense breast tissue than nondense breast tissue by 1.65-fold. The difference reached statistical difference as no overlapping of 95% CIs occurred between the two groups. Similar findings were observed based on the three age groups. However, only the result of young women ages 45 to 49 years was statistically significant. By fixing sensitivity as a constant parameter, we also found that dense breast tissue tended to have shorter MST than nondense tissue although with a lack of statistical significance (95% CIs overlapped between the two groups).

Discussion

Using long-term follow-up population-based screening data, this study confirmed the effect of breast density measured at baseline on an increased risk of breast cancer, which was supported by several significant findings: higher adjusted relative risks of dense versus nondense breast tissue in either the overall breast cancer or nonadvanced breast cancer (less affected by a masking effect and supporting a causal effect) and also preclinical inci-

dence rates estimated from the three-state disease natural history model. A masking effect, to a lesser extent, also showed a higher risk of finding advanced breast cancer (more likely to be affected by a masking effect) and also a shorter MST for women with dense breasts, which makes detection of cancers by mammography difficult.

We also found that dense tissue was significantly associated with increased mortality from breast cancer. This was partly due to its association with a higher incidence of the disease and partly to the nonsignificant association with poorer survival. Multiplying the relative risk for incidence, 1.40, by the relative hazard from the Cox regression, also 1.41, gives 1.97, which was close to the observed mortality relative risk of 1.91. This result was slightly higher but consistent with the mortality result based on the data from a Demark mammographic screening with 10 years of follow-up (6). The association of dense breast tissue with aggressive tumors was similar to the study of Aiello et al. (27). Within that study, large tumors (>1.0 cm) or lymph node positivity was found in women with dense breasts, especially in screen-detected cancers (27). However, the results on the histologic grade in their study were different from ours, which may have been due to a disparity between study designs. Consistent with the stronger association of density with node-positive or poor differentiation of breast cancers, survival was poorer in those with dense tissue, although this difference was not significant. Note that the association of density with survival becomes stronger after adjusting for these factors, which suggests that the

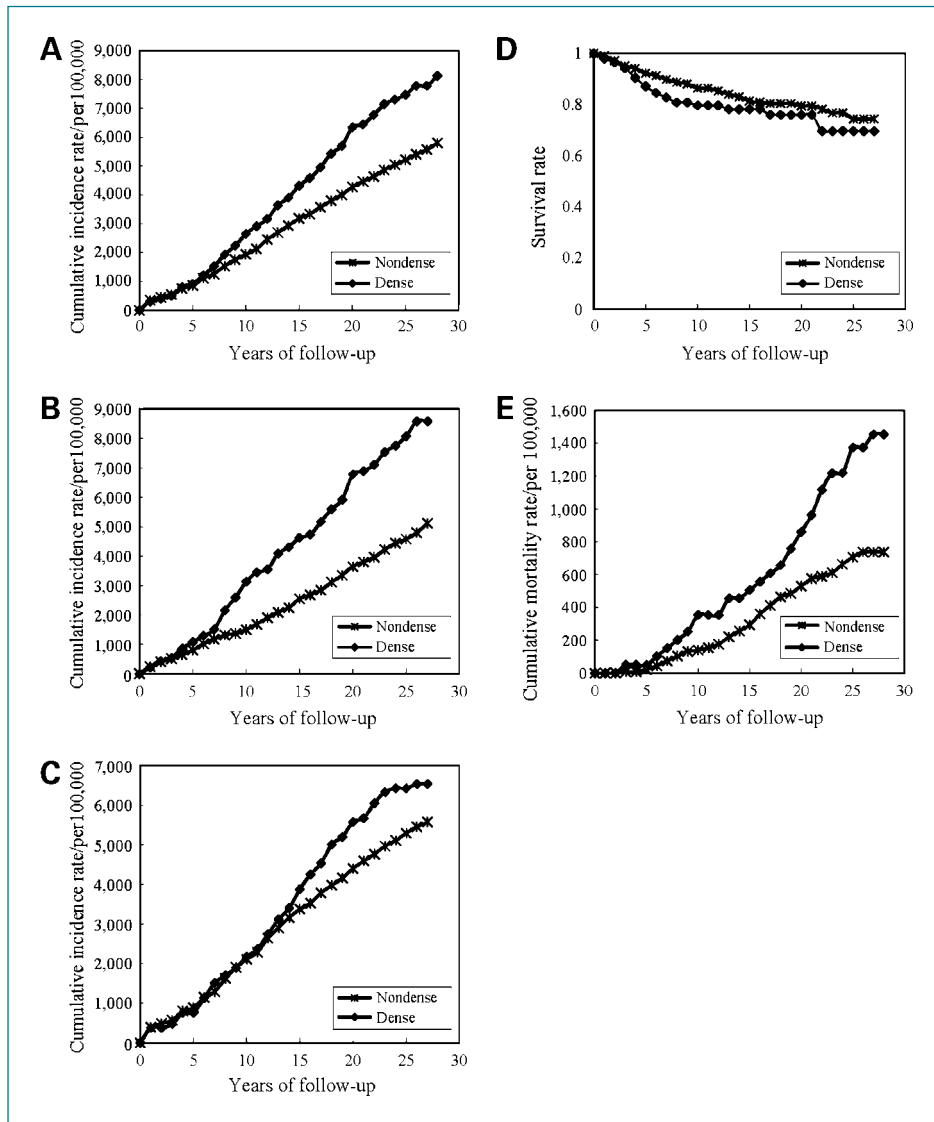


Figure 2. Cumulative curves of (A) incidence for overall, (B) incidence for age 45 to 49 years, (C) incidence for age 50 to 59 years, (D) survival, and (E) mortality of breast cancer by density.

possible association of density with poorer survival may not be due to an association with these characteristics. Van Gils et al. (28, 29) also found a suggestive but non-significant survival disadvantage in dense breasts. In contrast, the case fatality in Denmark was lower in dense than nondense breasts (6), which may be attributable to different age groups and shorter follow-up periods.

Note that the relative risk for developing breast cancer in our study was lower than that in other antecedent studies (5, 6, 15, 30). Two unique characteristics account for this inconsistency. Our prospective cohort design was made to classify breast density (exposure) at the entry of study rather than the date closer to diagnosis (age of incident cases) adopted in most of the previous studies. The other characteristic is that our cohort had 25 years of long-term follow-up, which was longer than in other studies (6, 30). The merit of such a study design with long-term follow-up can predict the risk of dense breast

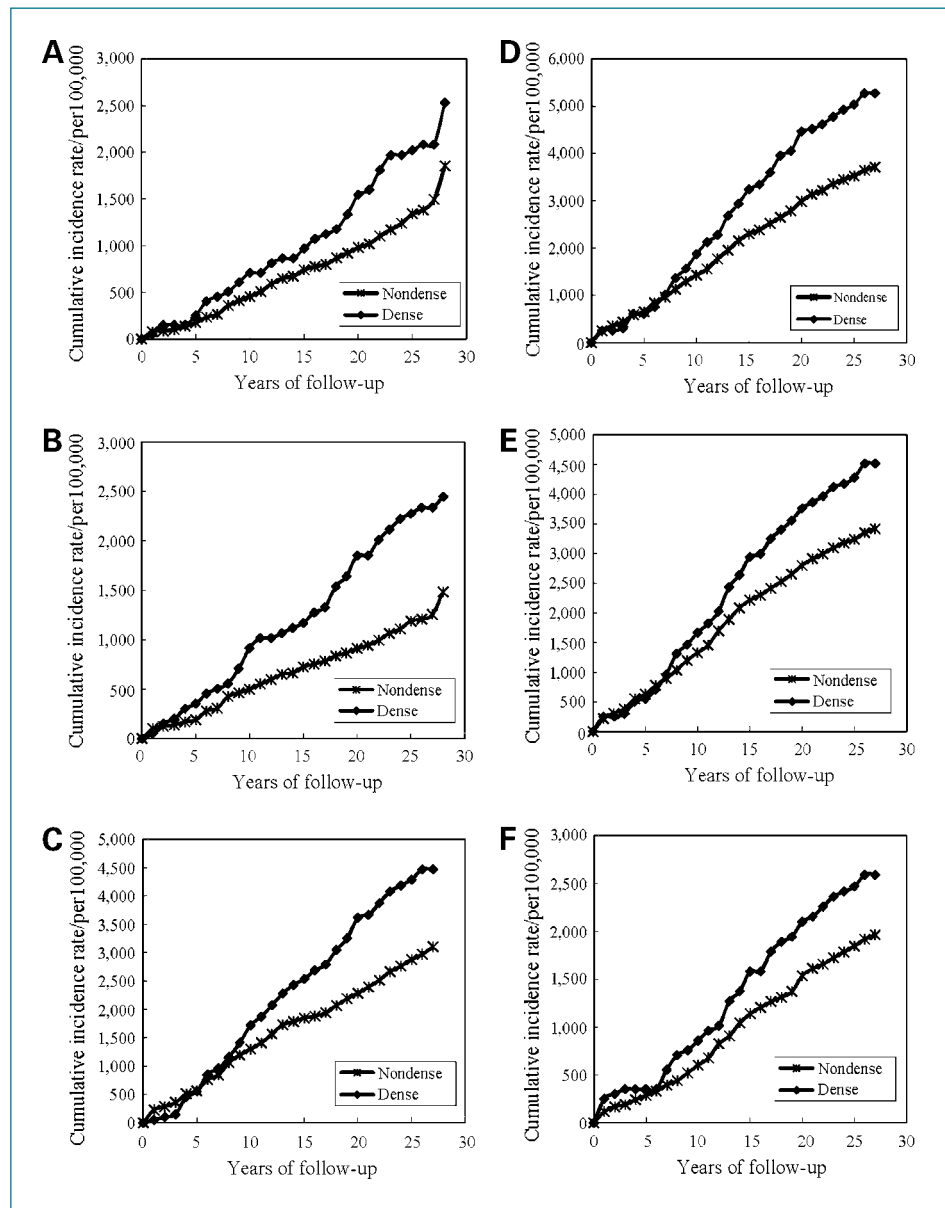
even if a woman's breast changes. However, the relative risk regarding the effect of dense breast on breast cancer risk was lower than that obtained in the previous study. The reason is that the change in breast density due to aging for women who were classified as having dense breasts at recruitment increased after their dense breast tissue changed to fat tissue. Such a dynamic change is particularly remarkable for a long-term follow-up cohort. Two other explanations may account for the lower relative risk, including suboptimal threshold for density classification and the quality of mammography. By combining pattern III into pattern IV or V according to the Tabár classification, the results after reanalysis show the relative rate slightly increased from 1.45 (1.21-1.74) to 1.57 (1.38-1.64). The low quality of a mammogram may also account for the lower relative risk. However, this is unlikely as the mortality reduction was 35% in the Two-County Trial, which was higher than in other

studies (31). Because the age at recruitment rather than age at diagnosis was used in our unique prospective cohort design as mentioned above and screening advanced the date of diagnosis, the incidence rate increasing with age was less remarkable after long-term follow-up (Table 2).

Our large population-based screening data also provide an opportunity to clarify the argument of whether the positive association between dense breast tissue and the increasing incidence of breast cancer is due to a masking effect (32) or the risk of breast cancer in association with breast density (causal effect; ref. 33). Using interval cancers only would underestimate the causal effect because they are composed of two types of breast cancers, false-negative cases masked at screening and newly diag-

nosed symptomatic cancers occurring after the last screen with true-negative findings. To separate false-negative cases from newly incident breast cancer, the previous study excluded interval cancer at the first year because the last negative screen assumed these excluded cases were false-negative cases as a result of a masking effect (1). This is not exactly true as false-negative cases may become symptomatic cancers after >1 year and newly incident breast cancer may also occur within 1 year. Day (34) therefore suggests considering the time dimension by correcting for the sensitivity based on the MST as estimated in our study. On the other hand, overestimation would occur if only breast cancers detected at screen are used. By the application of the three-state Markov model

Figure 3. Cumulative incidence of tumor attributes: (A) tumor size of >20 mm, (B) nodes positive, (C) histologic grade of 2 and 3, (D) tumor size of ≤20 mm, (E) nodes negative, and (F) histologic grade of 1.



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Table 3. Estimated results of the proportional incidence method and three-state Markov model by breast density and age

Group	Age of randomization, years	Proportional incidence method for sensitivity [1 - (I/E) × 100%]	Three-state Markov model	
			Preclinical incidence rate (λ_1)	MST* (95% CI; y)
Nondense Breast		82.0% (75.2-88.8%)	0.0020 (0.0018-0.0022)	3.29 (2.84-3.90)
Dense Breast		62.8% (47.2-78.3%)	0.0033 (0.0026-0.0039)	2.04 (1.53-3.10)
Overall		79.5% (73.3-85.8%)	0.0022 (0.0020-0.0024)	3.02 (2.64-3.52)
Nondense Breast	45-49	76.8% (64.9-88.8%)	0.0015 (0.0012-0.0018)	2.68 (1.98-4.18)
Dense Breast	50-54	83.8% (72.1-95.5%)	0.0021 (0.0018-0.0025)	3.27 (2.56-4.49)
	55-59	88.7% (78.4-99.1%)	0.0023 (0.0020-0.0027)	3.60 (2.93-4.65)
Overall	45-49	55.3% (35.0-75.6%)	0.0032 (0.0022-0.0041)	1.78 (1.18-3.63)
	50-54	77.7% (48.9-100.0%)	0.0028 (0.0017-0.0038)	1.90 (1.16-5.17)
	55-59	73.7% (38.5-100.0%)	0.0042 (0.0026-0.0058)	2.82 (1.71-7.91)

Abbreviations: I, incidence rate of interval cancer; E, expected incidence rate in the absence of screening (control group).

*The MST was estimated by fixing sensitivity as a constant equal to 79.5%.

to the information obtained from both breast cancers, our results not only showed a higher preclinical incidence in dense breast tissue but also a shorter sojourn time in dense breasts given that the sensitivity was controlled (see Table 3). These findings were commensurate with the effect of dense breasts on increasing the incidence and mortality of breast cancer with long-term follow-up. In addition, making use of full information on mammographically detected cancers (prevalent screen and subsequent screen), interval cancers, and cancers from the refuser group can also reduce the threat of length bias as prevalent screen-detected cancers are more likely to include a long sojourn time, whereas interval cancer or cancers from the refuser group are characterized by aggressive cancers with a shorter sojourn time.

Regarding the masking effect, dense tissue was associated with a reduced sojourn time. This finding was consistent with the results of the Nijmegen study (28), which showed that the occurrence of interval cancers after an initial examination preponderated in the first 2 years for dense breast tissue compared with nondense breast tissue and were not remarkable 2 years after the initial examination. This result supports the possibility of a masking bias effect by indicating that the average time for interval cancer diagnosis after the initial examination was 2.79 years, which was lower than 3.14 years for nondense breasts.

The consideration of phenotype of breast density may aid health policy makers to stratify the risk of breast cancer for the enhancement of efficiency in the prevention of breast cancer (30, 35-40). More importantly, our three-state modeling approach provides a new insight in recommending a screening policy with interscreening intervals and more sensitive screening methods by estimating the proportions of two components of interval cancer false-negative cases and newly incident cases, which cannot be directly observed and have not yet been

addressed in previous studies. The novel modeling approach is also helpful for projecting the effect of interscreening intervals on the proportion of interval cancers among all diagnosed breast cancers. In the simulation, the proportion of interval cancers with a 1-year interscreening interval was 22.4% (including 15.9% newly diagnosed cases and 6.5% arising from false-negative cases) for dense breast tissue and 13.6% (including 10% newly diagnosed cases and 3.7% arising from false-negative cases) for nondense breast tissue. As far as the effect of interscreening intervals is concerned, the proportion of interval cancers for dense breasts was reduced from 44.2% (including 36.9% newly diagnosed cases and 7.3% arising from false-negative cases to 22.4%) for dense breast as mentioned above if interscreening intervals were changed from a triennial program to an annual program. This 22% reduction in newly diagnosed interval cancers is partly due to the higher preclinical incidence rate and partly due to shorter MST. It could be argued that a fraction of breast tumors, particularly with breast densities >75% as illustrated in the Boyd et al. study (5), cannot be detected by mammography even when annual screening is applied. In light of the results of our modeling, dense breasts that do not allow for detection with the application of annual screening accounted for 7% of all interval cancers, which is only slightly lower than 11% estimated from Table 3 of Boyd et al. study (5), that can be only identified using alternative imaging techniques, such as digital mammography, ultrasonography, and magnetic resonance imaging.

One limitation in our study is that we classified breast density in a qualitative manner rather than using quantitative assessment based on the percentage of dense tissue using visual assessment or planimetry as reviewed by Harvey and Bovbjerg (41) and at least six categories (<25%, 25-50%, 50-75%, and ≥75%) used in a nested case-control study (5). Accordingly, the

dose-response for the trend on the degree of breast density in association with the risk for breast cancer cannot be obtained. This limitation may be addressed in a future study if such information can be obtained.

In conclusion, our study showed that dense breast tissue not only increases breast cancer risk but also leads to more aggressive tumors and mortality from breast cancer. This finding was further supported by higher preclinical incidence, due to the causal effect, and also a shorter window of opportunity for detecting cancer by mammography with difficulty (that is, the masking effect) in dense breast tissue. These results suggest the screening policy with a predominantly shorter screening interval (reducing the newly incident interval cancers) and with advanced imaging techniques (reducing false-negative interval cancers) as indicated in women

with dense breasts to reduce interval cancers and aggressive tumors.

Disclosure of Potential Conflicts of Interest

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