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Mammographic breast density and other risk factors in Malaysian women with breast cancer

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ABSTRACT

Aim: This study was performed to: (i) determine the association of breast cancer with dense breasts, and (ii) determine the breast cancer association with early onset of menarche, nulliparity, late age at first childbirth, not breast-feeding, and family history of breast cancer.

Methods: This was a retrospective hospital-based case-control study. The 231 cases were women diagnosed with breast cancer on histology during the study period from July 1998 to April 2005. The 231 controls were age-matched and randomly selected women who did not have breast cancer but had mammography performed during the same time interval. Tabar classification was used to classify the mammographic parenchymal pattern of the 462 samples. The same radiologist analysed the parenchymal pattern based on the craniocaudal and mediolateral oblique views. Statistical analysis was done using the SPSS package.

Results: Majority of women with breast cancer (55%) had dense breasts (29% Type IB, 19% Type IC, 4% Type IV, 3% Type V). Majority of controls (58%) had dense breasts (22% Type IB, 26% Type IC, 6% Type IV, 4% Type V). The majority of women with breast cancer had menarche at 12 years or older (93%), were parous (89%), had the first childbirth before 35 years old (91%), had breast-fed (67%), and did not have family history of breast cancer (84%). For controls, the majority had menarche at 12 years or older (88%) were parous (87%), had the first childbirth before 35 years old (98%), had breast-fed (66%), and did not have family history of breast cancer (85%). All factors explored, including breast density, were not significantly associated with breast cancer. The odds ratio for breast cancer among those with dense breast compared to those with non-dense breast is 0.8 (95% CI=0.6, 1.2).

Conclusion: This study found no association between breast cancer and dense breasts (p=0.398). There was also no association between breast cancer with early onset of menarche (p=0.174), nulliparity (p=0.448), older age at first childbirth (p=0.065), not breast-feeding (p=0.716) and family history of breast cancer (p=0.665).

Keywords: breast cancer, mammography, breast density, risk factors.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among Malaysian women [1]. Dense breasts on mammography has been reported as a risk factor for the development of breast cancer [2], apart from traditional risk factors such as early onset of menarche, nulliparity, late age at first childbirth, not breast-feeding, and family history of breast cancer [3]. It is reported that dense breasts cause a 2- to 6-fold increased risk of developing breast cancer [2]. This has a significant clinical implication because the majority of Malaysian women have dense breasts [4, 5]. However, dense breast as a risk factor for breast cancer is controversial. A more recent meta-analysis shows that the dense breast is not a significant risk factor [6].

This study was conducted to determine if breast cancer patients at the authors' centre have dense breasts and if other reported risk factors are present in these patients.

METHODOLOGY

This study was approved by the hospital technical and ethical committee. Patient informed consent was not obtained as this was a retrospective review.

Subjects

This was a retrospective hospital-based case-control study. Cases were women diagnosed with breast cancer on histology at a tertiary hospital during the study period from July 1998 to April 2005. Controls were women who did not have breast cancer, who had mammography performed at the same centre during the study period, and were chosen randomly. The controls were age-matched with the cases. The cases and controls included asymptomatic and symptomatic women, and also those on hormone replacement therapy. Women whose mammograms are not available for review were excluded from the study. Breast cancer patients aged less than 40 years old or more than 75 years old were excluded because of difficulty in finding age-matched controls. The sample population of 462 women comprised of: (i) 231 cases with breast cancer, and (ii) 231 controls without breast cancer.

Image acquisition

Two-view (cranial-caudal and medial-lateral oblique) film-screen mammography examinations were performed using the Siemens Mammomat 3000 (Germany).

Assessment of mammographic parenchymal pattern and density

For breast cancer patients, mammographic parenchymal pattern and density were analysed in the contralateral breast of mammograms that were performed at diagnosis. When these were not available for review, the mammogram performed within 2 years before diagnosis were analysed. All mammograms were

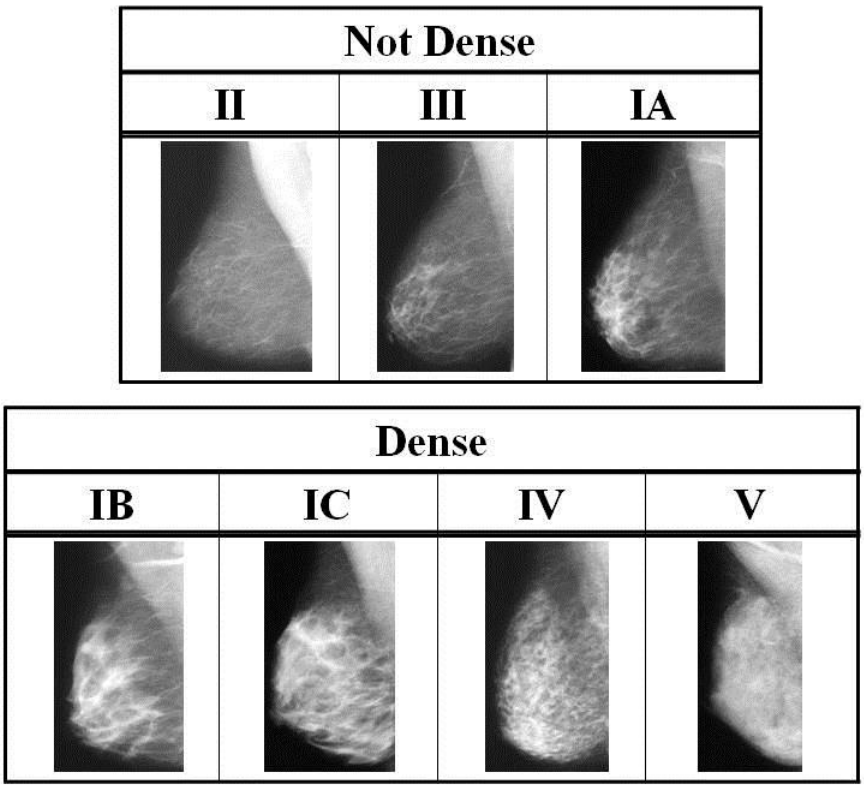

Figure 1 Classification of not dense and dense breasts.

analysed by the same radiologist who was blinded to the women's clinical data. Both the craniocaudal (CC) and mediolateral oblique (MLO) views were analysed. The mammographic parenchymal patterns were classified according to Tabar Classification which is based on anatomic-mammographic correlation [7]. Pattern I shows: (i) scalloped contour and Cooper ligaments, (ii) evenly scattered terminal ductal lobular units (TDLU) that appear as 1-2 mm nodular densities, (iii) oval-shaped lucent intra-mammary fat lobules. Pattern II shows: (i) mainly fat, (ii) linear opacities due to ligaments, ducts, or vessels. Pattern III shows: (i) mainly fat, (ii) retro-areolar ducts. Pattern IV shows: (i) convex contour, (ii) TDLU larger than 1-2 mm due to proliferating glandular structures. Pattern V shows: (i) smooth convex contour, (ii) homogenous opacity due to fibrous tissue.

Tabar Pattern I was found to have a wide spectrum of density and therefore it was further divided into 3 sub-groups [4]. In Pattern IA, glandular tissue (TDLU) occupies the distal one-third of the breast. In Pattern IB, glandular tissue occupies the distal two-third of the breast. In Pattern IC, glandular tissue occupies the entire breast.

Dense breast on mammogram was defined as at least 50% of the breast containing dense tissue. Therefore, Patterns II, III, and IA were classified as not dense. Pattern IB, IC, IV, and V were classified as dense (Figure 1).

Information regarding age at menarche, parity, age at first childbirth, breast-feeding status, and family history of breast cancer were taken from the mammogram request form. When any of this information had not been entered into the mammogram request form, the patient's records were viewed to retrieve the information required.

Statistical analysis

Prevalence odds ratios (OR) based on crude analysis were used to express the degree of association between breast cancer and mammographic breast density, early onset of menarche, nulliparity, late age at first childbirth, not breast-feeding, and family history of breast cancer.

RESULTS

Mammographic distribution of dense breasts among cases and controls

In general, 263 of the total 462 (57%) women in this study had dense breasts (Table 1). Women with breast cancer and had dense breasts comprised of: 29% Type IB, 19% Type IC, 4% Type IV, 3% Type V (Figure 2). Controls with dense breasts comprised of: 22% Type IB, 26% Type IC, 6% Type IV, 4% Type V (Figure 2). Women with breast cancer and had non-dense breasts comprised of: 16% Type II, 10% Type III, 19% Type IA. Controls with non-dense breasts comprised of: 10% Type II, 10% Type III, 22% Type IA.

Association between breast cancer and dense breasts

The majority of women with breast cancer and controls had dense breasts (55% and 58% respectively) (Figure 3). There was no association between breast

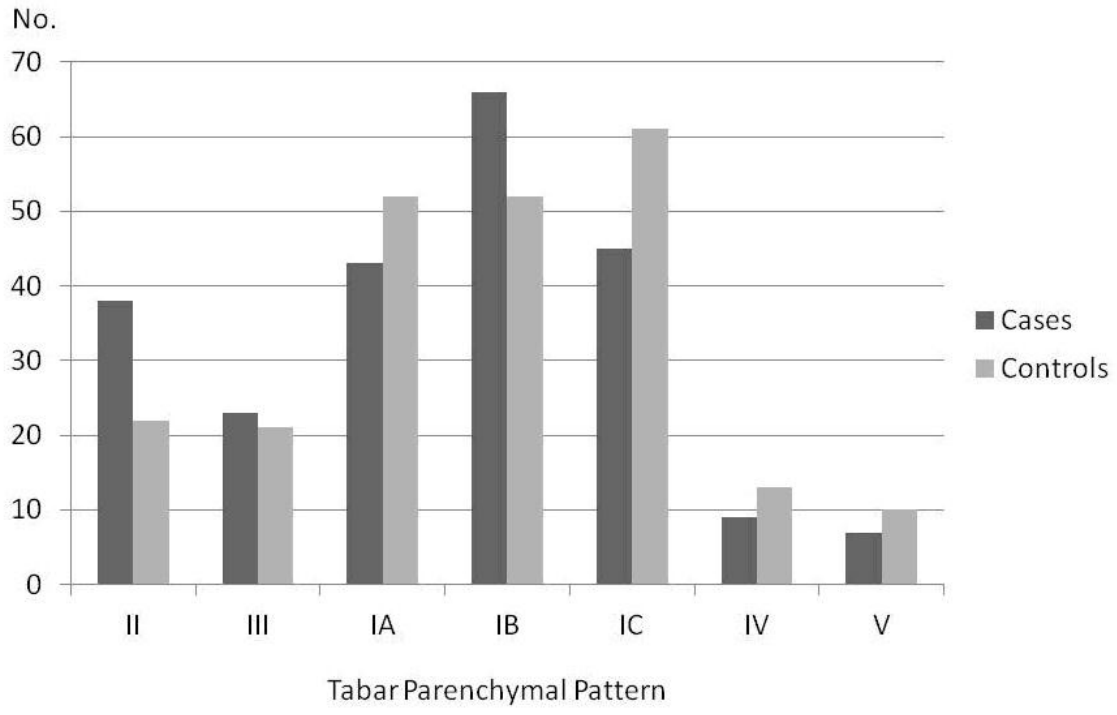

Figure 2 Distribution of mammogram parenchymal patterns in cases and controls. (The bars are arranged from left to right in order of increasing breast density i.e. Pattern II, III, IA, IB, IC, IV, and V).

cancer and dense breasts. The odds ratio for breast cancer among those with dense breasts compared to those with non-dense breasts is 0.85 (95% CI=0.59,1.23; p-value=0.398).

Breast cancer association with early onset of menarche, nulliparity, late age of first childbirth, not breast-feeding, and family history of breast cancer.

Table 1 shows that among women with breast cancer, 7% reached menarche at age less than 12 years compared to 12% having early menarche among controls. Breast cancer was not significantly associated with early menarche (p=0.174).

The majority of women with breast cancer and controls were parous. Only 11% of cases and 14% of controls were nulliparous and nulliparity was not significantly associated with breast cancer (p= 0.448).

The majority of cases and controls had their first childbirth at age less than 35 years. Nine percent of cases and 2% of controls had their first childbirth at age 35 years or older. Having first childbirth at an older age was not significantly associated with breast cancer (p=0.065).

Two-thirds of both women with breast cancer and controls breast-fed their children. There was no significant difference in the proportion of cases who did not breast-feed their children compared to controls (p=0.716).

Only 16% of cases and 15% of controls had positive family history of breast cancer in a first-degree relative. There was no significant association between family history of breast cancer in a first-degree relative and the occurrence of breast cancer (p=0.665).

DISCUSSION

Association between breast cancer and dense breasts

Based on meta-analysis, the risk of breast cancer for women with dense breasts has been reported to be 2 to 6 times that for women with non-dense breasts [2], a relative risk greater than most traditional risk factors such as early menarche and nulliparity. This meta-analysis found that relative risks were higher when breast density was classified quantitatively as percentage density (percentage of the mammogram with radiodense fibroglandular tissue) rather than with qualitative assessment such as with Wolfe and Breast Imaging Reporting and Data System (BIRADS) classifications. Relative risks were also higher in studies of incident cancer (the mammograms assessed were those taken before time of diagnosis) compared with prevalent cancer (the mammograms assessed were of the contralateral breast taken at time of diagnosis). Higher relative risks were found to be consistent in studies conducted in the asymptomatic patients (from screening of the general population), but were heterogenous when conducted in symptomatic patients.

Breast cancer originates from glandular tissue. It is believed that dense breasts, which contain more glandular tissue than non-dense fatty breasts, would have an increased risk of cancer. Increased risk of breast cancer in association with Tabar Pattern IV has been reported [8–10]. The Tabar classification, which is based on anatomic-mammographic correlation, attributes the increased density of Type IV to large terminal ductal lobular units (TDLU) due to proliferating glandular tissues [7]. It is during cellular proliferation that DNA alterations can occur that can lead to the initiation of cancer.

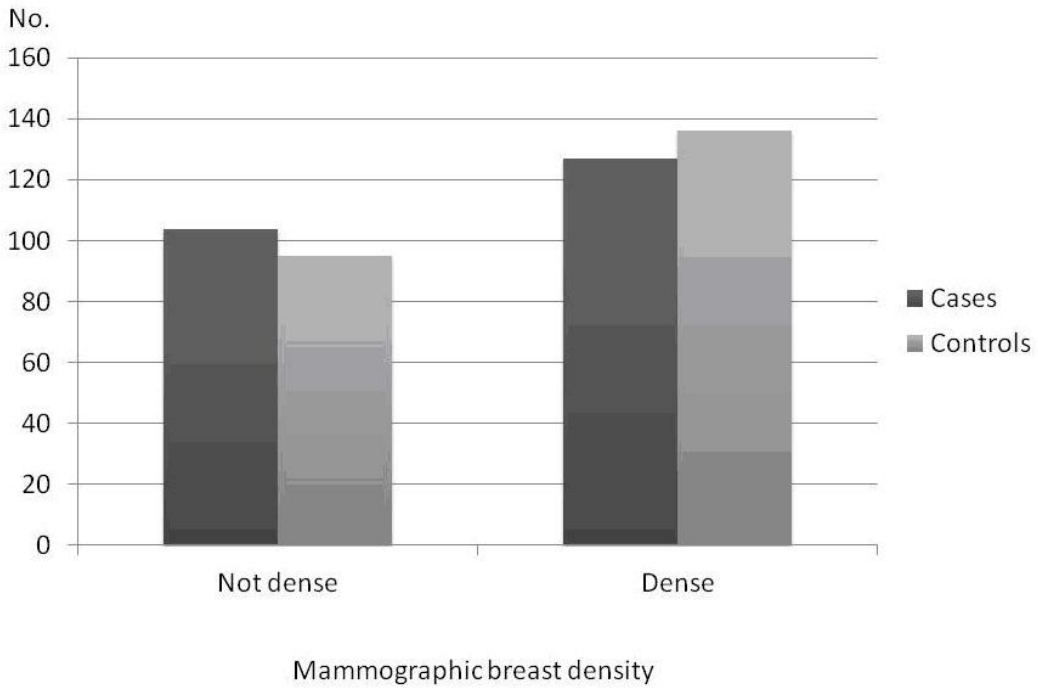

Figure 3 Distribution of not dense and dense breasts.

Table 1 Frequency and percentage distribution of explored variables among cases and controls.

Factors Explored		Cases n=231 f (%)	Controls n=231 f (%)	Total n=462 f (%)	OR (95% CI)	p value
Breast density*	Dense	127 (55)	136 (58)	263 (57)	0.8 (0.6, 1.2)	0.398
	[Not dense]	104 (45)	95 (42)	199 (43)		
Menarche	Less than 12 years-old	12 (7)	16 (12)	28 (9)	0.6 (0.3, 1.3)	0.174
	[12 years and older]	152 (93)	118 (88)	270 (91)		
Parity	Nulliparous	21 (11)	31 (14)	52 (13)	0.8 (0.4, 1.4)	0.448
	[Parous]	166 (89)	195 (86)	361 (87)		
Age at 1st Childbirth	35 years and older	8 (9)	2 (2)	10 (6)	4.0 (0.8, 19.4)	0.065
	[Less than 35 years-old]	81 (91)	81 (98)	162 (94)		
Breast-feeding status	Did not breast-feed	54 (33)	74 (34)	128 (33)	0.9 (0.6, 1.4)	0.716
	[Had breast-fed]	113 (67)	143 (66)	256 (67)		
Family history of breast cancer	Positive	31 (16)	31 (15)	62 (16)	1.1 (0.7, 1.9)	0.665
	[Negative]	157 (84)	177 (85)	334 (84)		

*[ ] Referent: e.g. Dense versus Not dense

Accepting dense breast as a risk factor for breast cancer has a significant clinical implication. It might lead to increased frequency of mammography for women with dense breasts, or increased use of other modalities such as ultrasound and magnetic resonance imaging. However, breast density as a risk factor is still controversial. Various studies have reported either differing risk levels or even no risk association [2, 6]. These differing results are because there is a lack of a standard method of breast density assessment and definitions for high breast density are varied. It has been suggested that digital mammography should help to re-evaluate the issue of breast density as a risk factor [6]. The need to establish and validate an international standard for volumetric breast density measurement based on digital mammography has been highlighted [11].

A more recent meta-analysis has concluded that the dense breast is not a significant risk factor [6]. The main controversy arises from the way the dense breast is defined in the various studies. The majority of epidemiological studies defined dense breasts as at least 25% of the mammogram showing radiodense fibroglandular tissue. The practice of radiologists is to consider dense breasts as at least 50% or even 75% of the mammogram shows radiodense fibroglandular tissue. Analysis of data from the Digital Mammographic Imaging Screening Trial (DMIST) [12] showed that dense breasts, defined as 50% or more of dense tissues, and when investigated by both film-screen and digital mammograms, does not constitute a significant risk factor [6].

This review of breast cancer patients at the authors' centre concurred with this recent report. There was no association between breast cancer and dense breasts (OR=0.85; 95% CI 0.59, 1.23; p-value=0.398). The majority of cases and controls had dense breasts. Majority of those with dense breasts had Type IB and IC

and not Type IV that has been associated with breast cancer. In this study, the dense breast was defined as at least 50% of breast containing dense tissue. Both incident and prevalent breast cancers were included and both asymptomatic and symptomatic women were included.

The majority of Malaysian women have dense breasts [4, 5]. Yet the breast cancer age-standardised incidence (ASR) of 47.4 in Malaysia [1] is significantly lower compared with ASR of 74.4 in the United Kingdom [1] and ASR of 92.1 in the United States [1]. The findings of this study, showing no association between breast cancer and dense breasts, is concordant with the lower ASR in Malaysia compared with other countries.

Breast cancer association with early onset of menarche, nulliparity, late age of first childbirth, not breast-feeding, and family history of breast cancer.

Reported risk factors for developing breast cancer include: being female, being older than 35 years old, early onset menarche (before 12 years old), late onset menopause (after 55 years old), nulliparity, first full-term pregnancy after age 30, not breast-feeding, having history of affected first degree relative, previous history of breast cancer, biopsy proof of atypical epithelial proliferation, biopsy proof of lobular carcinoma in situ [3, 13]. Of these risk factors, being female is the single most important risk factor, followed by increased age.

Risk factors such as early onset of menarche, nulliparity, late age of first childbirth, and not breast-feeding are related to hormonal status [3, 14–16]. Some have postulated that the breast is vulnerable to carcinogenesis when exposed to oestrogen for a longer cumulative duration. Others have postulated that it is the exposure to a longer cumulative duration of cyclical oestrogen and progesterone during uninterrupted menstrual cycles. These hormones stimulate cellular proliferation. Longer cumulative exposure to these hormones would occur in early onset of menarche, nulliparity, and late age of first pregnancy. During lactation, when ovulation ceases, there is reduced exposure to these hormones.

A family history of breast cancer in a first-degree relative is a widely recognised risk factor [13, 17]. Patients with an affected first-degree relative have 1.5 to 2 times higher risk when compared to controls without affected family members. The lifetime risk is 4 times higher if a mother and sister are affected.

This study failed to show any breast cancer association with early onset of menarche, nulliparity, the late age of first childbirth, not breast-feeding and family history of breast cancer. This study was very much dependent on the availability of information on the mammography request form. The requesting clinician is required to fill in information regarding age at menarche, parity, ages of children, history of breast-feeding, and family history of breast cancer on the request form. Information was retrospectively retrieved from the request forms. When any of this information had not been entered into the mammogram request form, the patient's records were viewed to retrieve the required information. It was noted that some information was not recorded and so the sample size of the related variable decreased. The reduced sample size for each variable could be the reason why the results were not statistically significant. Perhaps prospective collection of information in a multi-centre study would reveal more significant conclusions.

It has long been the anecdotal findings of Malaysian radiologists involved in breast imaging that the reported risk factors for breast cancer are not present in the majority of Malaysian breast cancer patients. It is therefore not surprising that the findings of this study show no association with these risk factors. There is a tendency to quote risk factors established by studies that are based on other populations. There are no previous large-scale population-based studies on the breast cancer risk factors amongst Malaysian women. It is difficult to conduct such a study because the country does not have a formal breast screening programme. Furthermore, the reported risk factors are unavoidable factors. It is not worthwhile spending time and money to establish whether these risk factors apply to the Malaysian population because it has little effect on reducing the incidence of breast cancer as these factors are by and large unavoidable. This is unlike, for example, cigarette smoking as a risk factor for lung cancer where the avoidance of cigarette smoking would reduce risk of lung cancer.

SUMMARY

This study found no association between breast cancer and dense breasts (OR=0.8; 95% CI=0.6, 1.2; p=0.398). There was also no association between breast cancer with early onset of menarche (p=0.174), nulliparity (p=0.448), older age at first childbirth (p=0.065), not breast-feeding (p=0.716) and family history of breast cancer (p=0.665).

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