Review Article

The epidemiologic factors associated with breast density: A review

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In recent years, some studies have evaluated the epidemiologic factors associated with breast density. However, the variant and inconsistent results exist. In addition, breast density has been proved to be a significant risk factor associated with breast cancer. Our review summarized the published studies and emphasized the crucial factors including epidemiological factors associated with breast density. In addition, we also discussed the potential reasons for the discrepant results with risk factors. To decrease the incidence and mortality rates for breast cancer, in clinical practice, breast density should be included for clinical risk models in addition to epidemiological factors, and physicians should get more concentrate on those women with risk factors and provide risk-based breast cancer screening regimens.

Key words: Breast cancer, breast density, epidemiological factors

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INTRODUCTION

Breast cancer has been a worldwide burden of women's health, as 2.3 million newly cases were diagnosed in 2020.[1] Breast density has been proved to be a significant risk factor associated with breast cancer.[2,3] To evaluate the factors associated with breast density, it has been regarded as a more important understanding of the etiology and potential pathways of breast cancer. Several epidemiologic studies have found that women with high breast density were more likely to develop breast cancer than those with low breast density.[3-5] In recent years, some studies have evaluated the epidemiologic factors associated with high breast density, such as age, body mass index (BMI), reproductive factors, and life style.[6-10] However, efforts are still warranted, as studies from different countries and ethnicities may contribute to inconsistent results.

The breasts were composed of fat, connective, epithelial tissues that reflected on the mammography according to their X-ray attenuation coefficient.[11] Fat was represented as light areas on mammography, while fibroglandular was dark. To assess breast density for consistent standard by radiologists, some measurement methods were proposed, such as Wolfe grades,[12] Tabar grades,[13] Breast Imaging Reporting and Data System (BIRADS),[14] and quantitative measurement depending on the proportion of area of dense breast tissue through planimetry, and computer assisted methods.[15] BIRADS was widely used in clinical practice and the 5th edition was proposed in 2013.[16] The 5th edition BIRADS system has four categories: (a) almost entirely fatty; (b) scattered areas of fibro glandular density; (c) heterogeneously dense; (d) extremely dense. High breast density including categories c and d may obscure detection of small masses and lower the sensitivity. Studies have reported that the sensitivity of detecting breast cancer by radiologists was 30%–64% in high density while 80%–98% in low density.[17,18] Higher breast density had the possibility to mask the tumor and lower the sensitivity for detecting cancer.

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Previous studies have elucidated that higher breast density might be associated with more aggressive characteristics, such as histopathological grade, tumor size, molecular subtypes.[19-27]

Breast density was modifiable and highly heritable. It was not clear whether the epidemiologic risk factors related to breast cancer were mediated through breast density. It is necessary to review previous epidemiologic studies and clarify the association between these epidemiologic factors and breast density. In our review, epidemiologic factors such as age, race, BMI, reproductive factors, hormone exposures, diet and lifestyle, influenced on breast density were addressed.

EPIDEMIOLOGIC FACTORS

Age and race

The association between age and breast density has been investigated in many studies. It was suggested that breast density decreased with aging.[28-34] The International Consortium on Mammographic Density investigated over 11,000 women from 22 countries worldwide and found that the breast density of both premenopausal women and postmenopausal women declined with increasing age.[35] The meta-analyses and pooled analyses showed that the decrease of percent breast density was 0.24 cm among premenopausal women and 0.38 cm among postmenopausal women for the 10-year increase of age.[35] Some studies found that the association between decreased breast density and increasing age was nonlinear,[28,29,31,32] and breast density was at plateau at the age of 65 years.[28,32] As age was regarded as one of the most important factors reflecting breast density, it was used to adjust for multivariable models in many studies. However, there were some outliers. Kang *et al*. reported that there was not significant association between breast density and age in women in the United Arab Emirates.[36] Another study based on the New York University Langone Medical Center in 2008 found that a small proportion (19%) of young women <40 years old had low breast density, while 44% of women at the age of 60s and 36% of women at the age of 70s had high breast density.[37] In several studies limited the sample size, different race and geographic area, the association between age and breast density was not clear, however, generally, the age was inversely associated with breast density.

The studies based on ethnic differences in breast density have been investigated. A number of studies have been investigated to find the association between breast density and races. Carmen *et al*.[38] compared the breast density among white, African Americans, and Asian women and did not find any differences across ethnic groups. Ursin *et al*.[39] reported that the breast density in Asians was higher than African Americans. After adjusting for age, BMI, and other factors, Chen *et al*.[40] investigated that the percent breast density in Asian women was lower than African women but was not varied from Caucasians. Another study reported that the percent breast density of Chinese women was significantly higher than Malays and Indians.[41] McCarthy *et al*. found that black women had higher breast density than white women after adjusting some risk factors.[42] Generally speaking, the breast density varied across different ethnic groups, and Asian women had higher breast density than western women.[43,44] Thus, the relationship of race to breast density may explain variation in breast cancer risk among different ethnic groups.

Body mass index

Most previous studies have investigated the inverse association between breast density and BMI.[45-52] Especially, BMI was negatively related to breast density in both premenopausal and postmenopausal women.[45] However, not all of the studies reported the consistent results, as Jeon *et al*. found that there was no association between BMI and breast density in premenopausal women.[53] The inconsistent results remained unexplained but largely caused by differences among the population. Compared to fibrous and glandular tissue, the amount of fat increased with the increasement of BMI, thus the absolute measurement of density was considered as a more important method.[54]

A number of studies have also been conducted to find whether the adiposity at early age influences the breast density. Some studies have reported the inverse association of adiposity at the early age with breast density.[7,55-59] Alimujiang *et al*.[55] found that a 1 kg/m^2 increase in BMI at age 10 was related to a 6.4% decrease in volumetric percent density and a 6.9% increase in nondense volume. The author also found that higher BMI at age 18 was associated with lower breast density in premenopausal women.[60] However, in another study, Rice[61] have found that there was not significant association between body fatness during childhood and breast density among Mexican women. The possible mechanism was adiposity in earlier life could modulate hormone exposure and growth factor levels, therefore, the breast cellular proliferation and breast density tissue development were influenced.[62-65]

Reproductive factors

Reproductive factors included menopause status, age at menarche, age at menopause, parity, breastfeeding, age at first birth, number of children, and so on. A large number of studies have investigated the reproductive factors associated with breast density.

Menopause status was one of the most important factors influencing the breast density. As lots of studies have been

reported, postmenopausal women usually had lower breast density and premenopausal women had higher density.[53,66-72] A longitudinal study included postmenopausal women and age-matched group of premenopausal women has investigated that menopause led to a reduction in the area of dense tissue, and an increase of nondense area.[71] Previous studies have reported that the average annual decline in percent density was 0.5%–2% and the maximum reduction was occurred during the menopausal transition.[30-32,71] According to Pike's hypothesis, the decline of breast density over the menopause was caused by the decreased rate of breast tissue aging.[73] Many studies had used subgroups analysis by stratifying the population based on menopause status to correct for confounding factors.

Age at menarche and menopause represented the time of a women exposure to endogenous and exogenous hormones that could influence breast tissue proliferation. The association between age at menarche and breast density was inconsistent reported by previous studies.[10,51,66,74-82] Some studies investigated the positive relationship,[51,80-82] while others reported no association between age at menarche and breast density.[32,74,77-79] Tehranifar *et al*. had found the inverse association between age at menarche and breast density.[66] Some studies have reported that late age at menopause was inversely associated with breast density,[83,84] while others investigated no significant association.[33,85,86] The evidence was far from conclusive, further researches were still warranted for verification in large sample size.

The association between other reproductive factors, such as parity, age at first pregnancy, and breastfeeding, and breast density has been far from conclusive among people from different races. Several studies have investigated that nulliparity or lower parity was negatively associated with breast density,[33,53,68,80,87] while others found no significant association.[67,77] Some studies showed that the age at first birth was positively associated with breast density,[33,69,74,88] however, other studies investigated the inverse association.[80,89] No significant association had been found between age at first birth and breast density.[67,77] Based on the Pikes model, the study had reported that later age at first birth could increase the cumulative exposure to breast density,[73] however, in different races, exceptions could still exist. Breastfeeding has been regarded as a protective factor for breast cancer in many studies, as during lactation, the level of prolactin increased and promotes cell proliferation.[90] Sung *et al*. have reported the positive association between breastfeeding and breast density,[53] while Yaghjyan *et al*. investigated that there was positive association between breastfeeding and absolute dense and nondense areas among premenopausal women.[72] Further researches were needed to clarify the association between breastfeeding and breast density.

Hormone exposures

Breast density could be influenced by hormonal environment, such as hormone replacement therapy (HRT), oral contraception that were used widely. Some studies have reported that HRT may increase the breast density among a substantial proportion of women.[91-94] The influence of different HRTs on the breast density needs more evidence to clarify. Tibolone was commonly used as a tissue-specific compound for treatment in postmenopausal women. It could rapidly convert into 2 estrogenic metabolites and the Δ4 isomer, which has progestogenic and androgenic activities.[95] *In vitro* and *in vivo* data have suggested that the effect of tibolone on breast density was different from conventional HRT.[96] Lundström *et al*. reported that women receiving continuous combined HRT had higher breast density than those receiving tibolone and placebo treatment.[92] However, another study illustrated that tibolone treatment was associated with lower breast density than continuous combination HRT among postmenopausal women.[97] Junkermann *et al*.[98] conducted a prospective, randomized study to evaluate the difference regimens between continuous combined HRT and sequential combined HRT, and the results showed that no significant difference between two treatment groups. Another study investigated four different regimens, including Group I which received conjugated equine estrogens (CEE), Group II which received CEE and continuous medroxyprogesterone acetate (MPA), Group III which received CEE and cyclic MPA, Group IV which received tibolone treatment, the results showed that there was significant difference between Group II and Group IV which indicated that continuous combination HRT was more likely to be associated with increased breast density than other forms of HRT regimens.[99] Interestingly, Harvey *et al*.[100] compared the transdermal and oral HRT associated with breast density and found that oral HRT had a higher incidence of increased breast density than transdermal HRT. Some studies also investigated whether the suspension of HRT influences breast density. Colacurci *et al*.[101] found that the suspension of HRT for 3 weeks might decrease the increased breast density before, while Weaver *et al*.[102] had an inverse conclusion that the cessation of HRT did not change breast density. However, it is worth to point that the change of breast density was dynamic during HRT, as it is increased with initiation and decreased with discontinuation.[103]

Some studies investigated the effect of different hormones, such as progestogen, oestrogen, corticoid, androgens, and so on. Gabrielson[104] emphasized that baseline breast density was influenced by hormones from the progestogen, estrogen, and corticoid pathways, however, the main driver was androgens. Another cross-sectional study reported that progesterone was significant associated with percentage

of breast density than estrogen among premenopausal women.[105]

White *et al*.[106] found that breast tissue is more radiographically dense in the luteal phase than in the follicular phase among premenopausal women aged 40–49, as some pathologic studies illustrated that epithelial cell proliferation, lobule size, and stromal edema are all greater in the luteal phase for breast tissues.[107-109] Colacurci *et al*. found that suspension of HRT for about 3 weeks could increase breast density, however, the included samples were limited.[101]

Diet and lifestyle

Previous epidemiologic studies have reported inconsistent findings about dietary, as the food was consumed by some combinations and nutrients intakes were highly related by interactive and synergistic effect. A study had found a weak and negative association between vegetables intake and breast density among Japanese women.[110] Another study found that decreased total or saturated fat intake or cholesterol intake was positively related to dense area of breast density.[111]

Some studies were conducted among Mediterranean population.[112-116] A study compared three patterns, such as a fruit–vegetable–cereal pattern, a salad–sauce–pasta/grain pattern, and a meat–starch pattern, and found that the fruit–vegetable–cereal and salad–sauce–pasta/grain patterns were negatively associated with breast density among smokers.[112] Another study found that high breast density was inversely associated with increased consumption of vegetables, olive oil, frequent intakes of cheese, high intakes of b-carotene, Vitamin C, calcium, and potassium.[113] Castelló *et al*. examined the difference between two different patterns (Western and Mediterranean) associated with breast density and found that women with western pattern were more likely to have higher breast density, while no significant association was found between Mediterranean pattern and breast density.[115]

Some studies not only concentrated on the dietary patterns but also the energy intake. A study investigated the positive association between energy intake and percent breast density during adulthood, and the effect of high fat and sugar dietary pattern greatly attenuated considering the total energy.[117] Another study dietary energy density was positively associated with breast density, as each 1 kcal/g unit increased in food-only energy density was associated with a 25.9% increase in percent dense breast volume.[118]

Vitamin D and calcium have been found to modulate cellular proliferation and differentiation in several tissues, including breast tissue.[119,120] The studies were conducted to find the association between Vitamin D and calcium and breast density. Be'rube *et al*. investigated that Vitamin D and calcium were inversely associated with breast density and suggested that they might regard as protective factors of breast cancer.[121] The results about Vitamin D were highly similar to other studies.[122,123] Vitamin D from sunlight and dietary intake was hydroxylated in the liver into 25-hydroxy Vitamin D (25[OH[D), and 25(OH) D was hydroxylated to the biologically active metabolite 1,25-dihydroxy vitamin D (1,25[OH] 2D) that probably in breast tissue.[124,125] Green *et al*.[126] found that there was not significant association between breast density and plasma 25(OH) D levels. However, another study found that high levels of 25(OH) D and Vitamin D substitution were negatively associated with breast density among premenopausal women.[127]

Soy effect was proposed to be a factor on breast cell proliferation. Ursin investigated the inverse association between soy and breast density, as the breast density was significantly different between the highest and lowest quartiles of soy intake.[88] A meta-analysis reported that isoflavones from soy and red clover would not change the breast density among postmenopausal women, however, it might cause a small increase among premenopausal women.[128] Another study investigated the association between milk intake and breast density in premenopausal women; the results showed that the low/reduced-fat milk intake was negatively related to volumetric percent density.[129]

Alcohol has been regarded as an established risk factor associated with breast cancer.[130-132] The evidence of the association between alcohol consumption and breast density was inconsistent. Most studies reported the positive association between alcohol consumption and breast density.[79,114,133-137] Jacobsen *et al*.[137] evaluated the types of different alcohol and found that there were not significant difference among beer, wine, or fortified wine. Alcohol could change the levels of estrogen, that might contribute to the increase of breast density.[138,139] However, another study found that alcohol consumption was not related to breast density among premenopausal women during adolescence and adulthood in the Nurses' Health Study II cohort.[140] In contrast, the inverse association was found between breast density and alcohol consumption in two US birth cohorts.[141] The evidence was not consistent, as the population from different geographic areas, the types of alcohol, detail timing of exposures, etc.

Previous studies have found inconsistent association between smoking and breast density. Some studies illustrated that smoking was inversely associated with breast density.[142-145] Cigarette decreasing the levels of circulation estrogen levels might influence the breast

density.[142] Another study reported the positive association among premenopausal women.[77] Other three studies found no significant association.[45,146,147]

Physical activity was supposed to reduce breast cancer through different mechanisms, such as weight loss, reduced hormone exposures and levels of insulin and insulin-like growth factor exposure, and so on.[148-150] The association between physical activity and breast density has also been evaluated in recent years.[67,146,151-156] Some studies have found that physical activity was not a determinant of breast density.[67,151,153,156] Other studies found that physical activity actually impacts the breast density.[152,154,155] Pilar *et al*.[152] found that those who reported at least 3.5 h of physical inactivity per day had higher breast density compared to those who reported 1 h or less. Another longitudinal study was carried out among Mediterranean population and reported that the increasing levels of leisure time for physical activity were negatively associated with higher breast density.[154] The biological mechanisms of the association between physical activity and breast density had not been established, however, several interesting possibilities might exist. Physical activity could reduce the hormone exposures that played important part in breast cell proliferation.[157] In addition, the levels of insulin-like growth factor-I (IGF-I) modulated by physical activity could influence breast epithelial cell mitogens.[158] The results have not been applied to different ethnic groups, further researches are needed to clarify the association between physical activity and breast density.

Others

Some studies evaluated the association between the breast density and other factors, such as residential traffic noise, education level, occupation, metabolic syndrome, socioeconomic status, and diabetes.[68,159-168] Roswall *et al*.[159] found no association between breast density and traffic noise exposure, either residential road or railway noise in a Danish cohort. Another study found that the socioeconomic status played a role in determining the amount of fat in breast.[160] However, another study found early life socioeconomic status, including education and income was not significantly associated with breast density in adulthood.[167] Lope *et al*.[161] found that the occupational exposures were associated with breast density, the women that exposure to perchloroethylene, ionizing radiation, mold spores, or aliphatic/alicyclic hydrocarbon had higher breast density. Another study was conducted to evaluate the influence of occupations and occupational exposure to physical, chemical, and microbiological agents on MD, the results found that premenopausal women in Spanish occupationally exposed to fungicides, herbicides, and insecticides were more likely to have lower breast density.[162] In addition, some diseases such as diabetes and the metabolic syndrome were reported to be related to breast density.[163,168]

Breast density has been regarded as having a polygenic basis.[169] Genome-wide association studies have suggested that multiple low and moderate penetrance breast cancer susceptibility loci in women, such as single nucleotide polymorphisms (SNPs).[169-177] However, it's not clear whether the etiological pathways increase the breast cancer risk due to the dense tissue. As Sartor *et al*.[171] had found that compared to major homozygotes, minor homozygotes of SNPs rs9383589, CCDC170 and rs6557161, ESR1 were related to high breast density and poorer breast cancer survival in a large independent breast cancer cohort. Stone *et al*.[174] also found associations between rs6001930 (MKL1) and both adjusted absolute dense and nondense areas and between rs17356907 (NTN4) and adjusted absolute nondense area. Vachon *et al*.[169] found that LSP1-rs3817198 and RAD51 L1-rs10483813 were associated with breast density and in the same direction as the breast cancer association, while another study found no evidence for the association between majority of SNPs and breast density.[173] Further studies based on the understanding the underlying mechanisms could help identify etiological pathways implicated in how dense density increased breast cancer risk.

CONCLUSION

Our review summarized the epidemiological factors associated with breast density. Although evidence has suggested that age, race, BMI, reproductive factors, hormone exposures, diet, and lifestyle have an influence on breast density, inconsistence results were observed due to a different size of populations and different race/ethnicity. Future studies with sufficient sample size and the same race/ethnicity and methodology are warranted. Given breast density was the most prevalent risk factor for developing breast cancer, in clinical practice, breast density should be included for clinical risk models and should be taken into account by the physicians. The consideration of breast density and other risk factors could provide comprehensive and individualized plans for breast screening, ultimately decrease the incidence and death rates for breast cancer.

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