Biological distinctions between breast cancer subtypes likely reflect differences in the pathways of tumor development. These distinctions often translate to different risk factors contributing to development of various breast cancer subtypes (1). One biologically relevant manner of distinguishing breast cancer subtypes is according to estrogen receptor (ER), progesterone receptor (PR), and HER2 expression (2–5). Breast cancers that are ER-positive are associated with overexpression of genes in the ER-signaling pathway (6). Triple-negative breast cancers (ie, ER negative, PR negative, and HER2 negative) are most likely to exhibit a basal-like pattern of gene expression, characterized by overexpression of genes in the cell proliferation pathway regulated by cyclin-dependent kinase inhibitor 1A (CDKN1A; also known as p21) and DNA replication pathway (6). HER2-expressing breast cancers (ie, ER negative, PR negative, and HER2 positive) exhibit overexpression of genes in the HER2-signaling pathway (6). Epidemiological studies indicate that reproductive risk factors, such as parity-related factors and age at menarche, and body mass index are more strongly associated with ER- or PR-positive tumors than ER- or PR-negative tumors (1,7–10). ER-negative, particularly triple-negative, breast cancer tends to be diagnosed at an earlier age and disproportionately affects African-American women relative to ER-positive breast cancer (11,12). Additionally, serum levels of bioavailable testosterone are inversely associated with risk of ER-negative breast cancer, whereas circulating estradiol levels are positively associated with risk of ER-positive breast cancer in postmenopausal women (13).

Mammographic breast density is one of the strongest known risk factors for breast cancer (14–17). The mechanisms through which breast density is positively associated with breast cancer risk are unclear. Breast density has been associated with the amount of collagen, stromal, and epithelial tissues in the breast; suggesting that increased epithelial and fibroblast cellularity and activity in dense tissue may contribute to the positive association between breast density and breast cancer risk (18,19). Characterizing the association between breast density and risk of tumor subtypes may enhance our understanding of how breast density influences breast cancer risk, as well as our understanding of how breast cancer subtypes differ in etiology.

Most studies that have evaluated the association between breast density and breast cancer risk by expression of biomarkers in the tumor have reported no difference in the magnitude of the association between breast density and risk for ER-positive vs ER-negative breast cancer (20–25). Two recent studies (26,27) reported greater mean percent density associated with ER-positive disease than ER-negative disease. The few studies that have evaluated the prevalence of high breast density among triple-negative, HER2-positive, and ER-positive invasive cancers or the association of breast density with triple-negative and HER2-expressing subtypes (24,28) have also reported no differences across subtypes.

In this issue of the Journal, Yaghjyan et al. (29) investigated whether breast density is associated with ER, PR, and HER2 subtypes and histopathology characteristics of tumor aggressiveness in a large case–control study of postmenopausal women within the Nurses’ Health Study. Consistent with previous reports (20–25,28), the results presented in this study (29) indicate that breast density is similarly associated with breast cancer risk regardless of PR or HER2 status. However, in contrast to previous
studies (20–28), Yaghjyan et al. (29) found that breast density has a stronger association with ER-negative than ER-positive tumors. Both etiologic and nonetiologic explanations could contribute to the observed stronger association between breast density and ER-negative disease. One important nonetiologic consideration is the potential influence of a masking effect (30). Masking of a tumor can occur because cancerous and mammographically dense tissues have similar x-ray attenuation, allowing tumors to go undetected on screening mammography examinations and progress to a more advanced and aggressive stage before detection. Yaghjyan et al. (29) did not account for whether tumors were detected by screening mammography. As such, it is possible that a masking effect (30) may have contributed, in part, to the greater association of breast density with ER-negative than ER-positive tumors because ER-negative tumors are more frequently missed by mammography (31,32). Masking may have also contributed, in part, to the greater association of breast density with larger tumors than smaller tumors. Inconsistent with a masking effect are the results that showed no difference in the association with breast density and nodal status (29).

In addition to a possible masking effect, it is plausible that tumors that arise in dense breasts may be more aggressive because of the interaction of increased numbers of stromal and epithelial cells (33). High breast density has been positively associated with breast tumor characteristics that are predictive of worse prognosis including larger tumor size (22,34,35), positive lymph nodes (22,31,36), and advanced stage (37), even when accounting for delay in tumor detection because of possible masking effect. The fact that tumors in dense breasts may progress more rapidly than those in fatty breasts is also illustrated by results of a recent study evaluating the interaction between breast density, hormone therapy use, and breast cancer risk (37), where the authors found that low breast density was associated with low breast cancer risk and decreased risk of advanced-stage disease regardless of hormone therapy use, whereas, in women with high density, hormone therapy use was associated with higher cancer risk and advanced stage at diagnosis. In addition, premenopausal women with high breast density were more likely to be diagnosed with advanced-stage disease. This suggests that the presence of extensive or high breast density, together with endogenous hormones in premenopausal women or exogenous hormones in postmenopausal women, may stimulate proliferation of the greater numbers of epithelial and stromal cells in the breast associated with high breast density (19) to promote tumorigenesis.

Lastly, studies evaluating risk factor associations according to tumor characteristics should consider the potential for bias because of missing tumor information. The exclusion of breast cancer with missing data on tumor characteristics may change the results if such data are not missing at random. Yaghjyan et al. (29), similar to most studies relying on clinical pathology reports, found considerable missing information on HER2 status (46%) and tumor grade (41%), and less missing (22%–23%) information on tumor size, and ER, PR, and nodal status. Tumors for which this information is unknown may differ from tumors with known tumor characteristics (38). For example, it is plausible that HER2 testing may not be done for tumors diagnosed at a more advanced stage, or that lymph nodes may not be evaluated for very small or large tumors if such testing will not change clinical management. Investigators studying the association between breast density and tumor subtypes must consider the possibility that excluding study subjects on the basis of missing data may affect comparisons across tumor subtypes.

Characterizing the association between risk factors such as breast density for specific breast cancer subtypes (ER positive, HER2 positive, and triple negative) can provide important clues as to how tumor subtypes differ in their etiologies, and may also inform the biological mechanisms through which risk factors influence risk for good and poor prognosis tumors. The results presented in this study (29) suggest that breast density is an important risk factor for a range of biologically diverse subtypes of breast cancer, including tumors exhibiting characteristics indicative of poorer prognosis. Application of these results could contribute to risk prediction models with better discrimination than current overall breast cancer risk prediction models (39–41). Given that the magnitude of the association with breast density is strong across all breast cancer subtypes and particularly for ER-negative disease (29), breast density should be included in risk prediction models across tumor subtypes. Developing risk prediction models that identify women at risk of tumor subtypes and then applying imaging modalities best suited to detect those disease subtypes and primary prevention targeted at specific subtypes could lead to optimized breast screening and prevention strategies.


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