Breast density: towards new therapeutic strategies for breast cancer prevention

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ABSTRACT — Breast cancer (BC) is the leading cause of cancer-related mortality worldwide, mostly occurred in United States and Western Europe. Scientists progressed in diagnosis and treatments for BC, contributing to the significant drop in the mortality rate. However, malignancy still accounts for more than 500,000 deaths annually worldwide. A major risk factor contributing to the breast cancer burden is mammographic density (MD) in breast tissue. In fact, more than 50% of women under 50 years of age exhibit high MD[1]. Several studies revealed that women with high breast density have a 4-6-fold increased risk of breast cancer compared to women with less breast density[2]. This review highlights some natural substances that may help in the prevention of breast cancer. Modern data suggest that women with high breast density experience significant clinical benefits when treated with a balanced composition including boswellic acid, betaine, and Myo-inositol. Without any side effects, this therapy is a valuable natural solution to ameliorate high breast density cases, preventing breast cancer and contributing to pain reduction.

KEYWORDS
Breast, Cancer, Breast density, Prevention, Myo-inositol.

BREAST DENSITY: DEFINITION AND AETIOLOGY

Mammographic density (MD) refers to the percentage of dense tissue of an entire breast. The percent mammographic density (PMD) is based on the appearance of MD in accordance with the different characteristics of X-ray attenuation based on breast tissue composition. Fat is radiologically translucent, so X- rays can pass unhindered through it, making it darker on a mammogram. Epithelial and connective tissue, including the glands, are radiologically dense, so as a result they appear lighter on a mammogram than fat tissue. Therefore, MD is defined as fibro glandular mammary tissue consisting of fibroblasts, epithelial cells, and connective tissue[1].

The breast density exhibits genetic and nongenetic components. For instance, hormonal mechanisms, like the growth hormone-mediated release of free fatty acids from adipocytes or the increase in the lipid substrate for oxidative damage, might be involved in the pathogenesis of breast cancer[3].

Genetics

Multiple studies revealed that genetic factors influenced the percentage of dense tissue in women between 40 and 70 years of age, with a range from 60% to 75%. The number of genes that influence mam-

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mographic density and their role in causing breast cancer, have not been determined yet. However, extensive mammographic density is commonly associated with a markedly increased risk of breast cancer. The genes responsible for familial correlation in mammographic density may influence susceptibility to breast cancer in a wide fraction of the population and they may contribute to some of the familial aggregation of the disease[4]. Wolfe et al[5] found more similarities in breast parenchymal patterns in pairs of sisters and in pairs of mother and daughter, than in age-matched control pairs. The newest evidence about heritability of breast density can increase awareness of breast cancer pathogenesis, considering familial aggregation.

Age, Parity status, BMI

Factors like age, body mass index (BMI), and postmenopausal status were inversely and significantly associated with mammographic density and with all the breast tissue measurements. Body weight was inversely and significantly associated with mammographic density, and with all the measurements except the one regarding glandular area. The age-related decline in mammographic density is likely to reflect the reduction in epithelium and stroma and the increase in fat tissue, which is described as involution. Pregnancy and the menopause are also associated with a reduction in mammographic density. In one study, parity status and number of births were significantly and inversely associated with percent collagen in the breast tissue density. Smaller breasts were also reported to be associated with a greater amount of collagen and glandular tissue.

Nonetheless, parameters of age, parity and menopause explain only about 20% of the change in mammographic density. Indeed, mammographic density is highly heritable, therefore after adjustment for age, parity and menopausal status, an additive genetic model explains about 60% of the residual variance.

The percentage of stroma, epithelium and fat that composes breast tissues are heritable and are related to radiological density. Genes responsible for cellular proliferation and regulation of the breast (epithelium, stroma, and extracellular matrix) seem likely candidates to be involved in determining MD[6].

Race and Ethnicity

Del Carmen et al[7] conducted a retrospective review of data collected from 15,292 women.

They observed that mammographic breast density differences endure across racial groups, compared to those associated with BMI and age at screening. The review found that breast density is higher in Asian women and lower in African American ones. Although breast density is linked with breast cancer risk, differences of innate mammographic breast density across racial groups do not explain the chances of breast cancer risk[7].

Diet

Mammographic density can vary in women with different dietary habits. In one study, women restricted to a western diet exhibit higher MD, compared with women less restricted to this diet. Women on a western diet were more likely to have high mammographic density (27%) than women with low adherence to that diet (19%). No link between Mediterranean diet and mammographic density was observed[8]. Along with the contribution of diet, alcohol intake can also modulate MD. A recent study proved this theory in a cohort of African American (42%), African Caribbean (22%), white (22%), and Hispanic Caribbean (9%) women (n=189, ages 40-61). It explained that women who consume more than 7 alcohol servings per week (especially with a BMI of less than 25 kg/m^2) have a 17% higher MD, compared to women who did not consume alcohol.

Thus, these studies indicate that dietary factors may have implications in the risk of developing breast cancer, by contributing to the increase of MD[1].

Hormonal Replacement Therapies

Hormonal replacement therapies (HRT) and treatment based on tamoxifen may increase MD. Nonetheless, estrogen therapy alone does not significantly increase MD. Previous articles found a positive correlation between MD and HRT, highlighting the consequential relationship between HRT and breast cancer risk.

American scientists found an association between a combined treatment based on conjugated equine estrogens (CEE) and progestin and an increased mammographic density. These results suggest the increased mammographic density as a marker for elevated breast cancer risk, especially in postmenopausal women who use estrogen/progestin therapies[9].

Consequently, it is reported that a valid correlation between a change in breast density (due to hormonal therapies) and breast cancer risk. All the findings suggest that multiple factors like race, genetics, diet, parity, menopausal status and HRT can modulate MD and influence women's risk for breast cancer[1].

INTERNATIONAL BREAST DENSITY MEASURE SYSTEM

The most used tool for determining MD on a mammogram is the breast imaging reporting and data systems (BI-RADS), which divides MD into four major categories[10].

a. Level 1 indicates breasts that are almost entirely composed of fat with 5–24% tissue density (10% of women in the US). Unless an area containing cancer is not included in the image field of the mammogram, mammography is highly sensitive in this setting.
b. Level 2 defines a breast tissue composed of scattered areas of density at 25–49%, but still composed of mainly fatty tissue (40% of women in US). In this category, there are scattered areas of fibro glandular density (historically, there are scattered fibro glandular densities). Distinguishing breasts in which there are a few scattered areas of fibro glandular-density tissue from those in which there are moderate scattered areas of fibro glandular-density tissue, may be helpful in clinical practice. Note that there has been a subtle change in the wording of this category, to conform to BI-RADS® lexicon use of the term "density" to describe the degree of x-ray attenuation of breast tissue but not to represent discrete mammographic findings.
c. Level 3 described as heterogeneous density, indicates areas of non-dense tissue with 50–75% tissue density (40% of women in US). The breasts are heterogeneously dense, which may obscure small masses. It is common finding some areas relatively dense while other areas primarily fatty. When this occurs, it may be helpful to describe the location(s) of the denser tissue in a second sentence, so that the referring clinician is aware that these are the areas in which small noncalcified lesions may be obscured. Suggested wordings for the second sentence include: "The dense tissue is located anteriorly in both breasts, and the posterior portions are mostly fatty" or "Primarily dense tissue is located in the upper outer quadrants of both breasts; scattered areas of fibro glandular tissue are present in the remainder of the breasts."
d. Level 4 is composed mostly of ≥ 75% tissue density with very little to nofatty tissue and is designated as extremely dense (10% of women in US). The breasts are extremely dense, lowering the sensitivity of mammography. The fourth edition of BI- RADS®, unlike previous editions, indicated quartile ranges of percentage dense tissue (increments of 25% density) for each of the four density categories, with the expectation that the assignment of breast density would be distributed more evenly across categories than the historical distribution of 10% fatty, 40% scattered, 40% heterogeneously, and 10% extremely dense.

Women with heterogeneously or extremely dense breast tissue are diagnosed with high MD[1]. The fifth edition of BI-RADS® no longer shows percentages of dense tissue, aiming to emphasize the text descriptions of breast density[10].

BREAST DENSITY AND ITS CORRELATION WITH BREAST CANCER DEVELOPMENT

Mammographic density presents two considerable issues. Firstly, high MD decreases the detection sensitivity of screening mammography; secondly, MD is an independent risk factor for breast cancer. In fact, women with highly dense breasts are at greater risk for developing breast cancer, compared to women with lower dense breast tissue.

Wolfe[5] first published the link between the presence of dense breast tissue and the occurrence of breast cancer. Since then, many studies have confirmed this correlation. In a large meta-analysis conducted by McCormack et al[12], which compared percentage of breast density with breast cancer incidence, the combined relative risk of breast cancer was 1.79 for level 1 MD, 2.11 for level 2 MD, 2.92 for level 3 MD and 4.64 for level 4 MD.

These data indicate the strong positive association between the increase of MD and the enhanced risk for breast cancer. In more than 14.000 women with breast cancer from 42 different studies, scientists found a significant positive correlation between high mammographic density and the increased risk of breast cancer. The breast cancer risk associated with high mammographic density did not differ by age, menopausal status, or ethnicity. Neither it could not be explained by the "masking effect" of cancer by dense tissue[11,12].

The role of stroma in the genesis of cancer has not been completely clarified. Undoubtedly, epithelial, and stromal cells, collagen and fat, are related to each other in several ways. Epithelial and stromal cells communicate with each other by paracrine growth factors. Collagen is produced by stromal fibroblasts, and adipocytes develop from the differentiation of stromal preadipocytes.

Therefore, disorders of the crosstalk among epithelial cells and the surrounding stroma are expected to participate in the aetiology of mammographic density and this interaction is considered relevant in breast carcinogenesis. Furthermore, many studies indicate that the average percentage of MD in the population decreases as increasing age, which is also associated with a reduction in average amounts of stromal and epithelial tissues in the breast.

Mammographic density may echo the aggregate exposure of breast stroma and epithelium to hormones and growth factors that stimulate cell division and modifications in MD[2].

A recent study counting 733 women with invasive breast cancers found a higher association of MD with ER-negative tumors, including triple-negative breast cancer (TNBC), compared to luminal breast cancers. In breast cancers clinically detected, but not in screening- detected ones, higher mammographic density was associated with ER-negative tumors including TNBC.

The presented study highlights the need for taking screening tools into consideration when addressing mammographic density and tumor biomarkers[13].

Scientists found a particular occurrence regarding an increased expression of an extracellular matrix proteoglycan (Lumican) in high density breast tissue compared to low density ones. High expression of Lumican can induce breast cancer by increasing angiogenesis, cell growth, migration, and invasion. Furthermore, higher levels of Lumican are associated with higher tumor grade.

Another cellular matrix proteoglycan, namely Decorin, acts similarly to Lumican, exhibiting higher expression in high density tissue than in lower one. However, the roles of Lumican and Decorin in high-density breast tissue need further exploration[1,14]

BREAST DENSITY DIAGNOSIS: MAMMOGRAPHY AND TOMOSYNTHESIS

Mammographic density has been associated with two main concerns. Firstly, a masking effect on mammography since dense tissue may obscure cancer cells. Secondly, an independent higher risk for developing breast cancer. According to the American College of Radiology (ACR), breast density should be classified into one of four categories BI-RADS. The four categories are the following: (a) almost entirely fatty, (b) scattered fibro glandular densities, (c) heterogeneously dense, and (d) extremely dense. Of course, there is inter- and intra-reader variability in radiologists' perception of breast density. Nonetheless, women with type 3 or 4 MD (heterogeneously dense and extremely dense) are commonly considered as women with dense breasts. About 43% of women aged 40–74 exhibit heterogeneously or extremely dense breasts by mammography[15]. Kamenov et al[16] administered a study of 11.130 women in which women with extremely dense breasts (asymptomatic for breast cancer) exhibit a reduction of 48% of mammogram sensitivity, compared to the whole sample of women exhibiting the 78% of mammographic sensitivity. Another study analyzed 8 years of screening mammograms from 329 breast cancer patients with levels 2–4 MD finding that only 19% of cancers were identified on time, while the 81% of breast cancers were missed after screening mammography because of the lack of clear visibility of dense tissue. The overlapping effect due to dense breast tissue can be reduced with the adoption of Digital Breast Tomosynthesis, while the risk factor for tumor development remains independent[15-19]. Numerous countries are adopting the Digital breast tomosynthesis for different clinical indications. Unlike digital mammography, tomosynthesis obtains multiple mammographic images with the x-ray source tracking down an arc over the compressed breasts. This technique allows a three-dimensional reconstruction of the breast[20]. By granting radiologists the chance to scroll through breasts slice-by-slice, tomosynthesis can modulate the masking effect of dense breasts with a better observation of small breast cancers[15].

NATURAL SUBSTANCES THAT HELP IN BREAST DENSITY REDUCTION

Myo-inositol is a six-fold alcohol of cyclohexane, can modulate inflammatory, metabolic, oxidative and endocrine pathways in a wide cluster of human diseases, such as cancer[16,17]. Likewise, boswellic acid and betaine both inhibit inflammation and exert protective effects on breast physiology. Myo- inositol may prevent pulmonary fibrosis after asbestos or inflammatory injury, inhibit chronic colon inflammation, by modulating altered redox balance[18]. In addition, Myo-inositol and Boswellia may contrast inflammation-induced fibrosis by modulating TGF-β activity. TGF- β1 isoform is a potent pro- fibro genic agent inducing collagen synthesis and regulating the balance between matrix-degrading metalloproteinases and their inhibitors, thus resulting as a prominent factor in regulating the crosstalk among epithelial cells and their microenvironment. Myo-inositol significantly modulates the expression of genes encoding TGF-βs and their receptors, and it exerts immune-regulatory effects on colonic epithelium under inflammatory conditions or during microbe-induced infection/inflammation to maintain the colonic mucosa in a non-inflammatory state or to counteract infection. TGF-β down- regulation has been observed in breast diseases, for instance breast fibrosis is usually characterized by an increase of breast density during mammographic examination[19-21]. Modulation of these important biological activities by Myo-inositol and Boswellia may improve the breast density. Myoinositol improves the clinic-pathological features of breast density, interfering with tissue metabolism both at local and systemic level. In fact, as demonstrated by a plentiful body of scientific data, Myo-inositol improves metabolic and hormonal patterns, modulating cell metabolism, improving glucose uptake, and normalizing lipid metabolism[22].

It may restore insulin sensitivity, contrast hyperandrogenism and modulate estrogen and FSH activity at ovary level in patients with PCOS[23,24].

Boswellia can modulate the expression of signaling molecules and cell cycle regulators such as the caspase-3 in the MDA-MB-231 breast cancer cells, and the phosphorylated levels of Akt (Ser473) and Erk1/2 (Thr202/Tyr204) in MCF7 cells. Boswellia is involved also in down-regulation of the expression of cyclin D1, a crucial cell cycle regulator involved in cancer development and progression[25-27].

Betaine is a nutrient involved in one-carbon metabolism and in methylation of DNA, influencing gene stability, expression and nucleotide synthesis and its intake could be useful in the prevention of breast cancer development[28].

TOWARDS NEW THERAPEUTIC STRATEGIES

Based on their mechanisms of action, all the mentioned natural substances may exert positive effects on breast density.

To investigate new therapeutic strategies to reduce breast density and to prevent the development of breast cancer, multiple clinical studies evaluated a combination with Myo-inositol, boswellic acid and betaine (Eumastós®). It resulted to be beneficial in breast density reduction, showing a pleiotropic effect on various pathways targeting inflammatory, metabolic and endocrine processes[29].

Pasta et al[2] reported the effects of an association of Boswellia, betaine and Myo-inositol in the treatment of mammographic breast density, according to a randomized, double-blind study. They found an unexpected major decrease in breast density among patients of the experimental arm (60%), whereas no significant differences were found in the placebo group. It is worth noting that among those women, reduction in tissue compactness was also associated to a significant pain reduction in almost all patients (13 out of 15). No significant adverse effects were recorded in both arms. Additionally, this combined formula ameliorated other symptoms, like anxiety and menstrual discomfort.

Data presented confirmed that women with high breast density experienced a significant clinical benefit when treated with a balanced composition including boswellic acid, betaine, and Myo-inositol (Eumastós®)[2].

Several vitamins and antioxidants were evaluated as support in the management and the prevention of breast diseases. Among many formulations, those including folate, vitamin B1, B6, B12 and antioxidants, such as N-acetylcysteine, have yielded positive results and to date, vitamins supplementation is usually recommended by general practitioners.

Considering that increased breast density is a decisive risk factor for breast cancer development, the choice of the best agent for the initial management of mammographic breast density is highly debated.

Since the lack of clear guidelines or protocols to adopt, the possibility to reduce mammary density with the use of a natural molecules may be recommended. Data reported demonstrated that the above mentioned natural substances may ensure a high response rate on breast density reduction without side-effects, making it a reliable therapy for prolonged periods[1].

CONCLUSIONS

The sensitivity of mammography is lower in women with dense breasts. The dense tissue can obscure small cancers, due to lack of clear visibility. With a level of 3 or 4 of density (referring to ACR BI-RADS International Density scale), radiologists struggle to exert a correct interpretation of a mammographic exam.

Additionally, breast density is associated with increased risk of developing breast cancer. Various clinical studies confirmed the positive correlation between these two occurrences. Breast density is an independent risk factor for breast cancer in women with high density, compared to those with fatty breasts.

Although heritable, breast tissue density may be modulated by external factors and therapies. There are gaps in the complete understanding of cellular and molecular mechanisms underlying the strong association of dense breast tissue with the incidence of breast cancer. Natural substances may help in the process of breast density reduction[1].

For women at intermediate to high risk, shared decision-making conversations should cover risks, benefits, alternatives, and patient preferences regarding supplemental screening.

A Cochrane review of trials examining personalized risk communication on informed decision making suggested that such communications related to breast cancer screening led to increased knowledge and accuracy in personal risk perception among patients[15].

Recent data suggest that women with high breast density, experience a significant clinical benefit when treated with a balanced composition including boswellic acid, betaine, and Myo-inositol with the aim to prevent breast cancer and to contribute to pain reduction. Without any side effects, this therapy is a valuable natural solution to ameliorate high breast density for prolonged periods.

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Conflict of Interest:
The authors L. Giannunzio and V. Unfer declare their conflict of interests as employees of Lo.Li. phar-ma Srl, manufacturer of food supplements containing Myo-inositol. The other authors declare no conflict of interest to disclose.

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