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Mammographic Density Under Hormonal and Hormone-Like Treatments

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1. Introduction

Mammographic screening is the only important intervention for the early detection of breast cancer. The ability of mammography to detect incipient breast cancer depends on breast density. Hormonal treatments, affecting the breast radiological density, are an important risk factor interfering mammography. In the same time, mammographic density is currently being explored as a biomarker of response in primary and secondary prevention trials. Important considerations for chemoprevention studies include maximizing intrareader reliability and minimizing variance resulting from technical and physiologic factors (Fabian & Kimler, 2006). While technical factors for maximizing intrareader reliability and minimizing variance depend on classifications and technology, it is also important to evaluate the impact of physiologic and pharmacological factors

2. Classifications of breast mammographic density

Mammographic breast density reflects mammary gland development and structure. From the multiple methods that have been developed to assess mammographic density, Wolfe`s classification identified four categories: N1, P1, P2 and DY (Wolfe), with density increasing from N1 to DY, the greatest relative risk being associated with the DY pattern (Wolfe, 1976). The BIRADS system developed by the American College of Radiology classifies breasts as 1) almost entirely fatty, 2) scattered fibronodular tissue, 3) heterogeneously dense and 4) extremely dense (American College of Radiology [ACR], 1993). The proportion of women having BIRADS category 3 and 4 dramatically decreases with age. BIRADS semiquantitative classification has a suboptimal intrareader reliability (Fabian & Kimler, 2006). For greater intraobserver reliability, continuous, computer assisted measurements have a better performance, being more suitable for prevention studies (Fabian & Kimler, 2006).

Byrne, using the mammograms from the Breast Cancer Detection Demonstration Project, developed a continuous density measurement system, in which the area of the breast occupied by increased density was measured relative to the total area of the breast (Byrne et al., 1995). Byrne`s classification has 5 categories of relative areas of increased mammographic density and give a better assessment of relative risk for breast cancer than the 4-category Wolfe classification. The authors observed that the area of increased density is a risk factor, while the total breast area is not.

Boyd et al divided breast density measurements into 6 categories similar to those of Byrne, using a similar computer-assisted system for detection of mammographic density (Boyd et al., 1995).

Continuous density measurement system studies reported that the 10% of women who had >75% increased breast density had a 4 to 5-fold greater risk of breast cancer than women with no areas of increased breast density, after corrections for weight, reproductive and family history (Byrne et al.,1995; Boyd et al., 1995). Women with 50–75% area of density have a 2.5 to 3.0-fold increase in risk. Boyd et al. have suggested that the increase in relative risk estimates resulting from a breast density measurement lasts at least a decade (Fabian & Kimler, 2006; Boyd et al., 2002).

This long-lasting influence of breast density further justifies the interest in evaluation of the impact of physiologic and pharmacological factors on mammografic breast density.

Mammographic density category							
Wolfe	Increased breast density	N 1			P 1	P 2	DY
Byrne		0 %	1-24 %		25-49 %	50-74 %	≥ 75 %
Byrne (absolute density)		0 cm^2	1-13.9 cm^2	14-22.9 cm^2	23-33.9 cm^2	34-52.9 cm^2	> 53 cm^2
Boyd		None	< 10 %	10- <25 %	25- <50 %	50- <75 %	≥ 75 %
Wolfe	Percent of women exhibiting breast density patterns	12 %			28 %	48 %	12 %
Byrne		11 %	27 %		25 %	28 %	8 %
Byrne (absolute density)		Control group divided in six approximately equal groups					
Boyd		7 %	17 %	21 %	27 %	19 %	9 %
Wolfe	Adjusted odd ratio	1.0			1.68	2.83	2,73
Byrne (adjusted for all confounding factors)		1.0	1.57		2.47	2.77	4.35
Byrne (absolute density)		1.0	1.48	1.99	2.08	3.24	3.35
Boyd (all ages)		1.0	1.2	2.2	2.4	3.4	5.3

Table 1. Risk of breast cancer development associated with mammographic density in Wolfe`s (Wolfe, 1976), Byrne`s (Byrne et al., 1995) and Boyd`s (Boyd et al., 1995) classifications (adapted from Fabian & Kimler, 2006).

3. Endogenous influences on breast mammographic density

Mammographic parenchymal patterns are a function of breast development. The development of breast is the sum of ducts and lobules genetic-induced development, under the control of endogenous factors, mainly endocrine. Estrogens are responsible for growth

and developments of the ducts, while the maturation of the breast acinus is progesteron-dependent. Progesteron is responsible for water accumulation at the end of menstrual cycle, increasing the breast density and whiteness on mammography. Declining in levels of estrogens and progesteron in menopause is associated with a decrease in breast density, making it easier to be examined by mammography.

4. Exogenous influences on breast mammographic density

Exogenous hormonal influences on mammografic breast density are best reflected by positive associations of mammografic breast density with postmenopausal hormone replacement therapy (HRT) and inverse associations with tamoxifen (Ghosh & Vachon, 2010).

4.1 Hormone replacement therapy

Hormone replacement therapy (HRT) increase the breast density (glandular tissue), which appears as white areas on a mammography, making microcalcifications and breast masses more difficult to detect, since breast abnormalities also appear as white areas on a mammography.

HRT is used by perimenopausal and early postmenopausal women, in the age group in which the incidence of breast cancer is maximum. As HRT contains a wide range of therapeutic interventions, its effects on mammography will vary according to several variables: HRT users versus non-users, age and window of opportunity, duration and dose of therapy, estrogen versus estrogen+progestin therapy, continuos combined versus sequential HRT, type of progestin, transdermal versus oral HRT.

The impact of HRT on mammographic screening is decreasing its sensibility, current use of HRT being associated with reduced sensitivity and specificity of mammographic breast cancer screening (Banks, 2001). Many studies suggest that current HRT users are more likely than non-users to have interval breast cancer (cancer occurring in the interval between screenings) (Banks, 2001; Cohen, 1997; Rosenberg et al., Litherland et al., 1999). Therefore, the benefit of mammographic screening may be reduced in HRT users, in terms of breast cancer mortality reduction, compared with non-users. Regarding the specificity of mammographic screening, many studies showed a lower specificity for current HRT users (Laya et al., 1996; Thurfjell et al., 1997), who may experience more false positive recall, compared with non-users (recalled for assessment after initial mammography, but found not to have breast cancer) (Clemons & Goss, 2001). Thurfjell et al (Thurfjell et al., 1997) divided current HRT users into three categories: less than 3 years of use, 3-6 years of use and more than 6 years of use. They reported specificities of 95%, 95%, and 92% respectively ($p=0.046$), revealing a trend for false positive recalls with increasing duration of use of HRT. These data are consistent with the study of Sala et al, who found that starting HRT pre- or perimenopausally and > 5 years of use will increase the probability of a high-risk mammographic density pattern, more difficult to evaluate (Sala et al., 2000).

Current HRT users have an increased probability of having a high risk pattern of breast density (Sala et al., 2000; Persson et al., 1997; McTiernan et al., 2005; Greendale et al., 2003; Chlebowski et al., 2003; Boyd et al., 2006). Current estrogen + progestin therapy users and current estrogen-only therapy users had greater odds of having dense breasts (98% [1.87–

2.09]) and 71%, respectively [1.56–1.87]), compared to never users (Aiello et al., 2006). Type of HRT regimen is an important factor, influencing breast mammographic density. Lundstrom E et al (Lundstrom E et al., 1999) found that increase in mammographic density was much more common among women receiving continuous estrogen + progestin HRT (52%) than among those receiving estrogen + progestin HRT (13%) and estrogen-only (18%) treatment. The increase in density was apparent already at first visit after the start of hormone replacement therapy. There was little change in mammographic status during long-term follow-up (Lundstrom E et al., 1999).

Transdermal HRT use is associated with a significantly lower incidence of increased mammographic breast density and breast tenderness compared with oral HRT (Harvey et al., 2005). In Harvey`s study (2005), 202 postmenopausal women were randomized to transdermal (estradiol+norethindrone) or oral (estradion+norethistron acetate) HRT. Significantly fewer women using transdermal HRT had an increase in mammographic breast density or breast tenderness compared to oral HRT. Of the women using transdermal HRT, 39.1% had no change in breast density compared to 15.7% for women using oral HRT. Only 4% of women using transdermal HRT had a marked increase in density (>25%) compared to 15.7% of women using oral HRT.

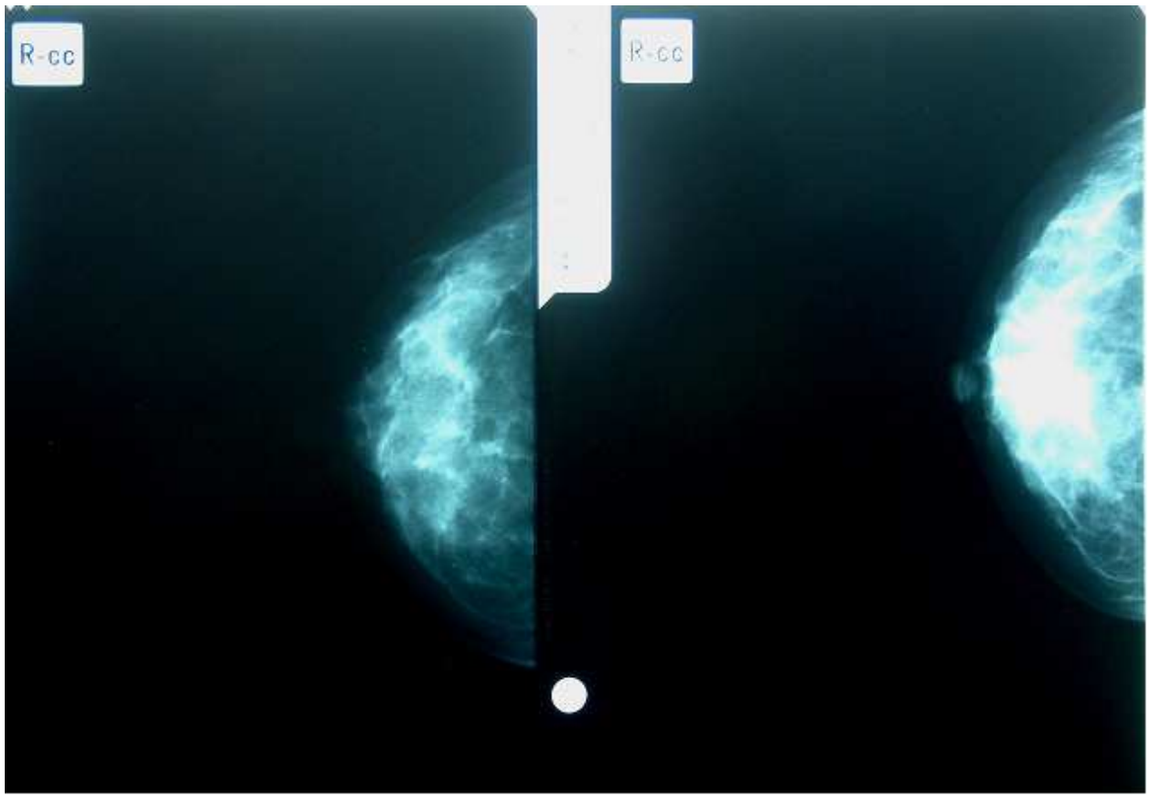

Fig. 1. Increase in mammographic breast density in a 53 years old patient on sequential combined hormonal therapy (1,5 mg estradiol transdermally+20 mg dydrogesterone orally). Left – mammography at baseline; right – mammography after 1 year of treatment. Procentual mammographic density raised from 23% to 55% (Russu et al., 2008).

The randomized, double-blinded PEPI trial (Greendale et al., 1999) compared the mammography before and after twelve months of treatment, for HRT patients versus placebo. Twenty percent of HRT patients had increased mammographic density, as compared to 0 % in placebo group. There was no difference in breast densities between continuous combined and sequential HRT groups. There was also no difference in breast densities with different progestins. Patients with estrogen-only therapy had a very small increase in breast density.

The WHI Study (Chlebowski et al., 2003) found that, after one year of estrogen plus progestin therapy, the percent of abnormal mammography was higher in estrogen plus progestin therapy group, compared with placebo group (9,4% vs 5,4%; P<0.001), and the difference was maintained throughout the duration of the study. In each year thereafter, the percentage of women with abnormal mammograms was significantly higher in the estrogen plus progestin group vs the placebo group. For the whole study, 31.5% of women in the estrogen plus progestin group had at least 1 abnormal mammogram vs 21.2% of women in the placebo group (*P*<.001). Thus, even short-term estrogen plus progestin use resulted in a substantial increase in abnormal mammograms requiring medical evaluation. The risk for breast cancer parallels the percentage of abnormal mammography. The authors concluded that E+P therapy increased the number of breast cancer and the number of not necessary interventions for false positive mammography in this group. However, most of the studies found a lower mortality for HRT users compared with non-users.

The Million Women Study showed that current users of HRT at recruitment were more likely than never users to develop breast cancer (adjusted relative risk 1.66 [95% CI 1.58-1.75], p<0.0001) and die from it (1.22 [1.00-1.48], p=0.05). Stopping HRT reduces breast cancer risk, as demonstrated in WHI study (Chlebowski et al., 2003), where the authors found that past users of HRT were not at an increased risk of incident or fatal disease (1.01 [0.94-1.09] and 1.05 [0.82-1.34], respectively).

Patients with estrogen-only therapy tend to have a small increase in breast density and lower risk for invasive breast cancer. In WHI study follow-up (La Croix et al., 2011), after 6 years of equine estrogens use and a mean 10,7 years after baseline, estrogen-only therapy was associated with a lower risk for invasive breast cancer than the placebo group (hazard ratio, 0.77; 95% confidence interval, 0.62–0.95); moreover, among younger women, estrogen use was associated with lower risk for CHD (HR, 0.59; 95% CI, 0.38–0.90). However, this does not imply that estrogen-only therapy should be recommended at this time for breast cancer chemoprophylaxis (Beral et al., 2003; Kaunitz, 2011; Jungheim & Colditz, 2011).

Progestin-releasing intrauterine devices are a type of hormone therapy addressed to women younger than 50 years of age, especially with associated uterine pathology (e.g., fibroids, menorrhagia).

A retrospective, population-based, case-control study (Dinger et al., 2011), performed on 25565 women (5113 breast cancer cases and 20452 controls) failed to observe any increase of breast cancer risk in levonorgestrel intrauterine device users.

Combination of levonorgestrel intrauterine device and low-dose oral estradiol valerate was associated with a slight increase in mammographic breast density. Lundstrom et al (Lundstrom et al., 2006) assessed 20 healthy patients with levonorgestrel intrauterine device and 2 mg oral estradiol valerate and they found an apparent increase in breast

density in only 3 women (15%). However, there was no increase in proliferation, as expressed by the percentage of MIB-1-positive breast cells in fine-needle aspiration biopsies. Given the small number of cases, these results need to be confirmed by larger studies.

Timing of HRT initiation influences the mammographic parenchymal patterns. Analizing a subgroup from EPIC-Norfolk cohort, Sala et al (Sala et al., 2000) found that women who are starting HRT, while still menstruating, were more likely to have a high-risk breast density pattern compared to women not exposed to HRT or to those who started HRT after menopause. A recent Million Women Study analysis update (Beral et al., 2011) focused on the influence of timing on breast cancer risk for the different treatment regimens. Relative risks were found to be higher if therapy was started before or soon after menopause than in the case of a longer interval between menopause and starting HRT ($p < 0.001$). Among current users of estrogen-only therapy, there was little or no increase in risk if use began 5 years or more after menopause (RR 1.05, 95% CI 0.89–1.24), whereas risk was increased if use began before or within 5 years after menopause (RR 1.43, 95% CI 1.35–1.51). A similar pattern was seen for users of E+P (RR 1.53, 95% CI 1.38–1.70 vs. RR 2.04, 95% CI 1.95–2.14). The timing of initiation of HRT relative to that of menopause appears to be an important factor that modulates the risk of breast cancer.

HRT effects on breast and mammography are reversible. After discontinuing hormone therapy, breast density decrease rapidly. Discontinuation of HRT a few weeks prior to mammography may improve mammographic performances. The rapid decrease in breast density after stopping HRT suggest that increased breast density in HRT users is different from increased breast density in non-users. Increased breast density in non-users reflects a genetic increased quantity of glandular and fibrous tissue, whereas increased breast density in HRT users may suggest a water retention at breast level, probably due to stromal changes, under hormonal influence (Alowami et al., 2003). In a retrospective study, Harvey at al analyzed breast density modifications after stopping HRT (Harvey et al., 1997). HRT-induced mammographic changes disappeared two weeks after HRT discontinuation. However, twelve patients in their study did not experienced mammographic reversal after HRT discontinuation, and, on biopsy, one case of atypical hyperplasia and one case of ductal invasive carcinoma were found. More recent studies failed to observe an improvement in mammographic diagnostic accuracy, following HRT suspension. The Buist`s randomised trial revealed that HT suspension was associated with small changes in breast density and did not affect recall rates. There was no evidence to support short-term HT suspension before mammography (Buist et al., 2009).

A few studies addressed the issue of reducing breast cancer risk in HRT population. Adding aromatase inhibitors to HRT may lower mammographic breast density in postmenopausal women. A small retrospective study (Mousa et al., 2008) demonstrated a statistically significant reduction in mammographic breast density occurred in the women who received hormone therapy plus an aromatase inhibitor letrozole, whereas no significant change was observed in the women receiving hormone therapy alone. Aromatase inhibitors could be good candidates for primary chemoprevention of breast cancer in postmenopausal women using hormone therapy (Mousa et al., 2008).

4.2 Oral contraceptive

A special type of exogenous hormonal therapy is oral contraceptive (OC) use. Modern OC consist in a combination of ethinilestradiol (20μg or 30 μg) and different types of progestins. Oral contraceptive use is an issue of young women, mostly before age of 40, a time when mammographic screening begins. Therefore, studies evaluating the impact of COC on mammographic breast density are lacking.

A Norwegian study (Gram et al., 2002) examined the relationship between oral contraceptive ever use and mammographic patterns among 3218 women, aged 40-56 years, who fulfilled a questionnaire about ever OC use, duration, and starting age of OC. Women ever having used OCs had an increased risk for high-risk mammographic patterns [OR 1.27; 95% CI (1.0-1.6)], compared with those reporting never having used OCs. There was no relationship between different types of OC use (different doses) and high-risk patterns. Nulliparous women, who ever used OCs, were four times more likely [OR 4.65; 95% CI (2.1-10.3)] to have high-risk patterns, compared with never users.

Breast cancer lifetime-risk of oral contraceptive use was addressed in a large study (Hunter et al., 2010), performed on 116.608 female nurses, aged 25 to 42 years at enrollment in 1989, among which 1.344 cases of invasive breast cancer were diagnosed until 2001. There was no relationship between past use of any oral contraceptive and breast cancer risk [RR= 1.12; 95% confidence interval (0.95-1.33)]. Current use of any oral contraceptive was only marginally related to a higher risk of breast cancer [RR=1.33; 95% confidence interval (1.03-1.73)]. However, users of triphasic oral contraceptive, with levonorgestrel as the progestin, were exposed to an excess risk of breast cancer, as high as 3.05 [95% confidence interval (2.00-4.66); $P < 0.0001$]. The authors (Hunter et al., 2010) concluded that current use of oral contraceptives is associated with an excess risk of breast cancer, levonorgestrel-based triphasic contraceptives accounting for this risk elevation.

4.3 Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonist (GnRHA) suppress ovarian function, decreasing circulating levels of estrogens, so it could be assumed that their administration would influence breast density. A special designed contraceptive study (Spicer et al., 1994) randomly assigned 21 patients, 27–40 years of age, with a 5-fold greater than normal risk of breast cancer, in a 2:1 ratio to special contraceptive group (14 women who received GnRHA (leucoprolide acetate) plus very low doses add-back conjugated estrogen and medroxy-progesterone acetate) or to a control group (7 women). The authors found that women on the contraceptive regimen showed significant ($P = 0.039$) reduction in mammographic densities between the baseline and 1-year mammograms, compared with control group. In a follow-up of this study (Spicer et al., 1994), 12 months after completion of treatment, the mean percentage of mammographic density in the treated group was no different from that at baseline ($P = 0.73$). Reductions in mammographic density for this special contraceptive regimen (GnRHA plus low-dose add-back estrogen-progestin) persist only during treatment period. The densities return to baseline when the women resume normal menstrual cycles.

A more recent study (Weitzel et al., 2007) performed on BRCA1 mutation high-risk patients, using GnRHA deslorelin, confirmed these data. Twelve months treatment with deslorelin,

plus low-dose add-back steroids, significantly decreased mammographic percent density in BRCA1 mutation carriers. This regimen may reduce breast cancer risk and improve the usefulness of mammographic surveillance by reducing density.

4.4 Selective tissue estrogenic activity regulator

Other forms of sistemic therapy for relief of climacteric symptoms and prevention of osteoporosis in postmenopausal women include selective tissue estrogenic activity regulator (STEAR), the most known being tibolone. Tibolone, a tissue-specific compound, constitutes an alternative for treatment in postmenopausal women (Moore, 1999).

It appears that tibolone exerts minimal effects of the breast tissue and mammographic density. In a prospective, randomized, double-blind, placebo-controlled study (Lundström et al., 2002), breast density was increased in 46-50% of oral continuous combined HRT users, as opposed to only 2-6% in oral tibolone users and 0% in placebo group. The authors concluded that in contrast to estrogen/progestogen treatment, tibolone seems to exert little stimulation of breast tissue.

According to Asia Pacific Tibolone Consensus Group, symptomatic HRT users with increased breast density that result in an unreadable mammogram could be switched on tibolone, in order to decrease mammographic density without losing the beneficial effects of HRT (Huang & Baber, 2010).

However, the relationship between tibolone use and increased risk of breast cancer remains inconclusive (Opatrny et al., 2008). A population-based case-control study, GPRD database (Opatrny et al., 2008), found that tibolone do not increase the risk for breast cancer in postmenopausal women (RR 0.86; 95% CI 0.65-1.13). Even more, LIFT trial (Cummings et al., 2008), which included 4538 osteoporotic postmenopausal women with no history of breast cancer, treated with tibolone, 1,25 mg/day, demonstrated a decreased risk of invasive breast cancer (RR = 0.32; 95% CI, 0.13 to 0.80; P=0.02).

However, in women with a history of breast cancer, data from the LIBERATE (Kenemans et al., 2009) study show that tibolone (2,5 mg/day) does increase the risk of breast cancer recurrence. LIBERATE population of women is mostly using adjuvant systemic therapy, 67% of women being on tamoxifen and 6.5% on aromatase inhibitors. Tibolone may interfere with the protective action of these agents, especially with the aromatase inhibitors, through an estrogen-agonistic action on dormant tumor cells. To date, tibolone should be contraindicated for women with a history of breast cancer.

Although comparison is not possible between LIFT and LIBERATE study, dose seems to be an important issue with respect to breast cancer risk, when using tibolone for vasomotor symptoms relief and osteoporosis treatment.

4.5 Selective estrogen-receptor modulators

Selective estrogen-receptor modulators (SERMs), previously called antiestrogens, are drugs that competitively inhibit estrogen binding to estrogen receptors (ERs), and have mixed agonist and antagonist activity (depending on the target tissue). SERMs affect a variety of biologic processes regulated by activated estrogen receptor. Depending on the target tissue,

levels and types of ERs, and their structure, SERMs may exhibit either estrogen antagonist or estrogen agonist effects (Fabian & Kimler, 2005).

Tamoxifen is a SERM with estrogen antagonist effects in the breast, weak estrogen agonist activity in the bone, cardiovascular system and CNS, and important estrogen agonist effects in the uterus, liver, and vagina.

Most of the data regarding tamoxifen effects on mammographic breast density came from prevention studies, performed on populations at high-risk for breast cancer or with a history of breast cancer. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized clinical trial of high-risk women, 5 years of tamoxifen therapy was shown to reduce invasive breast cancer risk by 49% and noninvasive breast cancer risk by 50% compared with placebo (Fisher et al., 1998).

Treatment with tamoxifen is associated with a reduction in breast density in both premenopausal and postmenopausal women (Ursin et al., 1996). However, the reduction in breast density in association with these factors has not yet been correlated with the reduction in the risk of breast cancer.

Slanetz (Slanetz et al., 2004) described mammographic density decrease on tamoxifen and return to the baseline density following termination of the drug, so they postulated that decrease in breast density could reflect the sensitivity to tamoxifen and be a marker of therapeutic benefit associated with tamoxifen. The more radiolucent pattern by tamoxifen allow enhanced mammographic detection and may further add benefit for women. After discontinuation of tamoxifen, breast density is returning to its initial pattern. The clinical significance of resumption of a dense breast pattern following discontinuation of tamoxifen remains to be determined (Ursin et al., 1996).

In high-risk populations (women with known breast cancer on adjuvant tamoxifen or women at high risk for breast cancer on tamoxifen for chemoprevention), tamoxifen produced a statistically significant reduction in mammmographic breast density and this reduction occurred more frequent in premenopausal than in postmenopausal women (54).

In a study (Son & Oh, 1999), performed on breast cancer patients who have undergone surgery, 87% of premenopausal women with breast cancer had a decrease in parenchymal area with tamoxifen use, whereas only 29% of postmenopausal women experienced a decrease.

A similar trend was observed in the Brisson`s study, performed on women with high-risk for breast cancer. Women younger than 50 experienced a decrease in parenchymal pattern classification in 67% of cases compared with 13% of postmenopausal women aged 50 or older (Brisson et al., 2000).

The duration of tamoxifen treatment is important. In a nested case-control study performed for IBIS-1 participants, Cuzick et al. noticed that the reduction in dense area for women treated for 4,5 years with tamoxifen is double compared with women given placebo (Cuzick et al., 2004). The majority of breast density reduction occurred in the first 18 months of treatment. There was a significant interaction with age such that a minimal decrease in area of density was observed for women over 55 treated with tamoxifen, that is, 1% compared to 13% for women younger than 45 (Cuzick et al., 2004). Importantly, reduction in breast

density predicted only one-third of the reduction in breast cancer incidence seen in prevention trials.

While tamoxifen is mostly recommended by the oncologists, both for curative or preventive breast cancer treatment, other SERM`s, like raloxifen, are largely recommended by general practitioners for the treatment of postmenopausal osteoporosis. Raloxifene has higher affinity for estrogen receptor and more intense antagonistic effects (by blocking ER-activating function domains, AF-1 and AF-2), than tamoxifen (which blocks only AF-2, but not AF-1) (Howell et al., 2001; Katzenellenbogen et al., 1996).

In the STAR trial (Vogel et al., 2006), tamoxifen and raloxifene had equivalent effects in reducing risk of invasive breast cancer in all examined subgroups, including women with a history of atypical hyperplasia or LCIS, who had the highest annual rates of invasive breast cancer. Most of the STAR cases were diagnosed as a result of mammograms demonstrating increasing calcifications, in conditions of reducted breast density. Because the lesions were early detected and small, most were treated surgically with lumpectomy.

In a retrospective analysis, performed on a subset of women enrolled in a multicenter, double-blind, randomized, placebo- and active-controlled phase 3 trial evaluating bazedoxifene for the treatment of postmenopausal osteoporosis, Harvey et al found that the changes in breast density with the newer SERM bazedoxifene 20 or 40 mg were similar to those with raloxifene 60 mg or placebo (Harvey et al., 2009).

The analysis of extraskeletal outcomes (Gennari et al., 2009) of PEARL study indicated that lasofoxifene 0.25 mg and 0.5 mg reduces the risk of ER positive breast cancer (by 84% and 67%, respectively). This effect was also evident for all breast cancers (a composite endpoint consisting of ER+, ER–, invasive, and ductal cancer in situ) with lasofoxifene 0.5 mg dose (65% and 79% risk reduction compared to placebo through 3 and 5 years, respectively) (Cummings et al., 2008).

4.6 Aromatase inhibitors

The aromatase inhibitors reduce breast and circulating estrogen levels in postmenopausal women. As a consequence, aromatase inhibitors may reduce mammographic breast density.

Vachon et al randomized 106 postmenopausal women to either aromatase inhibitor letrozole or placebo after 5 years of tamoxifen (Vachon et al., 2007). After 9 to 15 months, no difference breast mammographic density was found between the 2 groups.

MAP1 was a multicenter, randomized, double-blind, placebo-controlled, feasibility trial in which postmenopausal women with or without prior invasive breast cancer were randomized in a 2:1 ratio of letrozole (2.5 mg daily) or placebo for 12 months and followed for a total of 24 months. After one year treatment, letrozole does not appear to have a significant effect on mammographic percent breast density, compared with placebo (Cigler et al., 2010). Same author performed MAP 2 trial (Cigler et al., 2011) randomizing healthy postmenopausal women to exemestan (25 mg daily) or placebo for 12 months and followed them for a total of 24 months. The primary endpoint was change in percent breast density between the baseline and 12-month mammograms. For exemestan-treated patients, there was no significant difference in percent breast density from baseline to 6, 12, or 24 months; in the same time, there was no difference between exemestan and placebo group.

It was postulated that aromatase inhibitors could reduce mammographic breast density in women taking HRT. Two studies examined the influence of letrozole on MBD among postmenopausal women taking HRT: one found no change in percent MBD among 42 high-risk women on either estrogen alone or combination HRT (estrogen and progestins) after taking 2.5 mg letrozole per day for 6 months (64), whereas the other study found a reduction among women on low-dose combination therapy who were taking letrozole (2.5 mg) 3 times weekly for a median of 24 (range, 2-63) months (6.8% vs 1.4% reduction) (Mousa et al., 2008).

The effects of aromatase inhibitors on breast density, as well as on breast cancer risk, still require further investigation (Becker & Kaas, 2009).

4.7 Phytoestrogens

Phytoestrogens are plant derived substances that are structurally and functionally similar to estrogens and are found in many foods. They exhibit both weak estrogen and anti-estrogenic activity; therefore, they act as natural SERMs. There are 3 classes of phytoestrogens: isoflavonoids, coumestans and ligans (Malik & Prakash, 2004).

Maskarinec et al randomly assigned 220 premenopausal women, aged 39 – 46 years old, to soy intake intervention group or control group (Maskarinec et al., 2004). After 2 years of intervention, the authors observed no significant differences in mammographic densities by intervention status.

Association between regular green tea intake and high soy intake may have beneficial effects on the breast density. Wu, Ursin et al assessed the effects of the effects of regular green tea and soy intake on mammographic density, in a cross-sectional study performed on 3315 Chinese women in Singapore (Wu et al., 2008). For daily green tea drinkers, percent mammographic density was statistically significantly lower than for non-tea drinkers (19.5 % versus 21.7%; P = 0.002), even after adjustment for soy (P = 0.002). There was no association between black tea intake and percent mammographic density. Very high soy intake was associated with lower percent density only among postmenopausal women (compared normal or low soy intake; 18.9% versus 20.5%, P = 0.035); however, after adjustment for green tea intake, this association was no longer statistically significant (P = 0.52).

5. Conclusion

Mammographic density is a well-known risk factor for breast cancer, although the biologic basis of the relationship between breast cancer risk and increased mammographic density is not yet completely understood. Nor is the mechanism by which hormonal therapy influences mammographic breast density. Despite the beneficial effects on menopausal symptoms and osteoporosis, it is the fear of breast cancer that make menopausal women reluctant to take hormone therapy. Characterizing the association between breast density and hormonal influences may enhance the understanding of how mammographic density influences breast cancer risk for both pre- and postmenopausal women. Mammographic density reflecting directly the changes at the breast level, the influences generated by the associated therapies should be taken into account in screening and diagnostic programs.

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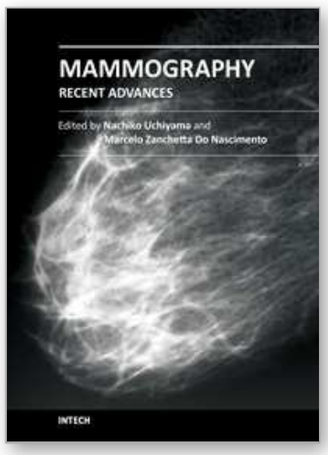

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In this volume, the topics are constructed from a variety of contents: the bases of mammography systems, optimization of screening mammography with reference to evidence-based research, new technologies of image acquisition and its surrounding systems, and case reports with reference to up-to-date multimodality images of breast cancer. Mammography has been lagged in the transition to digital imaging systems because of the necessity of high resolution for diagnosis. However, in the past ten years, technical improvement has resolved the difficulties and boosted new diagnostic systems. We hope that the reader will learn the essentials of mammography and will be forward-looking for the new technologies. We want to express our sincere gratitude and appreciation?to all the co-authors who have contributed their work to this volume.

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