

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Mammographic Density Under Hormonal and Hormone-Like Treatments

Șerban Nastasia

*University of Medicine and Pharmacy "Carol Davila" Bucharest
Romania*

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 mammographic 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 mammographic breast density are best reflected by positive associations of mammographic 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+progesteron therapy, continuous combined versus sequential HRT, type of progesteron, 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 + progesteron 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 (estradiol+norethindrone 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 ($P < 0.001$). 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. Analyzing 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 et 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 (20 μ g or 30 μ g) 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 systemic 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 on 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 mammographic 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 reduced 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 extraskelatal 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.

6. References

- Aiello, EJ; Buist, DSM; White, E. Do breast cancer risk factors modify the association between hormone therapy and mammographic breast density? *Cancer Causes and Control* Vol.17, No.10, (Dec 2006), pp.1227-35, Print ISSN 0957-5243, Online ISSN 1573-7225
- Alowami, S; Troup, S; Al-Haddad, S; Kirkpatrick, I; Watson, PH. Mammographic density is related to stroma and stromal proteoglycan expression. *Breast Cancer Research* Vol.5No.5, (Jul 2003), pp.129-35. Available from <http://breast-cancer-research.com/content/5/6/R129>
- American College of Radiology. Breast imaging reporting and data system (BIRADS). Reston, VA: American College of Radiology, 1993
- Arthur, JE; Ellis, IO; Flowers, C; Roebuck, E; Elston, CW; Blamey, RW. The relationship of "high risk" mammographic patterns to histological risk factors for development of cancer in the human breast. *The British Journal of Radiology* Vol.63No.755, (Nov 1990), pp. 845-9.
- Banks, E. Hormone replacement therapy and the sensitivity and specificity of breast cancer screening: a review. (Statistical Data Included). *Journal of Medical Screening* Vol.8, No.1, (Oct 2001), pp.29-34. Available from <http://jms.rsmjournals.com/content/8/1/29.long>
- Becker, S; Kaaks, R. Exogenous and endogenous hormones, mammographic density and breast cancer risk: Can mammographic density be considered an intermediate marker of risk? *Recent Results in Cancer Research* Vol.181, No.5, (2009), pp.135-57, Print ISSN 0080-0015
- Beral, V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *The Lancet* Vol.362, No.9382, (Aug 2003) pp.419-27, Print ISSN 0140-6736, Online ISSN 1474-547X
- Beral, V; Reeves, G; Bull, D; Green, J; Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *Journal of the National Cancer Institute* Vol.103, No.4, (Feb 2011), pp.296-305, Print ISSN 1052-6773, Online ISSN 1745-6614
- Boyd, NF; Jensen, HM; Cooke, G; Han, HL. Relationship between mammographic and histological risk factors for breast cancer. *Journal of the National Cancer Institute* Vol.84, No.15, (1992), pp.1170-1179.
- Boyd, NF; Byng, JW; Jong, RA; Fishell, EK; Little, LE; Miller, AB; Lockwood, GA; Tritchler, DL; Yaffe, MJ. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *Journal of the National Cancer Institute* Vol.87, No.9, (May 1995), pp.670-5, Print ISSN 1052-6773, Online ISSN 1745-6614
- Boyd, NF; Stone, J; Martin, LJ; Jong, R; Fishell, E; Yaffe, M; Hammond, G; Minkin, S. The association of breast mitogens with mammographic densities. *British Journal of Cancer* Vol.87, No.8, (Oct 2002), pp.876-82
- Boyd, NF; Martin, LJ; Li, Q; Sun, L; Chiarelli, AM; Hislop, G; Yaffe, MJ; Minkin, S. Mammographic density as a surrogate marker for the effects of hormone therapy on risk of breast cancer. *Cancer Epidemiology, Biomarkers and Prevention* Vol.15, No.5, (May 2006), pp.961-6, Print ISSN 1055-9965, Online ISSN 1538-7755

- Brisson, J; Brisson, B; Cote, G; Maunsell, E; Bérubé, S; Robert, J. Tamoxifen and mammographic breast densities. *Cancer Epidemiology, Biomarkers & Prevention* Vol.9, No.9, (Sep 2000), pp.911-5, Print ISSN 1055-9965, Online ISSN 1538-7755
- Buist, DS; Anderson, ML; Reed, SD; et al. Short-term hormone therapy suspension and mammography recall: a randomized trial. *Annals of Internal Medicine* Vol.150, No.11, (Jun 2009), pp.752-65, Print ISSN 0003-4819, Online ISSN 1539-3704
- Byrne, C; Schairer, C; Wolfe, J; Parekh, N; Salane, M; Brinton, LA; Hoover, R; Haile, R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *Journal of the National Cancer Institute* Vol.87, No.21, (Nov 1995), pp.1622-9, Print ISSN 1052-6773, Online ISSN 1745-6614
- Byrne, C; Schairer, C; Brinton, LA; Wolfe, J; Parekh, N; Salane, M; Carter, C; Hoover, R. Effects of mammographic density and benign breast disease on breast cancer risk (United States). *Cancer Causes Control* Vol.12No.2, (Feb 2001), pp.103-10.
- Chlebowski, RT; Hendrix, SL; Langer, RD; Stefanick, ML; Gass, M; Lane, D; Rodabough, RJ; Gilligan, MA; Cyr, MG; Thomson, CA; et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* Vol.289, No.24, (Jan 2003), pp.3243-53, Print ISSN 0098-7484, Online ISSN 1538-3598
- Chlebowski, RT; Hendrix, SL; Langer, RD; Stefanick, ML; Gass, M; Lane, D; Rodabough, RJ; Gilligan, MA; Cyr, MG; Thomson, CA; et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* Vol.289, No.24, (Jan 2003), pp.3243-53, Print ISSN 0098-7484, Online ISSN 1538-3598
- Cigler, T; Tu, D; Yaffe, MJ; Findlay, B; Verma, S; Johnston, D; Richardson, H; Hu, H; Qi, S; Goss, PE. A randomized, placebo-controlled trial (NCIC CTG MAP1) examining the effects of letrozole on mammographic breast density and other end organs in postmenopausal women. *Breast Cancer Research and Treatment* Vol.120, No.2, (Apr 2010), pp.427-35, Print ISSN 0167-6806, Online ISSN 1573-7217
- Cigler, T; Richardson, H; Yaffe, MJ; Fabian, CJ; Johnston, D; Ingle, JN; Nassif, E; Brunner, RL; Wood, ME; Pater, JL; Hu, H; Qi, S; Tu, D; Goss, PE. A randomized, placebo-controlled trial (NCIC CTG MAP.2) examining the effects of exemestane on mammographic breast density, bone density, markers of bone metabolism and serum lipid levels in postmenopausal women. *Breast Cancer Research and Treatment* Vol.126, No.2, (Apr 2011), pp.453-61, Print ISSN 0167-6806, Online ISSN 1573-7217
- Clemons, M; Goss, P. Estrogen and the risk of breast cancer. *New England Journal of Medicine* Vol.344, No.4, (Jan 2001), pp.276-285, Print ISSN 0028-4793, Online ISSN 1533-4406
- Cohen, MEL. Effect of hormone replacement therapy on cancer detection by mammography. *The Lancet* Vol.349, No.9065, (May 1997) p1624
- Cummings, SR; Eastell, R; Ensrud, K; Reid, DM; Vukicevic, S; LaCroix, A; Sriram, U; Thompson, S; Thompson, JR; Delmas, PD. The effects of lasofoxifene on fractures and breast cancer: 3-year results from the PEARL Trial. *Journal of Bone and Mineral Research* Vol.23, No Suppl S1, pp.81, (Aug 2008), Abstract 1288, Print ISSN 0884-0431, Online ISSN 1523-4681
- Cummings, SR; Ettinger, B; Delmas, PD; Kenemans, P; Stathopoulos, V; et al. LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *The New*

- England Journal of Medicine* Vol.359, No.7, (Aug 2008), pp.697-708, Print ISSN 0028-4793, Online ISSN 1533-4406
- Cuzick, J; Warwick, J; Pinney, E; Warren, RM; Duffy, SW. Tamoxifen and breast density in women at increased risk of breast cancer. *Journal of the National Cancer Institute* Vol.96, No.8, (Apr 2004), pp.621-8, Print ISSN 1052-6773, Online ISSN 1745-6614
- Dinger, J; Bardenheuer, K; Minh, TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception* Vol.83, No.3, (Mar 2011), pp.211-7, Print ISSN 0010-7824, Online ISSN 1879-0518, Epub 2011 Jan 7
- Fabian, CJ; Kimler, BF. Selective estrogen-receptor modulators for primary prevention of breast cancer. *Journal of Clinical Oncology* Vol.23, No.8, (Mar 2005), pp.1644-55, Print ISSN 0732-183X, Online ISSN 1527-7755
- Fabian, CJ; Kimler, BF. Biomarkers as indicators of cancer risk reduction following dietary manipulation. Mammographic density: use in risk assessment and as a biomarker in prevention trials. *The Journal of Nutrition* 2006;136:S2705–2708. Available from <http://jn.nutrition.org/content/136/10/2705S.full.pdf>
- Fabian, CJ; Kimler, BF; Zalles, CM; Khan, QJ; Mayo, MS; Phillips, TA; Simonsen, M; Metheny, T; Petroff, BK. Reduction in proliferation with six months of letrozole in women on hormone replacement therapy. *Breast Cancer Research and Treatment* Vol.106, No.1, (Nov 2007), pp.75-84, Print ISSN 0167-6806, Online ISSN 1573-7217
- Fisher, B; Costantino, JP; Wickerham, DL; Redmond, CK; Kavanah, M; Cronin, WM; Vogel, V; Robidoux, A; Dimitrov, N; Atkins, J; Daly, M; Wieand, S; Tan-Chiu, E; Ford, L; Wolmark, N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* Vol.90, No.18, (Sep 1998), pp.1371-88, Print ISSN 1052-6773, Online ISSN 1745-6614
- Gennari, L; Merlotti, D; De Paola, V; Nuti, R. Lasofoxifene: the evidence of its therapeutic value in osteoporosis. *Core Evidence* Vol.4, (Jun 2010), pp.113-29, Print ISSN 1555-1741, Online ISSN 1555-175X
- Ghosh, K; Vachon, CM. Mammographic breast density, endocrine therapies, and breast cancer risk. *Menopausal Medicine* Vol.18, No.1, (Feb 2010), pp.34-9
- Gram, IT; Funkhouser, E; Nordgård, L; Tabár, L; Ursin, G. Oral contraceptive use and mammographic patterns. *European Journal of Cancer Prevention* Vol.11, No.3, (Jun 2002), pp.265-270, Print ISSN 0959-8278, Online ISSN 1473-5709
- Greendale, GA; Reboussin, BA; Sie, A; et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Annals of Internal Medicine* Vol.130, No.4, (Feb 1999), pp.262-9, Print ISSN 0003-4819, Online ISSN 1539-3704
- Greendale, GA; Reboussin, BA; Slone, S; Wasilauskas, C; Pike, MC; Ursin, G. Postmenopausal hormone therapy and change in mammographic density. *Journal of the National Cancer Institute* Vol.95, No.1, (Jan 2003), pp.30-37, Print ISSN 1052-6773, Online ISSN 1745-6614
- Harvey, JA; Pinkerton, JV; Herman, CR. Short-term cessation of hormone replacement therapy and improvement of mammographic specificity. *Journal of the National Cancer Institute* Vol.89, No.21, (Nov 1997), pp.1623-5, Print ISSN 1052-6773, Online ISSN 1745-6614

- Harvey, J; Scheurer, C; Kawakami, FT; Quebe-Fehling, E; de Palacios, PI; Ragavan, VV. Hormone replacement therapy and breast density changes. *Climacteric* Vol.8, No.2, (Jun 2005), pp. 185-92, Print ISSN 1369-7137, Online ISSN 1473-0804
- Harvey, J; Holm, M; Ranganath, R; Guse, PA; Trott, EA; Helzner, E. The effects of bazedoxifene on mammographic breast density in postmenopausal women with osteoporosis. *Menopause* Vol.16, No.6, (Nov-Dec 2009), pp.1193-6, Print ISSN 1072-3714, Online ISSN 1530-0374
- Howell, A; Howell, SJ; Clarke, R; et al. Where do selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) now fit into breast cancer treatment algorithms? *The Journal of Steroid Biochemistry and Molecular Biology* Vol.79, No.1-5, (Dec 2001), pp.227-37, Print ISSN 0960-0760, Online ISSN 1879-1220
- Huang, KE; Baber, R; Asia Pacific Tibolone Consensus Group. Updated clinical recommendations for the use of tibolone in Asian women. *Climacteric* Vol.13, No.4, (Aug 2010), pp.317-27, Print ISSN 1369-7137, Online ISSN 1473-0804
- Hunter, DJ; Colditz, GA; Hankinson, SE; Malspeis, S; Spiegelman, D; Chen, W; Stampfer, MJ; Willett, WC. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiology, Biomarkers & Prevention* Vol.19, No.10, (Oct 2010), pp. 2496-502, Print ISSN 1055-9965, Online ISSN 1538-7755
- Jungheim, ES; Colditz, GA. Short-term use of unopposed estrogen: A balance of inferred risks and benefits. *JAMA* Vol.305, No.13, (Apr 2011), pp.1354-5, Print ISSN 0098-7484, Online ISSN 1538-3598
- Katzenellenbogen, JA; O'Malley, BW; Katzenellenbogen, BS. Tripartite steroid hormone receptor pharmacology: Interaction with multiple effector sites as a basis for the cell- and promoter-specific action of these hormones. *Molecular Endocrinology* Vol.10, No.2, (Feb 1996), pp.119-31, Print ISSN 0888-8809, Online ISSN 1944-9917
- Kaunitz, AM. Lengthened WHI Follow-up: Postmenopausal Estrogen Therapy. *Journal Watch Women's Health*, (Apr 2011). Print ISSN 1521-4710
- Kenemans, P; Bundred, NJ; Foidart, JM; et al. LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomized, non-inferiority trial. *The Lancet Oncology* Vol.10, No.2, (Feb 2009), pp.135-46, Print ISSN 1470-2045, Online ISSN 1474-5488
- LaCroix, AZ; Chlebowski, RT; Manson, JE; Aragaki, AK; Johnson, KC; Martin, L; Margolis, KL; Stefanick, ML; Brzyski, R; Curb, JD; Howard, BV; Lewis, CE; Wactawski-Wende, J; WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. *JAMA* Vol.305, No.13, (Apr 2011), pp.1305-14, Print ISSN 0098-7484, Online ISSN 1538-3598
- Laya, MB; Larson, EB; Taplin, SH; et al. Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. *Journal of the National Cancer Institute* Vol.88, No.10, (1996), pp.643-9, Print ISSN 1052-6773, Online ISSN 1745-6614
- Litherland, JC; Stallard, S; Hole, D; et al. The effect of hormone replacement therapy on the sensitivity of screening mammograms. *Clinical Radiology* Vol.54, No.5, (May 1999), pp. 285-288
- Lundström, E; Wilczek, B; von Palffy, Z; Söderqvist, G; von Schoultz, B. Mammographic breast density during hormone replacement therapy: Differences according to

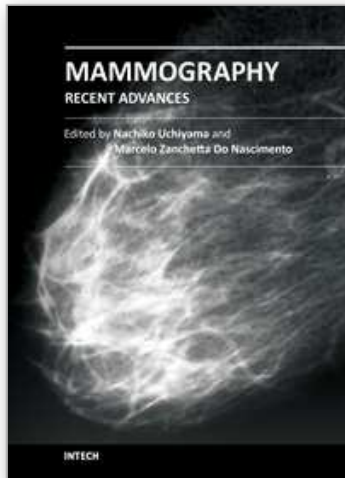
- treatment. *American Journal of Obstetrics & Gynecology* Vol.181, No.2, (Aug 1999), pp. 348-52, Print ISSN 0002-9378, Online ISSN 1097-6868
- Lundström, E; Christow, A; Kersemaekers, W; Svane, G; Azavedo, E; Söderqvist, G; Mol- Arts, M; Barkfeldt, J; von Schoultz, B. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. *American Journal of Obstetrics & Gynecology* Vol.186, No.4, (Apr 2002), pp.717-22, Print ISSN 0002-9378, Online ISSN 1097-6868
- Lundström, E; Söderqvist, G; Svane, G; Azavedo, E; Olovsson, M; Skoog, L; von Schoultz, E; von Schoultz, B. Digitized assessment of mammographic breast density in patients who received low-dose intrauterine levonorgestrel in continuous combination with oral estradiol valerate: a pilot study. *Fertility and Sterility* Vol.85, No.4, (Apr 2006), pp.989-95, Print ISSN 0010-7824, Online ISSN 1556-5653
- Malik, S; Prakash, V. Phytoestrogen and herbs. *Obstetrics Gynaecology Today* Vol.9, No.11, (2004), pp.733-40
- Maskarinec, G; Takata, Y; Franke, AA; Williams, AE; Murphy, SP. A 2-Year Soy Intervention in Premenopausal Women Does Not Change Mammographic Densities. *The Journal of Nutrition* Vol.134, No.11, (Nov 2004), pp.3089-94, Print ISSN 0022-3166, Online ISSN 1541-6100
- McTiernan, A; Martin, CF; Peck, JD; Aragaki, AK; Chlebowski, RT; Pisano, ED; Wang, CY; Brunner, RL; Johnson, KC; Manson, JE; et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: women's health initiative randomized trial. *Journal of the National Cancer Institute* Vol.97, No.18, (Sept 2005), pp.1366-1376, Print ISSN 1052-6773, Online ISSN 1745-6614
- Moore, RA. Livial: a review of clinical studies. *British Journal of Obstetrics and Gynaecology* Vol.106, Suppl No.19, (Mar 1997), pp.1-21, Print ISSN 0306-5456
- Mousa, NA; Crystal, P; Wolfman, WL; Bedaiwy, MA; Casper, RF. Aromatase inhibitors and mammographic breast density in postmenopausal women receiving hormone therapy. *Menopause* Vol.15, No.5, (Jun 2009), pp.875-84, Print ISSN 1072-3714, Online ISSN 1530-0374
- Opatrny, L; Dell'Aniello, S; Assouline, S; Suissa, S. Hormone replacement therapy use and variations in the risk of breast cancer. *British Journal of Obstetrics and Gynaecology* Vol.115, No.2, (Jan 2008), pp.169-75, Print ISSN 0306-5456
- Persson, I; Thurfjell, E; Holberg, L. Effect of estrogen and estrogen-progestin replacement regimens on mammographic breast parenchymal density. *Journal of Clinical Oncology* Vol.15, No.10, (Oct 1997), pp.3201-7, Print ISSN 0732-183X, Online ISSN 1527-7755
- Rosenberg, RD; Hunt, WC; Williamson, MR; et al. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183 134 screening mammograms in Albuquerque, New Mexico. *Radiology* Vol.209, No.2, (1998), pp.511-18, Print ISSN 0033-8419, Online ISSN 1527-1315
- Russu, M; Nastasia, S; Mubarak, N; Marin, JA; Hudita, D. Two years of lipid profile monitoring on transdermal estrogens and vaginal micronised progesterone compared to oral route of hormone therapy in healthy postmenopausal women. *Climacteric* Vol.11 No.2, (2008), Abstract Book, pp.232, Print ISSN 1369-7137, Online ISSN 1473-0804

- Sala, E; Warren, R; McCann, J; Duffy, S; Luben, R; Day, N. High risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case-control study. *International Journal of Epidemiology* Vol.29, No.4, (Aug 2000), pp.629-636, Print ISSN 0300-5771, Online ISSN 1464-3685
- Slanetz, PJ; Grandpre, LE; Yeh, ED; Kopans, DB; Mendel, JB. Effect of tamoxifen on breast tissue density in premenopausal breast cancer. *The Breast Journal* Vol.10, No.1, (Jan-Feb 2004), pp.27-32, Print ISSN 1075-122X, Online ISSN 1524-4741
- Son, HJ; Oh, KK. Significance of follow-up mammography in estimating the effect of tamoxifen in breast cancer patients who have undergone surgery. *American Journal of Roentgenology* Vol.173, No.4, (Oct 1999), pp.905-9, Print ISSN 0361-803X, Online ISSN 1546-3141
- Spicer, DV; Ursin, G; Parisky, YR; Pearce, JG; Shoupe, D; Pike, A; Pike, MC. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. *Journal of the National Cancer Institute* Vol.86, No.6, (Mar 1994), pp.431-436, Print ISSN 1052-6773, Online ISSN 1745-6614
- Thurfjell, E; Holmberg, L; Persson, I. Screening mammography: sensitivity and specificity in relation to hormone replacement therapy. *Radiology* Vol.203, No.2, (May 1997), pp.339-41, Print ISSN 0033-8419, Online ISSN 1527-1315
- Ursin, G; Pike, MC; Spicer, DV; Porrath, SA; Reitherman, RW. Can mammographic densities predict effects of tamoxifen on the breast? *Journal of the National Cancer Institute* Vol.88, No.2, (Jan 1996), pp.128-9, Print ISSN 1052-6773, Online ISSN 1745-6614
- Vachon, CM; Ingle, JN; Suman, VJ; Scott, CG; Gottardt, H; Olson, JE; Goss, PE. Pilot study of the impact of letrozole vs. placebo on breast density in women completing 5 years of tamoxifen. *Breast* Vol.16, No.2, (Apr 2007), pp.204-10, Print ISSN 0960-9776, Online ISSN 1532-3080
- Vogel, VG; Costantino, JP; Wickerham, DL; Cronin, WM; Cecchini, RS; Atkins, JN; Bevers, TB; Fehrenbacher, L; Pajon, ER Jr; Wade, JL 3rd; Robidoux, A; Margolese, RG; James, J; Lippman, SM; Runowicz, CD; Ganz, PA; Reis, SE; McCaskill-Stevens, W; Ford, LG; Jordan, VC; Wolmark, N. National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of Tamoxifen vs Raloxifene on the Risk of Developing Invasive Breast Cancer and Other Disease Outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA* Vol.295, No.23, (Jun 2006), pp.2727-41, Print ISSN 0098-7484, Online ISSN 1538-3598
- Warren, R; Lakhani, SR. Can the stroma provide the clue to the cellular basis for mammographic density? *Breast Cancer Research* Vol.5No.5, (Jul 2003), pp.225-7.
- Weitzel, JN; Buys, S; Sherman, WH; Daniels, AM; Ursin, G; Daniels, JR; MacDonald, DJ; Blazer, KR; Pike, MC; Spicer, DV. Reduced mammographic density with use of a gonadotropin-releasing hormone agonist-based chemoprevention regimen in BRCA 1 carriers. *Clinical Cancer Research* Vol.13, No.1-2, (Jan 2007), pp.654-8, Print ISSN 1078-0432
- White, E; Velentgas, P; Mandelson, MT; Lehman, CD; Elmore, JG; Porter, P; Yasui, Y; Taplin, SH. Variation in Mammographic Breast Density by Time in Menstrual Cycle Among Women Aged 40-49 Years. *Journal of the National Cancer Institute* Vol.90, No.12, (Jun 1998), pp.906-10, Print ISSN 1052-6773, Online ISSN 1745-6614
- Wolfe, JN. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* Vol.37, No.5, (May 1976), pp.2486-92

Wu, AH; Ursin, G; Koh, WP; Wang, R; Yuan, JM; Khoo, KS; Yu, MC. Green tea, soy, and mammographic density in Singapore Chinese women. *Cancer Epidemiology, Biomarkers & Prevention* Vol.134, No.11, (Nov 2008), pp.3358-65, Print ISSN 1055-9965, Online ISSN 1538-7755

IntechOpen

IntechOpen



Mammography - Recent Advances

Edited by Dr. Nachiko Uchiyama

ISBN 978-953-51-0285-4

Hard cover, 418 pages

Publisher InTech

Published online 16, March, 2012

Published in print edition March, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Şerban Nastasia (2012). Mammographic Density Under Hormonal and Hormone-Like Treatments, Mammography - Recent Advances, Dr. Nachiko Uchiyama (Ed.), ISBN: 978-953-51-0285-4, InTech, Available from: <http://www.intechopen.com/books/mammography-recent-advances/mammographic-density-under-hormonal-and-hormone-like-treatments>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen