Breast density changes associated with hormone replacement therapy in postmenopausal women. Effects on the specificity and sensitivity of mammographic screening

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Summary

Postmenopausal HRT use is associated with an increase of mammographic density and reduction of sensitivity and specificity of mammography results and an increase of false-positive and false-negative outcomes. The increased density does not allow a good evaluation of the exam.

Mammographic density is an independent risk factor for breast cancer, but the link between changes in breast density and difference in breast cancer risk, remain uncertain.

On the other hand, today specific guidelines and protocols to optimize the screening of neoplastic breast pathology in HRT users do not exist and it is unknown if short-term suspension of therapy improves mammographic sensitivity.

More information is required to define this important risk factor.

Key words: HRT; Mammographic density; Breast cancer detection.

Breast anatomy and hormonal phases

It is known that an increase in mammographic density on X-ray is the consequence of a relative increase in the amount of epithelial tissue ("mammographically dense" as connective tissue), in comparison to that of hypodense adipose tissue [1-5]. Such an increase is linked to the mitogenic effect of progesterone on stromal, ductul and glandular tissues, mediated by specific receptors and prepared by the estrogens of the same receptors that induce the synthesis [6].

It is not by chance that raloxifene, whose activity on selective modification of the receptor is known to be estrogenic, aims to reduce mammary density; the same effect is noted with tibolone, which has both an action of blockage on progestin receptors and androgenic properties of direct inhibition on mammary epithelium [7-9].

During the normal menstrual cycle mammary tissue undergoes regressive histological modifications during the follicular phase and proliferative histological modifications in the luteal phase when it is assisted by activation of the mitotic process, with volumetric variations of the lobule and increase of the acini, all phenomenons which reach the largest expression in the premenstrual phase. Potten *et al.* [10] have, in fact, observed that in normal menstruating women proliferation of the mammary epithelium achieves its peak on the 21st day and this would inversely be associated with the age of the woman. According to Anderson [11], however, apoptosis would reach its highest peak during the late luteal phase. On the other hand Malberger *et al.* [12], carrying out biopsies on mammary tissue in the pre and postovulatory phase, have found that the nuclear characteristics of the cells sampled during the luteal phase (wider, less compact and with more prominent nucleuses) do not differ from those of the preovulatory phase.

More recently, Olsson *et al.* [13], examining the mammary epithelium of 58 women who had undergone reductive mammoplasty, underlined, during the luteal phase, a significantly greater proliferative index in comparison to that of the follicular phase.

Soderqvist *et al.* [14], using the monoclonal antibody Ki-67/MIB-1 as a proliferative marker in bioptic samples withdrawn twice in the same menstrual cycle from 25 women, identified that the middle percentage of positive MIB-1 cells in the luteal phase is double that observed in the follicular phase.

Gompel *et al.* [15] have observed that in the expression of transmembrane receptors for tyrosine, as for epidermoidal growth factor and for c-erb-2, specifics of proliferation, are greater in the luteal phase.

Dabrosin *et al.* [16] have shown that the intra-tissue levels of ornithine, an essential amino acid for growth and cellular differentiation, decrease in the late menstrual cycle, with a larger expression that coincides with the luteal peak of proliferation and apoptosis. It appears, therefore, to be clear from the different studies, that the proliferative activity of the mammary gland is highest in the luteal phase. This, however, would not be enough to explain the 20% of volume increase in mammary tissue [17], as the increase in the glandular component can justify only an increase of

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10% of breast volume. The other changes which happen are linked to water retention and an increase in vascularization [11, 18].

Anderson [11] in fact suggests that hormonal changes can increase the acid mucopolisaccharides in the mammary matrix in such a way as to increase the content of water in the same mammary tissues. In postmenopausal women the breast is characterized by a smaller amount of glandular tissue and by a prevalence of adipose tissue which appears radiologically less dense in comparison to that of young women.

Annastassiades *et al.* [19] have examined the composition of mammary samples from 112 women of different age ranges: they found that in the 31 to 40 year age group, 54% of the breast samples were classified as being mainly composed of "solid tissue" (mammary parenchyma and fibrous stroma), while none of the specimens was particularly rich in adipose tissue. Among the samples from women over 70 years old, 46% were defined as consisting of "adipose tissue" and only 8% showed a prevalence of "solid tissue".

Brisson *et al.* [20], who have analyzed the data of 55,000 women included in the Breast Cancer Detection Demonstration Project, found that menopause was associated with a reduction in mammary density; for example, 23% of premenopausal women 50-54 years have "fat" breasts compared to 30% of menopausal women in the same age group. Spicer *et al.* [21] reported a reduction of 9% of mammary density in the period from pre- to postmenopause.

It is evident, therefore, that the breast in postmenopause loses density and volume, a process which can, to various degrees, be modified by hormonal replacement therapy (HRT); moreover mammographic density is correlated with age, height, body weight, age of first-term pregnancy, parity, phase of the menstrual cycle, menopausal status and sex hormone levels [17].

HRT and breast density-related RX

Increased density of mammary tissue constitutes an independent risk factor for breast cancer [2, 3, 22-25]. Many studies have found a relationship between HRT use in postmenopausal women and an increase in mammary density [2, 5, 9, 23, 25, 26, 34] with consequently more difficult individualization of small masses [6] at mammography and a reduction of sensitivity and specificity of this exam in the screening and prevention of breast cancer [4] (Table 1).

Table 1. — *Variation of the sensitivity and specificity of the mammography correlated to mammary density and hormonal replacement therapy in menopause* (McNagny S.E. [4], 1999).

	High-mammary density	Low-mammary density	HRT user	Non HRT user
Sensibility (%)	62.9	87.0	73.3	76.0
Specificity (%)	89.1	96.9	91.7	92.6

In fact Carney *et al.* [27], in an investigation considered HRT use and age of the patients as the variable of risk for breast cancer; they observed that HRT reduces the sensitivity of mammography by 2.7% (with maximum of 24.1% in extremely dense breast tissue) and the specificity by 0.9% (with values that reach 6.8% comparing non dense breasts to extremely dense breasts). The study confirms that mammographic density and age are important risk factors which influence the sensitivity and the specificity of mammographic screening.

Kavanagh *et al.* [30] in a study of 26,600 women on hormone replacement therapy, compared with 71,215 women who were not undergoing any hormonal therapy, showed a reduction of about 10% in the sensitivity of mammography at one-year follow-up and 15% after two years of therapy.

According to Kolb *et al.* [25], a report conducted on 27,825 mammographic screening exams found 246 cases of breast cancer; the sensitivity of the screening decreased from 77.6% to 48% for high-density breast tissue.

Laya *et al.* [35], reported a decrease of specificity of mammography from 86% in women who had never used HRT or who were new users to 82% for women on HRT with an increase in false-positive results of 4%; however, sensitivity was 94% in the first group and fell to 69% in the second group, with a consequent increase of 25% in false-negative results.

HRT and breast cancer

On the other hand, the use of HRT is associated with an increased risk of breast cancer [4, 31, 36, 37]. A study [36] conducted on 828,923 postmenopausal women who had not undergone mammographic screening reported a relative risk (RR) of breast cancer of 1.3 for those that used only estrogens versus those who did not use hormonal replacement therapy (values of 0.8, 1.25, 1.32 and 1.37, respectively, for use up to one year, 1-4 years, 5-9 years, and > 10 years.), and of 2.0 for those who used estroprogestin combined therapy (values of 1.45, 1.74, 2.17 and 2.31, respectively, for use up to one year, 1-4 years, 5-9 years, and > 10 years.).

In a large review, McNagny [4] found an increase of 30% in the risk of breast cancer in women who used HRT for more than five years.

Moreover the USPSTF (U.S. Preventive Services Task Force) [37] reported an increase in the incidence of breast cancer in HRT users after 6.8 years of follow-up (RR = 1.27 vs RR = 1 of non-user women); particularly the relative risk in users was 1.21 and 1.40, and 1.23 and 1.35 after five years of treatment, concluding that a correlation exists between hormonal therapy and breast cancer, but there was no increase in mortality.

RX, dose and HRT-related type

Table 2 shows data of the main epidemiological investigations on the relationships between hormonal therapies in peri- and postmenopause and mammary density; a large variability exists in the incidence of mammary density increase. Even if the data is hardly correlated (because of different times of follow-up, age groups, type of HRT and dose), it is clear that mammary density changes depend on the type of replacement therapy used (estrogens only, estroprogestins, tibolone), on modalities of treatment (cyclical or continuous), and on different individual responses to exogenous hormonal stimuli [23, 29, 31, 43, 41]. It should be added that there are further parameters (age, weight, nulliparity, advanced age at first pregnancy, increase of the plasmatic concentrations of IGF-I), as well as of a possible genetic predisposition [6, 24], not considered by other authors.

As for the type of replacement therapy and its effects on the mammary gland, a lot of investigations are difficult to interpret because they do not report the given dose.

Lundstrom *et al.* [31], in a random study of 166 postmenopausal women between 50 and 70 years old, found a significant increase in mammary density six months after beginning therapy in 46% of the women treated with estradiol/norethisterone acetate unlike women treated with tibolone and the untreated control group. In another study [9] of 175 postmenopausal women, the same authors reported that the density increase in the mammographic screening is more common and higher in women who received continuous HRT versus women in cyclical treatment or versus estrogens only: in the first group 52% of the patients had already shown an increase in density at the first follow-up (it is not specified how long after the beginning of the treatment), while the values for the women in cyclical treatment with estroprogestins or with only estrogens were 13% and 18%, respectively. In the same study, a subgroup of 19 women treated with combined and continuous therapy had the first mammography six months after beginning the treatment; an increase in mammary density was found in 47% of the cases according to the data for the whole group. The same results were found in 34% of the women on estrogen therapy only and in 18% of those treated with cyclical estroprogestin therapy.

Ozdemir *et al.* [32] analyzed 118 postmenopausal women and mammary tissue response to the different types of HRT, and found an increase in mammary density in 34% of cases: particularly, the women in continuous treatment with estroprogestins showed greater mammary density (43-46%) versus the women using tibolone (28%) or only estrogens (18%).

In a study of 216 women treated with HRT, Sendog *et al.* [42] reported an increase in mammary density in 34.1% of the cases on continuous estrogenic therapy and combined with norethisterone acetate, in 23.5% of the cases on cyclical treatment with medroxyprogesterone acetate (MEPA), in 3.9% of the cases on treatment with estrogens only and in no case under tibolone, respectively.

For Colacurci *et al.* [7], an increase in mammary density was found in 33% of the women treated with estroprogestins versus 11% of women on therapy with tibolone.

In an investigation conducted on 202 women, Vochon *et al.* [41] studied the qualitative and quantitative changes of mammary density before and during hormonal replacement therapy, finding an increase of 13.7% in mammary density in women presently undergoing treatment compared to 2.8% in the untreated group. The correlation between the type of HRT and mammary response to HRT has shown that the increase in mammary density is 29.1% in estrogen-only users, 64.5% for combined estroprogestins, and 2.9% for only progestins.

RX, HRT and age-related

Nyström *et al.* [39] analyzed the effects of mammographic screening on mortality for breast cancer in a total of 247,010 women; age was the only variable considered. Mammographic screening for the prevention of neoplastic mam-

Table 2. — *Comparative intercurrence among hormonal replacement therapies in menopause and percentual increase of mammary density.*

Reference	No. of cases	No. of controls	Age	No. of mammary glands	E.P. cy	E.P.c	E_2	Ti	Follow-up	E.P. cy ↑%	E.P.c ↑%	E_2 ↑%	Ti ↑%	C ↑%
Lundstrom *et al.* [31]	154	55	50-70	308	48			51	6 months		46		2	0
Gail *et al.* [2]	307		55-62	917					12 months	23.5	19,4	3.5		0
									24 months	23.5	22.7	8.3		0
Sendag *et al.* [42]	216		46-60	958	44	61	76	35	20 ± 8 months	23.5	34	3.9	0	
Ozdemir *et al.* [32]	88	30	42-56		21	24	22	21	16.92 ± 7.65 months	43	46	18	28	
Vachon *et al.* [41]	172	172	66,4						24 months		64.5	29.1		2.9
Lundstrom *et al.* [9]	175		40-74	914	75	50	50		6 months	47		13	18	
									24 months	52		13	13	
Colacurci *et al.* [7]	32	12	48-58		15			17	12 months	33			11	0

E.P.cy = cyclic estroprogestins; E.P.c = continuous estroprogestins; E_2 = estradiol; Ti = titolone; C = controls with placebo.

marian pathology was more important in women aged between 55 and 69 years versus the group between 50 and 54 years. If age and HRT use are considered as risk factors, the increase in HRT-related mammary density was lower below 55 years [40], even if influenced by the presence of other risk factors such as elevated body mass index (BMI), late first-term pregnancy [40, 41] and increased plasmatic concentrations of IGF-I [24].

In a cohort study on 5,212 women in spontaneous menopause over 40 years of age, Rutter *et al.* [33] indicate that hormonal replacement therapy increased mammary density but reversed with interruption of the therapy. In this study 92.4% of the women on HRT used estroprogestinic therapy. At the mammographic follow-up (on average between 11 and 25 months) an increase in mammary density was found in 28.4% of women that had used replacement therapy after performing a preliminary mammography, while in women examined during treatment, density increase was found in 10.8% of those on cyclic therapy and in 14.0% of those on continuous therapy. The relative risk of increased mammary density at mammographic screening in new users under 60 years was 1.77, but it increased to 3.02 among the 60 to 69-year-olds and up to 4.34 for those over 70 years. These values for women on treatment with periodic suspensions are 0.8; 1.6 and 0.39, respectively. In continuous HRT users the RR of increase in mammary density was 1.09 for under 60-year-olds, to 1.41 in the 60 to 69-year-olds and to 1.54 in women over 70 years. On the other hand, when therapy was suspended between the two mammographic exams, there was a significant reduction in mammary density in the follow-up, with an RR of 1.49, 2.79 and 1.73 for the age groups < 60 years, 60-69 years and > 70 years, respectively. Another significant relationship was found between BMI and increased mammary density in a group of women where they resorted to periodic suspensions of the therapy. The RR of increased density was significantly greater in cases of a BMI > 25 kg/m^{2}s (1.52) in comparison to a BMI < 25 kg/m2s (0.6), a situation that was not observed either in the group of the first users, in which the contrary appears instead (3.26 and 249, respectively), or in the group of those that had not undertaken any suspension (1.26 and 1.46, respectively).

Greendale *et al.* [2] on 307 postmenopausal women, aged between 45 and 64 years, found an increase of mammary density in 8% of the women treated with estrogens only and between 19-24% of those on estroprogestinic treatment. This study showed that the increased mammary density occurred in a short time period: after 12 months an increase of density was already observed in 3.5% of patients treated with conjugated equine estrogens (CEE), in 23.5% of those treated with CEE + cyclical MEPA, in 19.4% of those treated with continuous CEE + MEPA and in 16.4% of women treated with CEE + micronized progesterone (MP). After 24 months there was a further increase in mammary density of 4.8%, 0%, 3.3% and 2.3%, respectively, with no other increases in the controls after 36 months from the beginning of the treatment. The odds ratio (OR) for the increased mammary density to 12 months is, therefore, equal to 13.1 for CEE + cyclical MEPA versus CEE, 9.0 for continuous CEE + MEPA versus CEE and of 7.2 for CEE + MP versus EEC which means that the users of estrogens associated with progesterone or progestins have a 7-13 fold greater chance of developing higher mammary density versus users of EEC only, independently of the progestin regimen adopted.

RX, HRT and length of related treatment

Sala *et al.* [5] did not report the type of replacement therapy adopted in 203 studied cases but indicated a direct correlation among the mammographic parenchymal pattern of risk, according to the classification of Wolfe [44] (Table 3) and the use of HRT: a higher risk pattern was also found in women that began the replacement therapy even if spontaneous menstrual cycles were present, in comparison to those who began the therapy after menopause. If they used HRT for more than five years, the probability of developing a high-risk pattern was 10-fold greater than for the women in the first group compared to those in the second group. The RR of developing a pattern of elevated risk, considered equal to 1.0 for non users, increases to 1.30 for women on replacement therapy, to 1.04 at the suspension of therapy. More specifically it was 1.47 for women on therapy for under one year, 1.20 when therapy was extended between one and four years and 1.42 after five years of therapy.

Speroff [40] reported that the continuous administration of estroprogestins is correlated with greater effects on mammary density versus sequential administration. Increased density was seen from the first month of treatment reaching a plateau in continuous users; there was a decrement with the cessation of hormonal replacement therapy but in no specified times.

Table 3. — *Wolfe classification of mammographic parenchymal patterns* (Wolfe, [44] 1997).

Wolfe's pattern	Description	Risk
N1	Parenchyma composed primarily of fat with smallest amounts of "dysplasia". No ducts visible.	Low
P1	Parenchyma consisting of chiefly fat with prominent ducts in the anterior portion occupying up to 25% of the volume of the breast. There may be a thin band of ducts extending into a quadrant.	Low
P2	Severe involvement with prominent duct pattern occupying more than 25% of the volume of breast.	High
DY	Severe involvement with "dysplasia" - often describes an underlying prominent duct pattern.	High

Relation time/last used HRT

To minimize the risks due to increased mammary density and to make every mammographic investigation more accurate for prevention and early detection of breast cancer, Harvey *et al.* [43] suggest suspending hormonal replacement therapy in postmenopause at least two weeks before performing a mammography, which would have to be integrated with an ultrasonographic exam where radiological suspicion appears. The restrictions of this work are that the investigation is retrospective, has not been performed in a double-blind study and is founded on a limited number of cases.

Baines and Dayan [17], in one of their editorials, concluded that, to improve the sensitivity and specificity of mammographic exams for women on hormonal replacement therapy, it is better to suspend all hormonal treatment by at least 10-30 days before the mammographic screening to avoid a false-positive outcome linked to the increased mammary density considering that, in their experience, such an increase has been found in 25% of HRT users.

Also Colacurci *et al.* [7, 18] recommend suspending HRT for at least 14 days before performing a control mammography. In their experience the increased mammary density found in 36.8% of women under treatment with estroprogestins and in 21% of those treated with estrogens only decreased to 5% and 5.5%, respectively, after 14 days of suspension.

More recently Evans [23], in an attempt to minimize the negative effects on mammographic screening of increases in mammary density due to replacement therapy, suggested short-term suspension of HRT (not quantified) and advise that the exams be performed in a double projection, mainly when combined estroprogesterone therapy was used.

Banks *et al.*, [45] analyzing the outcome of the "Million Women Study" enrolling 87,967 postmenopausal women invited to routine breast cancer screening, found that false-positive findings were significantly increased in current users of hormone replacement therapy (RR 1.64, 95% CI 1.50 to 1.80, $p < 0.0001$) and past users (1.21, 1.06 to 1.38, $p = 0.004$) versus never users. The relative risk of false-positive findings decreased significantly with increased time suspension (2 (df = 1) for trend = 14.0, $p < 0.0001$), and was still significantly raised among women who had stopped HRT in the past five years. No significant variations were found in the RR of false-positive findings between current users of estrogen only (1.62, 1.43 to 1.83) and combined estrogen and progestogen (1.80, 1.62 to 2.00) (2 (df = 1) for heterogeneity = 2.3, $p = 0.1$), nor were there significant differences in risk according to dose or types of hormone replacement therapy. Today, users of hormone replacement therapy have a significantly increased risk of having a biopsy compared with never users (RR 1.42, 1.14 to 1.78, and 0.94, 0.69 to 1.30, respectively (2 (df = 1) for heterogeneity = 6.5, $p = 0.01$)). The risk of a false-positive recall is significantly increased in current and recent users of hormone replacement therapy; this effect persists for several years after suspension and, in current users, is associated with an increased risk of having a biopsy performed.

Conclusions

This review, in accordance with other reports, concludes that for breast cancer screening in HRT women it is important to consider all risk factors: previous mammary pathologies, familiarity, parity, age, BMI, etc., and the type of HRT used, considering that natural estrogens, synthetic estrogens, estroprogestins, tibolone, etc., do not seem to have the same effect on mammary density. Despite the different indications and the numerous epidemiological studies that underline the negative aspects that increased mammary density has on the sensitivity and specificity of mammography in breast cancer detection, and despite the numerous studies that underline the increase of mammary density in relationship to use (above all if extended), of hormonal therapies in peri- and postmenopausal women, at the moment there are no specific guidelines or protocols to optimize the screening of neoplastic mammary pathology. In the "American Cancer Society Guidelines for Breast Cancer Screening" [46] published in 2003 it is affirmed that "Because there are many complex issues, unanswered questions, and research needs related to hormone replacement therapy and mammographic density, there is insufficient evidence at this time to make a specific recommendation regarding differential screening for older women who take hormone replacement therapy and/or who have radiographically dense breast".

It is important, therefore, to suspend hormonal therapy before a woman undertakes a mammography and further complementary investigations. One hypothesis to optimize the screening could be represented by performing investigations when, all therapy has been suspended and a stable and typical hormonal order for peri- and post-menopausal age restored. The problem related to the time of regression of mammary density induced by the different types of HRT used remain unresolved and surely is influenced by the atherogenicity of the individual response. Surely, however, conditions to uniform the results and elaborate specific guidelines should be created.

References

[1] ACOG committee opinion. Routine Cancer Screening. Number 247, December 2000. *Int. J. Gynaecol. Obstet.*, 2003, *82,* 241.

[2] Greendale G.A., Reboussin B.A., Sie A., Singh H.R., Olson L.K., Gatewood O. *et al.*: "For the Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Effects of estrogen and estrogen-progestin on mammographic parenchymal density". *Ann. Intern. Med.,* 1999, *130,* 262.

[3] Greendale G.A., Reboussin B.A., Slone S., Wasilauskas C., Pike M.C., Ursin G.: "Postmenopausal hormone therapy and change in mammographic density". *J. Natl. Cancer Inst.,* 2003, *95,* 30.

[4] McNagny S.E.: "Prescribing hormone replacement therapy for menopausal symptoms". *Ann. Intern. Med.,* 1999, *131,* 605.

[5] Sala E., Warren R., McCann J., Duffy S., Luben R., Day N.: "High-risk mammographic parenchimal patterns, hormone replacement therapy and other risk factors: a case control study". *Int. J. Epid.*, 2000, *29,* 629.

[6] Gayet A., Esteve J., Seradour B., Piana, L. Jacquemier J.: "Does hormone replacement therapy increase the frequency of breast atypical hyperplasia in postmenopausal women? Results from the Bouches du Rhone district screening campaign". *Eur. J. Cancer,* 2003, *39,* 1738.
[7] Colacurci N., Mele D., De Feanciscis P., Costa V., Fortunato N., De Seta L.: "Effects of tibolone on the breast". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1998, *80*, 235.
[8] Eral C.T., Elter K., Akaman C., Ersavasti G., Altug A., Seyisoglu H., Ertungealp E.: "Mammographic changes in women receiving tibolone therapy". *Fertil. Steril.*, 1998, *69*, 870-87546 - American Cancer Society Guidelines for Breast Cancer Screening: Update 2003. *CA Cancer J. Clin.,* 2003, *54*, 141.
[9] Lundström E., Wilczek B., von Palffy Z., Söderqvist G., von Schoultz B.: "Mammographic breast density during hormone replacement therapy: Differences according to treatment". *Am. J. Obstet. Gynecol.,* 1999, *181,* 348.
[10] Potten C.S., Watson R.J., Williams G.T., Tickle S., Roberts S.A., Harris M. *et al.*: "The effect of age and menstrual cycle upon proliferative activity of the normal human breast". *Br. J. Cancer,* 1988, *58*, 163.
[11] Anderson T.J.: "Mitotic activity in the breast". *J. Obstet. Gynaecol.,* 1984, *4,* S114.
[12] Malberger E., Gutterman E., Bartefeld E., Zajicek G.: "Cellular changes in the mammary gland epithelium during the menstrual cycle. A computer image analysis study". *Acta Cytol.,* 1987, *31,* 305.
[13] Olsson H., Jernstrom H., Alm P., Kreipe H., Ingvar C., Jonsson P.E. *et al.*: "Proliferation of the breast epithelium in relation to menstrual cycle phase, hormone use, and reproductuve factors". *Breast Cancer Res. Treat.,* 1996, *40,* 187.
[14] Soderqvist G., Isaksson E., van Schoultz B., Carlstrom K., Tani E., Skoog L.: "Proliferation of breast epithelial cells in healthy women during the menstrual cycle". *Am. J. Obstet. Gynecol.*, 1997, *176*, 123.
[15] Gompel A., Martin A., Simon P., Schoevaert D., Pilu-Bureau G., Hugol D. *et al.*: "Epidermal growth factor receptor and c-erb-2 expression in normal breast tissue during menstrual cycle". *Breast Cancer Res. Treat.,* 1996, *38*, 227.
[16] Dabrosin C., Hallstrom A., Ungerstedt U., Hammar M.: "Microdialysis of human breast tissue during the menstrual cycle". *Clin. Sci. (Colch)*, 1997, *92*, 493.
[17] Baines C.J., Dayan R.A., Tangled Web: "Factors likely to affect the efficacy of screening mammography". *J. Natl. Cancer Inst.,* 1999, *91,* 833.
[18] Colacurci N., Fornaro F., De Franciscis P., Mele D., Palermo M., del Vecchio W.: "Effect of a short-term suspension of hormone replacement therapy on mammographic density". *Fertil. Steril.,* 2001, *76,* 451.
[19] Anastassiades O.T., Spiliades C., Tsakraklides E., Gogas J.: "Amount and distribution of solid and fatty tissues in the female breast and their ralationship to carcinoma". *Pathol. Res. Pract.*, 1983, *176,* 200.
[20] Brisson J., Morrison A.S., Khalid N.: "Mammographic parenchymal features and breast cancer in the Breast Cancer Detection Demonstration Project (published erratum appears in *J. Natl. Cancer Inst.* 1989, *81,* 1513)". *J. Natl. Cancer Inst.,* 1988, *80,* 1534.
[21] Spicer D.V., Ursin G., Parisky Y.R., Pearce J.G., Shoupe D., Pike A. *et al.*: "Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk". *J. Natl Cancer Inst.,* 1994, *86,* 431.
[22] Chlebowski R.T., McTiernan A.: "Biological significance of interventions that change breast density". *J. Natl Cancer Inst.,* 2003, *95*, 4.
[23] Evans A.: "Hormone replacement therapy and mammographic screening". *Clin. Rad.*, 2002, *57,* 563.
[24] Haiman C.A., Hankinson S.E., De Vivo I., Guillemette C., Ishibe N., Hunter D.J., Byrne C.: "Polymorphisms in steroid hormone pathway genes and mammographic density". *Breast Cancer Res. Treat.,* 2003, *77,* 27.
[25] Kolb T.M., Lichy J., Newhouse J.H.: "Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations". *Radiology,* 2002, *225*, 165.
[26] Bulbul N.H., Ozden S., Dayicioglu V.: "Effects of hormone replacement therapy on mammographic findings". *Arch. Gynecol. Obstet.,* 2003, *268,* 5-8. Epub 2002 June 06.
[27] Carney P.A., Miglioretti D.L., Yankaskas B.C., Kerlikowske K., Rosenberg R., Rutter C.M. *et al.*: "Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography". *Ann. Intern. Med.,* 2003, *138*, 168.
[28] Carney P.A., Miglioretti D.L., Yankaskas B.C., Kerlikowske K., Rosenberg R., Rutter C.M. *et al.*: "Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography". *Ann. Intern. Med.,* 2003, *138,* 168.
[29] Dixon J.M.: "Hormone replacement therapy and the breast". *Br. Med. J.,* 2001, *323*, 1381.
[30] Kavanagh A.M., Mitchell H., Giles G.G.: "Hormone replacement therapy and accuracy of mammographic screening". *Lancet,* 2000, *355,* 270.
[31] Lundström E., Christow A., Kersemaekers W., Svane G., Azavedo E., Söderqvist G. *et al.*: "Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density". *Am. J. Obstet. Gynecol.*, 2002, *186,* 717.
[32] Ozdemir A., Konus O., Nas T., Erbas G., Cos S., Is S.: "Mammographic and ultrasonographic study of changes in the breast related to HRT". *Int. J. Gynaecol. Obstet.*, 1999, *67,* 23.
[33] Rutter C.M., Mandelson M.T., Laya M.B., Seger D.J., Taplin S.: "Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy". *JAMA,* 2001, *285,* 171.
[34] Slanetz P.J.: "Hormone replacement therapy and breast tissue density on mammography". *Menopause,* 2002, *9,* 82.
[35] Laya M.B., Larson E.B., Taplin S.H., White E.: "Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography". *J. Nat. Cancer Inst.,* 1996, *88*, 643.
[36] Million Women Study Collaborators: "Breast cancer and hormone-replacement therapy in the Million Women Study". *Lancet,* 2003, *362,* 419.
[37] U.S. Preventive Services Task Force: "Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale". *Ann. Intern. Med.,* 2002, *137*, 834.
[38] Egan R.L., Mosteller R.C.: "Breast cancer mammography patterns". *Cancer,* 1972, *40,* 2087.
[39] Nyström L., Andersson I., Bjurstam N., Frisell J., Nordenskjöld B., Rutqvist L.E.: "Long-term effects of mammography screening: updated overview of the Swedish randomised trials". *Lancet,* 2002, *359*, 909.
[40] Speroff L.: "The meaning of mammographic breast density in users of postmenopausal hormone therapy". *Maturitas,* 2002, *41,* 171.
[41] Vachon CM, Sellers TA, Vierkant RA, Fang-Fang Wu, Brandt KR. Case-Control Study of Increased Mammographic Breast Density Response to Hormone Replacement Therapy. Cancer Epidemiol *Biomarkers Prev.*, 2002, *11*, 1382.
[42] Sendag F., Cosan Terek M., Ozsener S., Oztekin K., Bilgin O., Bilgen I., Memis A.: "Mammographic density changes during different postmenopausal hormone replacement therapies". *Fertil. Steril.*, 2001, *76*, 445.
[43] Harvey J.A., Pinkerton J.V., Herman C.R.: "Short-term cessation of hormone replacement therapy and improvement of mammographic specificity". *J. Natl Cancer Inst.*, 1997, *89*, 1623.
[44] Wolfe J.N.: "Breast patterns as an index of risk for developing breast cancer". *Lancet*, 1997, *350*, 1047.
[45] Banks E., Reeves G., Beral V., Bull D., Crossley B., Simmonds M., Hilton E., Bailey S., Barret N., Briers P., English R., Jackson A., Kutt E., Lavelle J., Rockall L., Wallis M.G., Wilson M., Patnick J. : "Impact of use of hormone replacement therapy on false positive recall in the NHS breast screening programme: results from the million women study". *Br. Med. J.*, 2004, *328,* 1291.

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