

# Mammographic Density – a Risk Factor for Breast Cancer

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**Abstract:** The mammographic density belongs to risk factors for breast cancer. The increased density enhances the risk of interval breast cancers and it also increases the number of false negative as well as false positive results of the mammography. The increase in the mammographic density during the hormone replacement therapy is not identical with the enhanced mammographic density, which is a risk factor for the breast cancer. The mammographic density associated with the hormonal treatment recedes within 14 days after its withdrawal. The high mammographic density is not contraindication of the hormonal treatment, but it results in a preference of tibolone and estrogen replacement therapy over the estrogen-gestagen treatment.

### Introduction

Breast cancer is the second most frequent cause of the mortality of women for cancer diseases, next to lung carcinoma. In spite of this, its etiology has not yet been completely explained. Known risk factors can elucidate only certain cases of breast cancer and they are subjects of discussions.

Risk factors include the age, ethnicity, social-economic conditions, reproduction characteristics, hormonal therapy, life style (alcohol, obesity...), familial anamnesis of breast cancer, ionizing radiation, high bone density, personal history of benign breast diseases, presence of genetic factors with high (BRCA 1, BRCA 2, p53, PTEN, ATM, NBS1, LKB1) as well as low (genes of cytochrome P450 – CYP1A1, CYP2D6; genes of glutathione-S-transferase – GSTM1, GSTP1; genes of the DNA repair – XRCC1, XRCC3, XRCC4/XPF; genes coding cellular signalisation molecules – PR, ER, TNFalpha, hsp70) penetration and, last but not least, also the mammographic density [1].

### Assessment of the mammographic density

In studies, the mammographic density is expressed in percent, by using the BI-RADS (Breast Imaging Reporting and Data System) criteria (almost entirely fatty, scattered fibroglandular tissue, heterogeneously dense, extremely dense) [2] or the system by Wolfe (N1, P1, P2, DY). BI-RADS and Wolfe, similarly as a modification of Wolfe by Tabár (I.–V.), are considerably burdened by the interpersonal variability of the evaluation and thus also by a reduced statistical usefulness. In the evaluation of 987 mammograms by two roentgenologists, the Pearson correlation coefficient of 0.86 was achieved for the quantitative evaluation (software Cumulus and Madena), but only 0.51 was obtained for the evaluation by Wolfe and Tabár [3]. Digital mammography with automatic calculations of the density is considered as a perspective approach.

### Affecting of the mammographic density

The mammographic density is given as a ratio of the fibrous and epithelial (ductal and glandular) tissues to the adipose tissue. It has an important hereditary

component [4] and is affected by the endogenous estrogen production as well as exogenous noxae, age, body mass index, age at the first delivery [5]. No dependence on circulating levels of sexagens and prolactin [6] was demonstrated.

There is a different dependence in women in the senium; in women over 70 years of age, the mammographic density is considerably inversely associated with the body mass index and parity. Higher density is observed in non-smokers and women after iatrogenic menopause [7].

In climacteric medicine, there is an essential relationship between different types of the hormone replacement therapy (HT) and risk for the breast cancer and possibly also mammographic density. Based on current knowledge, estrogens are not able to induce carcinogenesis, but they are certainly promoters of the growth of existing breast cancer cells. Proapoptotic and anti-proliferation effects of certain progestins on the breast cell determined in vitro has not been demonstrated in any clinical trial. The main metabolic pathway of the effective estrogen synthesis in human cells is the conversion of non-active estron sulfate with sulfatase into estrone. It is more important than aromatase, which unidirectionally converts androgens to estrogens. The activity of sulfatase in the breast tissue is higher by a factor of 130 to 200 than that of aromatase. Tibolone exerts neither antiestrogen action nor inhibition of the aromatase activity, but it considerably inhibits the sulfatase activity. Tibolone also stimulates the activity of 17-hydroxysteroid dehydrogenase, which converts estradiol to estrone.

Due to different effects of different regimens of the estrogen-gestagen substitution on the mammographic density, it is of importance to remember the natural control of the mammary gland proliferation. The division of cells, i.e. the process making possible origination of mutations resulting in the carcinoma development, occurs in 1 to 10% of mammary gland cells in each menstruation cycle with subsequent controlled cell death through the apoptosis. The maximum apoptotic activity occurs within 2 to 3 days after the peak proliferation at the luteal stage. The apoptosis seems to be triggered by a decrease in the progesterone level [8].

### **The mammographic density and breast cancer**

In the study Breast Cancer Detection Demonstration Project [9] as well in the Canadian National Breast Screening Study (Table 1) [10] the risk for the breast cancer in women with the density over 75% was higher by a factor of five compared with those, whose density was under 5%. This fact was repeatedly demonstrated in studies of cases and controls (Table 2).

In a study of 15 254 women and in a case-control study of 208 carcinomas and 436 controls, Kerlikowske demonstrated that the relative risk (RR) for women with a high density is three times higher (2.7, CI 1.4–5.4) compared with women with a low density (in a classification using 6 grades) [11].

The mammographic density is an important independent risk factor in both premenopausal and postmenopausal women [12]. In premenopausal women, the

mammographic density is a risk factor together with the age, familial anamnesis and breast surgery, and in postmenopausal women the ethnicity, body mass index, age at the time of menopause, hormone treatment and false positive mammography are added [13].

The increased breast density enhances the risk of interval breast cancers [14] and increases the number of false negative [15] as well as false positive mammographic results [16]. As much as 70% of interval carcinomas are associated with a high mammographic density in women under 50 years of age [17].

The mammographic density is a more significant risk factor than the age at the first delivery, age at menarche or benign breast surgery. Higher risk is given only by personal history of breast cancer, lobular carcinoma in situ or atypical ductal hyperplasia or BRCA1 and BRCA 2 mutation [18].

A higher (over 50%) mammographic density is also a significant risk factor in the population of women carrying BRCA 1 and BRCA 2 mutations with OR 2.29 (1.23–4.26,  $p = 0.009$ ) [19].

**Table 1 – Canadian National Breast Screening Study**

Breast density (%)	Cases	Controls	Odds ratio
0	10	25	1.0
<10	29	61	1.2
10–24	65	73	2.2
25–49	94	97	2.4
50–74	90	67	3.4
75+	66	31	5.3

**Table 2 – Certain trials demonstrating the mammographic density as a risk for the breast cancer**

	Number of cases	RR
Boyd NF, Br J Cancer 1982, 45: 185–93	183	2.8–6.0
Brisson J, Am J Epidemiol 1982, 115: 428–37	408	3.8–5.4
Wolfe JN, Am J Roentgenol 1987, 148: 1087–92	160	4.3
Brisson J, Am J Epidemiol 1989, 130: 14–24	290	5.5
Saftlas AF, Cancer 1991, 67: 2833–8	260	4.3
Boyd NF, J Nat Cancer Inst 1995, 87: 670–5	354	4–6
Kato I, Cancer Causes Control 1995, 6: 431–8	197	3.6 premenop. 2.1 postmenop.
Byrne C, J Nat Cancer Inst 1995, 87: 1622–9	1880	3.1–6.1
Van Gils CH, Eur J Cancer Prev 1999, 8: 509–15	108	1.5–7.2
Lam PB, Cancer 2000, 89: 369–75	529	1.9–10.6
Mascarinec G, Breast Cancer Res Treat 2000, 63: 153–61	647	1.1–3.0
Kerlikowske KJ, Natl Cancer Inst, 2005, 97(5): 368–74	436	1.4–5.4
Gill JK, Breast Cancer Res, 2006, 8(3): 30	482	3.58
	119 DCIS	2.92

About 7% of cases of the increased mammographic density do not correlate with calculations of the individual risk of the breast cancer based on the Gail model, where the risk higher than 15% is associated with a doubled density compared with the lower risk. Thus, it is suitable to adjust this calculation based on non-modifiable risk factors according to the mammographic density [20].

The mammographic density is unambiguously demonstrated as one of the strongest risk factors for the breast cancer in a systematic outline and meta-analysis of 42 trials (Table 3) including over 14 000 cases and 226 000 controls [21]. The risk is more significant in the percent evaluation of the density compared with the qualitative evaluation. No effect of the age, menopause and ethnicity was demonstrated. The relative risk still remains significant after elimination of carcinomas detected in the first year after the initial mammogram. The meta-analysis also excluded a possibility that the dependence found could only be an artefact or bias phenomenon due to a deteriorated quality of the evaluation of mammograms exerting a higher density.

### **The mammographic density and hormone replacement therapy**

Increased densities of the breast in women on the HT are obvious only in women over 55 years of age: individually in a range of 20 to 70% of the group. The change is manifested in the course of the first year, the longer time of the treatment having no more effect on the breast density [22]. This generally accepted statement is not in agreement with results of a group of 1007 Norwegian postmenopausal women, who exerted a significant increase in the mammographic density in the use of a combination estradiol + norethisterone; the density was significantly ( $p < 0.001$ ) higher in the treatment for a time period longer than five years (7%) compared with the use for a shorter time period (4.8%) [23].

After the HT withdrawal, this density dropped to the baseline level within 14 days [24]. Speroff recommends a withdrawal of the replacement treatment 14 days before the mammography in all the women over 65 years of age and in younger women invited for a control due to a suspect mammogram [25].

In an outline of seven trials, Banks demonstrated a decrease in the mammography sensitivity in the use of the HT, in six of them with establishing the relative risk of interval carcinomas of 1.7 (CI 1.2–2.4) for women over 50 years of age [26]. An interesting Canadian study compared 450 cases of carcinomas

**Table 3 – Meta-analysis of the risk of enhanced mammographic density**

Density (%)	RR	95 % CI
5–24	1.79	1.48–2.16
25–49	2.11	1.00–2.63
50–74	2.92	2.49–3.42
≥ 75	4.64	3.64–5.91

detected in the screening with 87 omitted carcinomas and 288 interval ones. It demonstrated a risk increasing with increasing density for each 25% of the enhancement with odds ratio (OR) of 1.77 (CI 1.07–2.95) for omitted carcinomas and 2.16 (CI 1.59–2.94) for interval ones. In the adjustment with respect to the density, the OR for the solely estrogen therapy (ET) was of 1.75 (CI 1.11–2.83), comparable with the value for the estrogen-gestagen therapy (EPT) 1.79 (CI 1.1–2.9) [27].

An Australian trial also indicates a decrease in the OR for the interval carcinoma in women on the HT from 1.99 (CI 1.4–2.9) during adjustment with respect to the mammographic density to 1.54 (CI 1.0–2.3). An effect of the breast tissue hyperaemia was assumed there [28].

In a three-year randomized prospective study PEPI, all the increases in the density were manifested in the first year of the study: in 8% of women on the ET, 19–25% in the EPT without differences between medroxyprogesteron acetate and micronized progesterone and 2% in the placebo group (Table 4) [29]. In a Swedish study, the mammographic density was increased by 5% in women on the ET; by 10% in the cyclic EPT and by 28% in the continuous EPT [30]. The obvious difference in the assessment of EPT regimens compared with the PEPI study is explained by the dose of progestins.

A Turkish study comparing different HT regimens in 216 postmenopausal women, employed on average for 20 months, also demonstrated an increase in the density in 31.1% of women on the continuous EPT compared to 3.9% of women on the ET. Surprisingly, no case of the density enhancement was detected in the group with the cyclic EPT similarly as with tibolone. A direct dependence of increases in the mammographic density on the elevation of estrone levels was described in the group of the trial PEPI with the EPT, but not with the ET [31].

Six-month continuous administration of combinations of estradiol valerate + dienogest and estradiol + norethisterone in 50 postmenopausal women led to increases in the proliferation by a factor of 3 to 4 (found by histology of the fine-needle biopsy) correlating with the increase in the density evaluated in percent as well as in accordance with Wolfe in 50% of these women [32].

There are many studies demonstrating that the EPT causes higher increases in the mammographic density compared to the ET or tibolone [33].

**Table 4 – PEPI trial**

Treatment	Number	Average change in density (%)	P
Placebo	112	–0.07	
CEE	113	1.17	0.240
CEE + MPA sequentially	109	4.76	<0.001
CEE + MPA continuously	121	4.58	<0.001
CEE + progesterone sequentially	114	3.08	0.002

In a prospective one-year comparative study, tibolone (18 patients) induced a decrease in the mammographic density due to the reduction in the proliferation and stimulation of the apoptosis in contrast to the combination equine estrogens + medroxyprogesteron acetate (19 patients). After a year, a significant difference ( $p = 0.007$ ) was achieved in the mammographic density and in its change ( $p = 0.00053$ ), expression of the proliferation marker Ki67 and apoptosis Bcl-2 [34].

In a prospective, randomized, double-blind, placebo-controlled trial with the EPT in the combination 2 mg estradiol (E2) + 1 mg norethisterone acetate, tibolone demonstrated a significantly ( $p < 0.001$ ) lower negative effect on the mammographic density comparable with placebo. In this study, the risk of the mammographic density enhancement in the use of tibolone was of 0.12 (0.04–0.37) [35].

The long-term safety of tibolone from the view point of the mammographic density is demonstrated by results of 10-year monitoring of 22 women taking tibolone and 10 women without the treatment, in which there was no difference in the mammographic density between the groups and between baseline values and values after the treatment [36]. There are several reasons for believing that the increase in the mammographic density in using the HT is not identical with the high mammographic density, which presents a risk for the breast cancer [37]. On the other hand, the generally recognized effect of tamoxifen on lowering the risk of the breast cancer is simultaneously associated with a drop in the mammographic density after a 12-month treatment [38].

The increase in the mammographic density in the use of the HT or, in contrast, the absence of this effect cannot be used in the prediction of the risk of the breast cancer in association with the HT. In a retrospective study, Boyd revealed an enhanced mammographic density by 0.5% ( $p < 0.001$ ) in users of the HT compared with non-users in a group of women with subsequently detected carcinoma, but the difference from controls, where the density was higher by only 1.6% was not significant ( $p = 0.3$ ) [39]. The way to the explanation of different reactions of the mammographic density to the HT administration probably leads through the polymorphism of receptors, as demonstrated e.g. by an increase in the density in the genotype of the estrogen receptor ESR1 PvuII Pp or pp in contrast to PP, ESR1 XbaI Xx or xx in contrast to XX or progesteron receptor PGR +331 GG in contrast to GA or AA [40].

## Conclusions

A panel of experts at the 11<sup>th</sup> World Congress of Gynecological Endocrinology agreed that the mammographic density is an important factor for the breast cancer.

They recommended its evaluation by the digitalization of standard mammograms with taking into account the body mass index of the patients. They recognized the

mammographic density as a risk factor for benign breast lesions. They considered the mammographic density higher than 50% as a contraindication for the administration of the EPT but not for the use of ET and tibolone. They recommend withdrawal of the EPT 14 days before performing the mammography for enhancing its sensitivity. They did not find sufficient data for relationships between the increase in the mammographic density in using the HT and prediction of the risk for the breast cancer [41].

The currently existing data from the literature suggest the following facts:

1. The mammographic density is unambiguously a risk factor for the breast cancer.
2. For the evaluation of the increase in the density in the use of the HT as well as for negative findings, there is a lack of demonstration. Its rapid receding after withdrawing the HT indicates a lower importance of this parameter.
3. The high mammographic density itself as well as its increase in the HT enhances the risk of interval carcinomas and reduces the sensitivity and specificity of mammography.
4. The high mammographic density is no contraindication for the HT, but it is one of criterions for choice of climacteric syndrome's therapy.

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