

**Key Words:** *breast cancer, risk factors, mammographic density.*

## THE HIGH MAMMOGRAPHIC DENSITY AS RISK OF BREAST CANCER DEVELOPMENT

**Summary.** *This article is about the most studied risk factors of breast cancer and devoted first of all to the- mammographic density (MD). It represents a phase of pathological changes in the breast, preceding the development of oncologic process. Breast cancer screening is ineffective due to high mammographic density. For this reason we need introducing obligatory gradation of women during mammography screening, according to their MD. This will allow us to select group of high- risk persons with high MD. In this group of patients it is important to provide -screening by specific schemes that include additional application of the MRM — magnetic resonance mammography, and breast ultrasound (dopplerography and elastometry).*

Prophylaxis of various diseases is based, first of all, on the identification of their cause and risk factors. Measures for the determination of risk factors of development of malignant neoplasm, in particular, of breast cancer (BC) and reducing of their impact on woman' organism form the basis of primary prophylaxis. Among the most studied BC risk factors are the following: age > 50, genetic inclination, impact of ionizing radiation, lifestyle (diet, bad habits – smoking and alcohol abuse), absence of pregnancy and childbirth, intake of hormones, disorder of work and rest regimen, lack of physical activity, high mammographic density (MD). The last one represents the stage of pathological changes in mammary gland (MG), which precedes the development of cancer process [1].

According to the statistics, BC develops mostly in the age after 50. For this reason, it is necessary for the timely diagnostics to carry out screening of the disease, starting from this age.

In what countries is the highest incidence of BC and what it is the reason of this? Mostly this problem is to be found in the developed countries of Europe and America. The typical for the women of this region lifestyle is considered to be the main cause of such state of things: late first childbirth (after 30), sometimes no children at all, since women are often lonely, most of the time they devote to their job, disturbing the work and rest regimen (especially harmful job in night shifts). Diet is characterized by intake of food rich in proteins and animal fats, lack of plant food that causes the metabolic syndrome and obesity and is accompanied with hormonal misbalance. Women with overweight are marked with increased level of estrogens that is extremely dangerous in the age after menopause. It has been proved that decrease of body mass on 10 kg and more in the period of menopause contributes to the decrease of BC risk on 56% [1-3].

For reproductive and hormonal risk factors are referred: the menarche under 12 and late menopause (after 55), absence of pregnancy during the life, abortions (especially during the first pregnancy), first childbirth after 30 or no children, refusal from breast feeding, and breaking of lactation. According to the data of the most studies, long (over 5 years) intake of hormonal contraception or hormone-dependent therapy during the menopause increases the risk of BC in these patients [4].

Bad habits, such as smoking and alcohol abuse, contribute to the emergence of BC. Smoking before the puberty and fist pregnancy negatively influence the normal development of MG and in future it becomes the cause of MG cancer diseases in the most cases. It has been proved that risk of BC increases if the intake of alcoholic beverages increases too. Regular intake of alcohol in quantities of 15-50 g is associated with relative risk 1.5 compared with women, who do not drink alcohol [4, 5].

For the prophylaxis of BC, it is recommended to do regular physical exercises, go swimming or jogging, in general any kind of physical activity, which contributes to the balance of body mass, reduce of excess of fats and hormones [4, 6]. It has been also noticed that BC develops rarely in people of Southern regions, where the sun impact is higher and enough vitamin D is being formed – the important factor of full immunity [7].

Hereditary inclination to BC conditioned by inheritance of mutagenic genes *BRCA-1* and *BRCA-2* is to be found in 10% of cases and is characterized by the development of this pathology in the young age [8].

Thus, there are many risk factors of BC that complicates the carrying out of the full prophylaxis. The question concerning the prophylaxis of hereditary BC via prophylactic mastectomy or hormonal therapy is solved easier. For prevention of sporadic BC, the correction of lifestyle with adherence to the principles of its healthy type, as well as early diagnostics of the disease, is important [1].

**Early diagnostics of BC. Screening.**

Early diagnostics of BC, the same as other cancer diseases, is the main principle of diagnostics in oncology. Maximally early detection of pathology provides the determination of diagnosis at lack or minimal possibility of metastasis. At the same time, period is relatively unimportant, since sometimes metastasis develops even at the early diagnostics, but this phenomenon occurs rarely than at diagnostics in the later stages of the disease. Thus, measures aimed at detection of the disease in the early stage, constitute the basis of the secondary cancer prophylaxis – prophylaxis of metastasis.

For the BC early metastasis is typical. It has been determined that tumor of size under 1 cm, which is often not detected by palpation, also has micrometastases in 30% of cases. It is possible to diagnose such stages at active case finding via screening of risk groups.

In the developed countries of Europe and America, screening for a long period of observation has showed its efficacy for decrease of BC mortality in group of women, who show the oncologic alarm through active self-examinations and regular mammographic examinations [9]. American Cancer Society and Association of European Cancer Leagues have developed complex of recommendations for the screening (Table) [10].

**Significance of MD for detection of BC during the screening**

Following the mentioned recommendations concerning screening seems to give no chances for neglecting the disease, if it was not difficult to identify the early stages of BC on the background of the increased MD.

Radiological presentations of unchanged MG are often various and individual that manifests itself by various pictures of mammary gland and its radiological density. The extension of mucous and adipose tissue is symmetric in the both glands. Asymmetry of MG MD is typical both for the nonneoplastic (asymmetric involution of gland tissue, posttraumatic and postinflammatory changes, adenosis) and for the neoplastic (BC) processes [11]. High MD is associated with significant increase of BC risk (1.8-6.0 times) [10-14]. At that, out of all risk factors, despite the numerous studies, this factor is least studied [15].

MD is the level of extension of radiologically dense fibroglandular tissue in MG [16]. Mammogram demonstrates the presence of two components of MG – fibroglandular and adipose tissue, which have different coefficient of weakening of X-rays. The lesser coefficient has adipose tissue; therefore its zones look darker on the picture. Fibroglandular complexes determining the MD look lighter [17].

**Table**

**Recommendations for the screening of BC [10]**

Age of woman, years	Procedures	Frequency of examinations
Under 20	Self-examination of mammary glands (SMG)	Girls are informed about necessity to carry out SMG, terms, importance of visit to a specialist (surgeon, gynecologist and oncologist) if specific symptoms arose
20–40	SMG + clinical examination of MG	Women are recommended to carry out regular SMG. It is necessary to teach women the SMG technique according to the instruction. It is recommended to undergo clinical examination of MG as component of the other general medical examinations, one time in three years if possible. The ultrasound investigation is given prevalence as instrumental method. In cases of diagnosis of tumor, the mammography is indicated.
40–50	SMG + clinical examination of MG + mammography	It is recommended to undergo clinical examination of MG as component of other general medical examinations, one time in a year if possible. In the USA it is recommended to undergo yearly mammography start at age of 40.
After 50	SMG + clinical examination of MG +	Screening mammography with interval 2-3 years. Between screenings women carry out

Age of woman, years	Procedures	Frequency of examinations
	mammography	SMG and undergo MG every year.

Significantly higher content of collagen and expression of stromal proteoglycans of lumican and decorin in areas of high MD and their low content in cases of low MD in women in postmenopause has been correspondingly determined [16, 18]. Age involution of MG is manifested by decrease of collagen and glandular tissue as well as increase of content of adipose tissue that correlates with decrease of risk of aggressiveness of BC. Collagen and stroma, due to their mechanical properties, contribute to invasion of tumor. In major BC cases, the adhesive capacity of stromal E-cadherins is significantly reduced that causes the disorder of intercellular contacts and makes easier the release of cell from primary tumor node. It has been proved that mediated by adhesion receptors attachment of tumor cells to laminine and fibronectin determines the further development of invasion and metastasis [18, 19].

The determination of MD is influenced by large amount of technical and physiological factors, including the exposition of film, positioning, stage of mammary gland compression, changes in hormonal status, body mass, alcohol intake [20].

High MD is positively connected with other BC risk factors, such as: compromised family history of cancer, increase of level of serum insulin-like growth factor in women in premenopause, prolactin in postmenopause; combined estrogen-progesterone hormone-dependent therapy [22, 23]. The inverse relation is observed between MD and factors, which reduce BC risk – early first pregnancy and possession of many children.

Replacement therapy in postmenopause increases the MD mainly in older women, and the effect is manifested in first months of application and remains unchanged during the application. Regression of hormone-induced changes occurs during 2 weeks after the end of treatment [22]. In premenopause, the tamoxifen and agonists of gonadotropin-releasing-hormone insignificantly (<10%) reduce MD [21]. Data of study IBIS-1 show that application of tamoxifen with prophylactic aim decreases the risk of BC on 40% [6]. At the same time, drug effect may be foreseen by changes of MD, which turned out to be the only statistically significant prognostic risk factor. If MD decreases 10%, the risk of BC decreases 52% [20-22].

The evaluation of MD as risk factor is unfortunately complicated with the fact that this index reduces also at increase of impact of such important BC risk factors as age and body mass index [24]. It is obvious that with the age and with increase of body mass the glandular tissue is replaced with adipose tissue. Reduction of MD in menopause constitutes approximately 8%. Cumulative level of senescence of MG tissue along with the risk of BC increases with the age, but the speed of its growth decreases. In all age groups, MD is higher in women with developed BC [25].

The results of comparative study of monozygotic and dizygotic twins have demonstrated essential impact of genetic factors on variability of MD in women of 40-70. According to the classical twin model, inheritance of the certain MD level achieves 60-75% of individuals. However, if taking into account other significant factors of this feature, the significance of genetic component decreases up to 10%. Possible impact of heredity is mediated by peculiarities of hormonal-metabolic homeostasis. Genes influencing the decrease of MD remain undefined, the same as their role in development of BC [12].

The fact is interesting that there is no connection between free circulating sex hormones (estriol, estradiol, progesterone, and testosterone) and MD at positive correlation of the last one with increase of level of sex-hormone-binding globulin [25]. High MD is considered the powerful predictor of BC risk, which allows to trace the effectiveness of measures concerning the decrease of such risk as well as can become intermediate or final in study of causes of BC [26].

### MD classification

Starting from 70<sup>th</sup> of the previous century, various methods of determination of MD for the practical use have been developed. In general, they can be divided into 2 groups: qualitative and quantitative methods. Qualitative methods are based on visual determination of certain features of MG tissue on mammograms [27-30]. Quantitative methods are based on the calculation of ratio of area of dense structures to the whole tissue of MG on mammogram. To the last ones are referred plane geometry, computer method and visual distribution. Result is given in percentage or absolute area of density (pixels, cm<sup>2</sup> or mm<sup>2</sup>) [27, 28]. Quantitative methods of determination of MD are applied, as usual, in large clinical or prophylactic investigation. In routine practice are mostly applied qualitative methods due to their simplicity and availability [27-30].

To the qualitative methods are referred Wolfe and BI-RADS classifications. The last one is standardized visual classification of mammographic findings developed by American College of Radiology. According to this classification, 4 categories of MD are defined: **category 1** – almost fully adipose structure of tissue (dense structures occupy <25% of gland area); **category 2** – particular fibroglandular densities (dense structures – 25-50% of gland area); **category 3** – heterogeneous density (dense structures – 51-75% of gland area); **category 4** – extreme density (dense structures – >75% of gland area). Categories 1 and 2 are characterized as low MD and categories 3 and 4 – as high.

The F. Boyd [27] classification includes 7 stages of density: I stage – up to 10% of fibrous tissue; II stage – up to 15%; III stage – 20%; IV stage – 25% V□stage — 50%; VI□stage — 75% and VII□stage — 100% of fibrous glandular tissue. First 4 stages are determined as low MD, all other belong to the increased density. This classification is mostly applied recently.

Modern computer mammographs are capable to determine the percentage of MD due to special software. Wide introduction of the evaluation of MD during the mammography allows wider use this BC risk factor in the screening [30].

## CONCLUSION

Thus, data of the survey of modern professional publications shows that increased MD is a factor of BC risk. In the presence of increased MD, the carrying out of the early diagnostics of BC upon the conditions of screening is more complicated. For the successful screening of BC, it is necessary to implement the evaluation and staging of MD for the further separation of groups with high risk – individuals with high MD. It is important in this group of patients to carry out screening using additional methods of examination, which include application of magnetic resonance mammography, ultrasound investigation of MG with Doppler technique and elastometry.

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