Physiology and pathology of the mammary gland in women in different periods of life (menopausal period and pregnancy)

Fizjologia i choroby gruczołu piersiowego w różnych okresach życia kobiety (menopauza i ciąża)

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Summary

Knowledge of physiology of the mammary gland help us understand pathological processes which can occur in this organ, for example carcinogenesis. The results of epidemiological studies indicate an increased incidence of breast cancer in women receiving sex steroids, but the data concerning this issue are not unequivocal. The results of WHI (Women Health Initiative) and HERS (Heart and Estrogen/Progestin Replacement Study) studies point out to an elevated risk of neoplasia in the mammary gland among women taking hormone replacement therapy, which evokes a great deal of concern, uncertainty and fear both among doctors and patients. This fear should be replaced by the algorithm of professional medical management and a suitable choice of therapy in relation to a woman's age, genetic load, history of diseases and expected benefits. Directing a therapeutic option to the patient and supporting it with scientific data on HRT can convince women that the treatment will prevent, to a large extent, fractures, depression, Alzheimer's disease, colon cancer, stroke and heart attack. The risk of possible breast cancer death is much lower than compared to the affliction caused by estrogen depletion during early menopause. In the following review we present data which deal with physiology of the mammary gland in different periods of the woman's life, especially menopause. Moreover, the molecular mechanisms that may potentially play a role in neoplasia are discussed.

Key words: mammary gland, breast cancer, hormone replacement therapy.

Streszczenie

Znajomość fizjologii gruczołu piersiowego kobiet pomaga w zrozumieniu mechanizmów odpowiedzialnych za rozwój procesów patologicznych tego gruczołu, w tym raka. Wyniki badań epidemiologicznych wskazują na wzrost częstości występowania raka piersi u kobiet przyjmujących hormony płciowe, ale dane dotyczące tej kwestii nie są jednoznaczne. Wyniki badań WHI (*Women Health Initiative*) i HERS (*Heart and Estrogen/Progestin Replacement Study*) zwracają uwagę na podwyższone ryzyko nowotworzenia w gruczole piersiowym w grupie kobiet stosujących hormonalną terapię zastępczą. Wywołuje to wiele niepokoju, niepewności i obaw zarówno wśród lekarzy, jak i pacjentek. Obawy te powinny zostać zastąpione przez profesjonalny algorytm postępowania i odpowiedni dobór terapii w zależności od wieku pacjentki, jej obciążenia genetycznego, chorób współistniejących i spodziewanych korzyści dla układu kostnego, pokarmowego, nerwowego i krążenia. Odpowiednie przedstawienie tej opcji terapeutycznej i podparcie jej danymi naukowymi może przekonać kobiety do hormonalnej terapii zastępczej i wynikających z niej korzyści, takich jak zmniejszenie ryzyka wystąpienia złamania kości udowej, zapobieganie depresji i chorobie Alzheimera, profilaktyka raka jelita grubego, udaru i zawału serca. W niniejszej pracy zaprezentowano przegląd artykułów poruszających kwestię fizjologii gruczołu sutkowego w różnych okresach życia kobiety, poświęcając szczególną uwagę okresowi menopauzy. Ponadto przedstawiono mechanizmy molekularne, które mogą brać udział w rozwoju raka piersi.

Słowa kluczowe: gruczoł piersiowy, rak piersi, hormonalna terapia zastępcza.

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Introduction

Breast cancer is the most common malignancy in women in Poland, which is responsible for about 5000 deaths each year. The risk of developing breast cancer during woman's life is about 12% and it increases with age [1]. The highest number of recorded cases is among women who are in their 50s [2]. The analysis of epidemiological data and molecular regulatory mechanisms involved in pathogenesis of breast cancer requires that special attention should be paid to documented occurrence of risk factors predisposing to the disease and at the same time indicates divergence in the results of epidemiological studies. A reliable observation deserving special attention is that despite a slightly higher incidence of breast cancer in a group of women using hormone replacement therapy (HRT), mortality rate due to this malignancy in these women is significantly lower in comparison with those not using the therapy [3, 4]. In the review we present data concerning physiology of the mammary gland in different periods of the woman's life and molecular mechanisms that may potentially play a role in neoplasia.

Action of hormones on the mammary gland

Taking into consideration the action of sex hormones on the mammary gland two important steps in their long-term action and short-term monthly fluctuations should be distinguished. The first of the long-term action stages is puberty, the second – pregnancy. Biological effects of estrogens (E) on the mammary gland are exerted in two ways: through estrogen receptors (ER) by means of genomes, i.e. the so-called "receptor mechanism", and omitting receptors ("extrareceptor mechanism"). A more complex receptor way with the participation of type α and β estrogen receptors and several isoforms of α receptor is more important and associated with greater stimulation of the genome [5]. Non-genomic activation concerns mainly stimulation of membrane transport, participation in oxidation and reduction reactions, and to a lesser extent, in the case of normal tissue, stimulation of the cell genome through formation of DNA adducts.

Cooperation of prolactin and its receptors is essential for the formation of ERs during the development of the mammary gland, and the formation of progesterone receptors (PR) is induced by estrogen receptors. The presence of the growth hormone, cortisol, thyroxin and insulin is also indispensable for normal growth of the mammary gland in puberty. In women of the reproductive age an increase in the proliferative activity of the mammary gland epithelial cells in the follicular phase of the menstrual cycle is mostly affected by estradiol (E2), whereas in the secretory phase by progesterone (P) and estradiol metabolite – 16α-hydroxyestrone. It was found that mitotic activity in the breast, assessed immunohistochemically with the use of proliferation markers, is the highest during luteal phase of the cycle and depends on progesterone concentration. The estrogen receptor content remains decreased in the follicular phase, whereas progesterone receptor content remains unchanged throughout the whole menstrual cycle [6]. The regulation of ER expression depends, among others, on the normal function of BRCA genes. BRCA genes are activated by estrogens and their products decrease the density of estrogen receptors [7].

Menopausal period

It is widely known that postmenopausal women with previously diagnosed benign breast diseases have an increased risk of invasive breast cancer. However, this observation was statistically confirmed on the basis of histopathological examination of mammary gland biopsy in 10 thousand women with atypical ductal hyperplasia as well as with lobular hyperplasia. The atypical findings in these studies bring about a medium risk (CR) – 5.3 of carcinoma but an increased risk (CR) – 9.8 can be found within 10 years after the initial diagnosis [8]. The incidence of breast cancer in the remaining cases is slightly higher (CR) – 1.13 to 1.57, what in fact confirms lack of contraindications for HRT.

Maintained increased CR during a 10-year period after detecting atypical changes or lobular hyperplasia is important from a medical point of view. During this time HRT or OC should be avoided [8].

Weak estrogens considered to have week activity can effectively alter the lipid profile. The most potent estrogen – estradiol, could be metabolized to estrone by the removal of hydrogen at carbon 17. However, the process is reversible but the level of reduction is low. These in turn cause an increase in the local estrone concentration in the mammary gland. Further steps of estrogen transformation affect A and D ring of the steroid. Different enzymes are involved in the process, which is irreversible. Metabolism of A ring causes the formation of catechol estrogens in the form of 2- and/or 4-hydroxyestrone. Oxidation of D ring in the position 16α leads to the formation of 16α-hydroxyestrone with subsequent favourable elimination in the urine in the final form of estriol. The described D ring metabolites constitute the main pool of biologically active estrogens in the man. A further, reversible stage like binding with sulphate or glucuronate residue causes solubility and could undergo subsequent methylation.

Studies conducted by Seeger pointed out a significant role of 16α-hydroxyestrone in the mammary gland neoplasm promotion in women [9]. Concentration of 16α-hydroxyestrone was significantly higher in

the tissue surrounding neoplasm comparing to the mammary tissue of women with no breast cancer [10].

It was demonstrated, that cultured TDLU cells can metabolized estrogens in the process of C17 oxidation as well as C2- and C16-hydroxylation. Preference of C16-hydroxylation occurs in the cells obtained in luteal phase of the menstrual cycle, when proliferative activity of the breast cells is the highest [11].

It was also stated, that intensity of hydroxylated C16-derivates of estrogens in relation to the C2-derivatives is associated with the predisposition to breast cancer in man [12, 13].

Estriol poses protective action, by blocking for the short time the estrogen receptor in mammary gland. 16α-hydroxyestrone shows two types of interaction with the estrogen receptor and additionally extrareceptor activity. The first type of reaction is similar to estradiol, non-covalent binding with a limited time of action. The second one is covalent bond with long time binding and a marked metabolic effect. The extragenomic effect probably may prevail in women with breast cancer. It was proven by adding 16α-hydroxyestrone to the mammary epithelial gland culture, what induced uncontrolled cell proliferation [12]. What is more, an increased concentration of 16α-hydroxyestrone is observed in blood serum of women and urine of women with neoplasmatic disease of the mammary gland. It was also found that progesterone plays a role in the proliferation of mammary gland cells. This steroid increases hydroxylation of estrone at C16 position in cultured breast cell lines [12]. 16α-hydroxyestrone induces proliferation and neoangiogenesis, the processes involved in metastasis formation and spread of the neoplasm [14].

Apart from estrogens and gestagens, other hormones, such as insulin competing with growth factors and androgens, play a significant role in initiation (triggering) of the proliferation process. It was observed that androgens, especially androstenedione that is converted to etiocholanolone shows abnormal values (etiocholanolone) 6 times more frequently in women with breast cancer in comparison with a normal group of women – below 0.4 mg or above 1.0 mg when extracted from urine during 24 hours. A decreased concentration of androstenedione and increased concentration of gonadotropins in serum of women are thought to be responsible for higher aromatase activity in the breast tissue. It may lead to a higher concentration of estrone in the breast, especially in women in the perimenopausal and postmenopausal period.

Normally an excessive amount of produced estrone can be inactivated through binding to sulphate residue by sulphotransferase forming 16alpha-hydroxyestrone.

Further metabolism of 16α-hydroxyestrone leads mainly to the formation of estriol characterized by weak estrogenic activity. This is caused by a short period of binding with estrogen receptor. However, exposition for those estrogens for a long period of time causes, contrary to the prevailing opinion, a stimulating and not suppressive effect. It was proved in a study on mice where neoplastic tumour was induced by both estradiol and estriol as well [15].

Metabolism of A ring of estrogens causes the formation of catecholestrogens. One of them is 2-hydroxyestrone whose action is modulated by catechol-orthomethyltransferase (COMT). The COMT is present in almost all cells of the human organism. Its suppressive effect (action) against the breast carcinoma cells growth seems to be more prominent after we concern the action of derivatives methylated by COMT. Methylation does not inactivate estrogen derivatives formed as a result of A ring changes. For example, the derivatives of estradiol (2-methoxyestradiol) have an inhibitory effect on cultured fibroblast, smooth muscle cells and even adipocytes proliferation [16]. On the other hand, it was proved that non-methylated derivative such as 2-hydroxyestradiol stimulates proliferation of breast carcinoma cells contrary to methylated derivatives strongly inhibiting carcinoma cells proliferation. Antiproliferative effect of 2-methoxyestradiol is possible due to production of p53 protein by the stimulated cell. This protein induces apoptosis and has a beneficial influence on cellular tubules responsible for maintaining the normal spatial structure of the cell [17]. Another extremely important feature of 2-methoxyestradiol is inhibiting of angiogenesis. Zhu *et al.* claim that among metabolites of estrogens with multifunctional effects on mammary gland cells, 2-methoxyestradiol seems to play a significant role in inhibiting the growth of mammary gland neoplasm [18].

Other A ring estrogen metabolites such as 4-hydroxyestrogens can be transformed into quinones and semiquinones forming adducts after binding strongly to DNA. This result in forming of free radicals such as hydroxydeoxyguanosine responsible for toxic reaction with DNA [19]. Elevated values of 4-hydroxylase causing a significantly increased concentration of 4-hydroxyestradiol are found in breast tumour tissue [20]. However, there are a number of reducing factors in human organism such as vitamins C and E, glutathione, COMT transferase and estrogens, which effectively decrease activity of free radicals.

Analysis of how different estrogen fractions result in neoplasia in the breast tissue indicates that the prevalence of one of estrogen metabolic pathways is not only genetically determined but there is also an influence of external factors acting as cofactors modulating action of estrogens e.g. diet (phytoestrogens decrease the concentration of estrogens and their metabolites) as well as enzymatic liver function.

An increased ovarian estrogen synthesis after menopause is not possible in physiological conditions. However, an elevated concentration of gonadotropins

result in increased aromatization of adrenal androgens into estrogens in this period of life.

Mammary gland tissue possesses other essential enzymes that metabolize estrogens apart from aromatase. It includes sulphotransferase (binding sulphate group to estrone), sulphatase (converting estrone sulphate into estrone) and dehydrogenase initiating interconversion of estrone to estradiol and estradiol to estrone. Sulphatase is the dominant enzyme in the breast and its action is modulated by the activity of sulphotransferase.

As regards significant local enzymatic activity of the mammary gland tissue it seems that rather local production of estrogens than circulating in the blood, causes 10 to 40 times higher concentration of estradiol in the breast tissue, both before and after menopause [21]. The uptake of circulating estrogens by receptors seems to play a secondary role, as neoplastic tissues, devoid of estrogen receptors, also show an increased estrogen concentration. Initiation of HRT after menopause results in an increased risk of breast carcinoma in slim women, possessing a relatively higher (in relation to the body mass) tissue concentration of estrogens and gestagens despite the fact that the obesity increases the risk of the women not receiving HRT.

The concentration of estradiol in women after the menopause with an increased risk of neoplasia disease does not exceed the values found before the menopause, i.e. 400-500 pmol/l (max. 1750 pmol/l). Epidemiological studies indicate a slight increase in the risk of breast cancer in patients currently using HRT, despite the fact that a blood serum estradiol concentration is lower, of 200-360 pmol/l [2].

An important role in maintaining the normal balance between the proliferation and apoptosis processes in the mammary gland cells is played by suppressor proteins BRCA-1, BRCA-2, p53 and RB and oncogenic proteins of BCL and RAS families or tyrosine kinase pathway: ERB-B2, EGFR, HER2-NEU, TGF-β growth factors, cyclins and signal pathway proteins RAS-RAF-MAP, PhIP3-D1. The abilities to control apoptosis (proteins BCL-2, BAX, p53) and repair the existing mutations (Mismatch Repair – MMR) constitute important additional control of cell proliferation [22, 23]. MMR proteins, controlling the DNA transcription processes, are responsible for the occurrence of the so-called mutator phenotype, creating favourable conditions for and increasing the occurrence of mutations in many different places of the genome which very rapidly lead to neoplastic transformation [24]. Epigenetic factors modifying DNA are important likewise as they enable creation of adducts and force DNA polymerases to perform abnormal translesion synthesis (TLS) which may lead to transmitting mutation to a newly synthesized DNA strand in the mechanism of slipped mutagenic intermediate [25].

Altered BCL-2 and p53 proteins play a minor role in the mammary gland physiology. Only small changes were found in the values of both proteins in women using or not using HRT, showing a slight increase in the "survival protein", i.e. BCL-2 and a decrease in p53 content in the neoplastic breast cancers of patients receiving HRT. These changes did not cause expected aggressive growth of cancer but the opposite: the use of HRT was associated with better prognosis of survival [26]. However, the authors did not describe the type of cells adjacent to those with altered BCL-2 and p53 expression. Some of those could be cells of primary, undifferentiated type I lobules, proliferating intensely under the influence of estrogens.

Russel *et al*. presented a hypothesis that a reaction of one type of the oncogenes HER-2NEU with an estrogen receptor is the key to solve this enigmatic, contradictory, stimulating-inhibiting proliferation function of estrogens and their derivatives [27]. It seems that an excessive expression of HER-2NEU was connected with the loss of function by the estrogen receptor in the mechanism of down-regulation. Estradiol, acting mainly through binding to ER, could not react without its presence, and estrogen metabolites (16α-OH and 4-OH), acting through an extra-receptor way, could activate growth of tumours containing large amounts of HER-2NEU. The activation concerns tyrosine kinase pathway strongly stimulating proliferation, also associated with TGFβ and stimulated by estrogens in an autocrine fashion.

Association between suppressive functions of BRCA proteins with action of estrogens and activity of their receptors (ER) is important in understanding the mechanism of oncogenesis. Estrogens stimulate BRCA proteins which in turn inhibit ER functions [7]. In order to explain mutual relationships of BRCA proteins, ERs and estrogens, the influence of estrogens should be considered in relation to patient's age. In young women in whom accumulation of mutations has not reached the initiating point for promotion of neoplasm, activation of BRCA protein synthesis by estrogens stabilizes the genome. In this group of patients estrogens do not constitute a risk factor. In older women, the mammary gland cells have already accumulated a certain number of mutations, and related to age increased methylation of BRCA promoter impairs its expression; thus a slight amount of BRCA protein being formed cannot inhibit stimulation associated with estrogens. At any age, genetically conditioned excessive methylation of BRCA1 promoter or hereditary mutation of this gene disturb its suppressive function and enable formation of DNA lesions, creating favourable conditions for inducing neoplasia. Large amounts of estrogens formed in the mammary gland (active aromatase and sulphatase) facilitate creation of DNA adducts with estrogens and cause instability of the genome (MSI). In the case of hereditary neoplasms, carriers of mutations in BRCA1

are found to have disturbances in morphology of the breast consisting of the histologically differentiated type I lobules with the highest proliferative potential. Type I lobules manifest great sensitivity to various factors stimulating growth, among others estrogens [7].

The function of BRCA proteins enables us to explain adverse influence of alcohol consumption upon the mammary gland. Addition of alcohol to breast cancer cells culture caused, even at a low concentration level, stimulation of type α estrogen receptor and activation of transcription with a simultaneous decrease in suppressive BRCA-1 protein content and an increase in cell proliferation [26].

Breast cancer and pregnancy

Cancer coexisting with pregnancy is quite rare and complicates 1-2% of all pregnancies. One of the most common cancers occurring during pregnancy is breast cancer which is associated with high concentrations of estrogens, progesterone and prolactin, combined with elevated concentrations of thyroxine, insulin and growth hormone as well as placental lactogen [4, 27]. All these hormones cause final differentiation in mother cells of the terminal ductal lobular unit (TDLU) of the breast [4]. Moreover, the completion of pregnancy at term before the age of 30 cause TDLU cells to be proliferatively "exhausted" and show little susceptibility to excessive stimulation in the future.

Breast carcinoma is rarely diagnosed in pregnancy despite high concentrations of estrogens, and pregnancy after the treatment of the disease does not deteriorate the survival rate. Tamoxifen, competing as an anti-estrogen for a binding site of estrogen receptor, improves the survival rate, despite the fact that it contributes to a (very high) increase in estrogen concentration in the blood. Similarly surprising is the epidemiological observation concerning a decreased risk of breast cancer in women who were pregnant after the age of 30 (which condition increases the risk of cancer) and receive HRT during the menopause in relation to those who were pregnant after the age of 30 but do not receive HRT [28].

Conclusions

Breast cancer is still the most common malignancy affecting women. Scientific data confirmed an increased risk of breast cancer among women receiving HRT for more than ten years and those observations evoke patients' dramatic fear of HRT. This fear should be replaced by the algorithm of professional medical management and a suitable choice of therapy in relation to a woman's age, genetic load, history of diseases and expected benefits for the bones and digestive, nervous and circulatory systems. Directing a therapeutic option to the patient and supporting it with scientific data on HRT can convince women that the treatment will prevent to a large extent fractures, depression, Alzheimer's disease, colon cancer, stroke and heart attack. The risk of possible breast cancer death is much lower as compared to the affliction caused by estrogen depletion during early menopause. Data from WHI study analyzing women at the age of 50-59 clearly indicate that the risk of breast cancer among them is in fact lower than among women who did not receive HRT.

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