ETIOPATHOGENIC CORRELATIONS IN BREAST CANCER

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ABSTRACT

The classic treatises, as well as the latest studies regarding the breast neoplasms emphasize the importance of several favorable factors in the genesis of the breast neoplasm.

The physiological personal history (age of the patient, age of first menstruation, late menopause, late-life sex, reduced breastfeeding, etc.), the personal pathological history, the heredocolateral history (breast, uterine neoplasia, other neoplasms) play a significant role, as well as the living and working conditions (stress, smoking, coffee, alcohol consumption), and dietary factors (hyper-lipidemic and hypoproteinemia regimens).

In order to evaluate the impact of these factors in the etiopathogenesis of breast cancer, we followed their incidence in a prospective study performed on the cases of breast neoplasm hospitalized and surgically performed in the period between 2012-2018 in the 1st Surgery Clinic.

Keywords: breast cancer, etiopathogeneses, incidence

Introduction

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hypoproteinemia regimens).

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Material and Method

Between 2012-2018 the incidence of breast cancer was 1.81% compared to the total number of surgeries and 1.55% of the total number of hospitalizations.

Table 1 - Distribution by years - 2012-2018

Year	2012	2013	2014	2015	2016	2017	2018	Total
Number of Admissions	5132	4134	4728	4704	4566	4480	3495	31239
Number of Surgeries	4443	3639	3978	4539	4279	3531	2372	26781
Number of Mammary Neoplasms	64	62	76	100	53	61	70	486
%	1.44%	1.70%	1.91%	2.2%	1.23%	1.72%	2.95%	1.81%

Results

1. Hormonal factors

- 1.1. The menarche before the age of 12 is considered to present a 2.3 times higher risk in developing a breast neoplasm compared to the girls who have it after this age. In the case study, a number of 48 patients (10.52% of the whole group) acquired the menarche early, before the age of 12.
- 1.2. Short or irregular menstrual cycles are characteristic of women with breast tumors. The data obtained shows that 7.35% of women have or had short or irregular menstrual cycles.
- 1.3. Nulliparity of the women in the studied group was 7.01% (32 women).
- 1.4. Late menopause is another risk factor to be considered. Within the studied group, late menopause occurring after the age of 50 was present in 55 patients (12.06%).

2. The personal pathological backgrounds

The personal pathological history shows a relatively high percentage of benign mammary or uterine disorders in patients diagnosed with breast neoplasm.

Thyroid pathology associated with breast neoplasms is significant.

These results, however, cannot be taken separately, but need to be also correlated with data on the patient's genetic traits, diet, living and working conditions, hormonal levels and other factors.

2.1. Biliary lithiasis

Research carried out in this field shows a new risk factor associated with the breast neoplasm: people with a history of bladder lithiasis have a higher risk of developing breast cancer than the people without this pathology.

Within the study group 18 patients had a personal history of biliary lithiasis, representing 3.94%.

3. Collateral hereditary predisposition

The collateral hereditary predisposition of patients with breast cancer plays an important

Table 2 - Personal pathological background

Nr.	Pathological personal histor		Number of cases	Percentage (%)
1.	Total hysterectomy with bilateral anexectomy	(fibroids)	15	3.28
		(borderline ovarian cyst)	3	0.65
2.	Total hysterectomy		6	1.31
3.	Anexectomy	Unilateral	3	0.65
		Bilateral	6	1.31
4.	Ovarian cyst	Involving a surgical procedure	15	3.28
		No surgical procedure involved	3	0.65
5.	Unoperated uterine fibroid		3	0.65
6.	Cervical dysplasia with endometrial adenomatosis		3	0.65
7.	Thyroid pathology	Hyperthyroidism	12	2.63
		Nodular goiter	6	1.31
		Autoimmune thyroiditis	3	0.65
8.	Market osteoporosis (at age 64)		3	0.65
9.	Left neoplasm basal pleurisy		3	0.65
10.	Biliary lithiasis		18	3.94
	Total		102	22.36

Table 3 - Medical history of the hereditary predisposed patients

Nr.	Collateral hereditary history		Number of cases	Percentage (%)
1.	malignant breast pathology	1st degree relatives (mother, sister, daughter) relatives	18	3.94
		2nd degree (niece, cousin)	6	1.31
2.	malignant uterine pathology (mother, sister)		10	2.19
3.	other malignant diseases (esophageal, gastric neoplasm)		9	1.97
	Total		43	9.42

role and can provide information about the predisposing genetic load.

4. Smoking

According to the latest studies in the field of breast cancer, smoking is another contributory factor.

From the data mentioned in the observation sheets, 22.36% of the patients (102 cases) were smokers.

5. Diet

F. de Waard stated that, in general, menopausal and postmenopausal cancer occurs in obese and hypertensive women, characterized by adrenal hyperproduction of estrogen.

The effects of dietary lipid surplus in postmenopausal women on the one hand increase the transformation of androstenedione into estrogen in excess adipose tissue and, on the other hand, increase the nocturnal prolactin level. Consequently, under the unintentional action of estrone and prolactin on an ontogenetically "programmed" breast in hypotrophy, there is a rise in the occurrence or evolution of tumor foci.

In this study, approximately 37% of the cases were diagnosed with obesity at different stages (from grade I to grade III).

6. Stress

Stress is an important factor in the etiopathogenesis of breast neoplasms. It seems to favor the development of breast cancer and aggravate its development. Almost one third (29%) of the patients treated within the study period were affected by stress.

7. Psychic disorders

Research in the field suggests a relationship between depression and the breast cancer incidence.

The incidence of depression among the patients studied was 7%.

8. Oral contraceptives

Prolonged use of oral contraceptives

substantially increases the risk of breast cancer, doubling it, especially among women who have benign mastopathies or a family history of breast cancer.

In the studied group, the use of oral contraceptives was relatively restricted, a possible cause being the lack of education in this regard.

Table 4 - Numerical and percentage incidence of patients who had a history of oral contraceptives usage

Oral contraception	Number of cases	Percentage (%)
< 5 years	29	6.35
5 - 10 years	16	3.50
> 10 years	9	1.97
Total	54	11.84

Discussions

Having the knowledge of these exogenous or endogenous risk factors, their pathophysiological mechanisms of action as well as the periods of life when they can trigger or favor the development of breast neoplasia, is nowadays of major importance in the strategy of prophylaxis and therapeutics of breast cancer.

The analysis of these factors in the prospective study carried out between the period of 2012-2018 on the cases of breast neoplasm admitted to the 1st Surgery Clinic allowed us the following considerations regarding the prediction of the occurrence of breast cancer:

1. Although any family history of breast cancer may be associated with increased risk, the history of breast cancer in females with a 1st degree relative (mother, sister, or daughter) is associated with the highest risk, especially if the relative was diagnosed at a young age (1).

The presence of family history of mammary neoplasms (18 cases - 3.94% in first-degree relatives and 6 cases -1.31% in second-degree relatives) and genital (10 cases - 2.19%

in first-degree relatives) as well as neoplasms of the digestive tract (9 cases - 1.97% in first degree relatives) in the patients studied. Family history does not represent the highest risk for breast cancer, which is evidenced by the small percentage of women who have inherited a genetic predisposition for breast cancer (2). Rather, the high risk is more subtle and probably best explained by similar lifestyles among family members and an inherited predisposition for the influence of those risk factors, such as hormonal factors associated with reproductive types, obesity, etc. (3).

2. Personal history is very important in determining the possible risk factors for breast cancer. The following are relevant: early menarche (before age 12), short or irregular menstrual cycles, late menopause (after age 50), nulliparity, the use of oral contraceptives (4).

The development of the mammary gland may form the picture of the evolution and possible hormonal interactions that the patients with breast cancer are undergoing.

Starting with menarche, the progressive development of lobes begins, depending on the circulating levels of estrogens and progesterone, cyclically produced by the ovaries. Estrogens stimulate ductal proliferation. The association of progesterone in the second part of the cycle gives a greater differentiation of the epithelial cells that are organized in the lobes. It is worth mentioning that the episodes of preferential estrogen production, as it happens during anovulatory cycles, favor a more differentiated development.

Not all mechanisms are known, but it is considered that the highest risk period for environmental carcinogens is in adolescence, when the correct differentiation is not yet ensured. It can be concluded that the breast epithelium is particularly vulnerable in those periods represented by the beginning and end of genital activity, when the ovaries do not provide sufficient progesterone production (5).

If it is considered that each menstrual cycle repeats for thirty to forty years an incomplete process of development during which the glandular tissue is exposed to the lesion aggression of the carcinogenic agents, it can be better understood why the breast represents for the woman the organ most commonly touched

by malignant pathology. Conversely, an early suppression of the ovaries would remove virtually any risk of breast neoplasia.

It has been shown that the most vulnerable periods for carcinogen action are between the ages of 0-4 years and from puberty to the full term pregnancy (6).

3. It is considered that for the girls with menarche before the age of 12, the risk is 2.3 times higher for a breast neoplasm compared to those in which the menarche appeared after this age.

Korenman provided an explanation for the fact that girls with early menarche have long anovulatory cycles, which means that exposure to estrogen action is not counterbalanced by progestins. This hypothesis, however, is far from being accepted because other studies have shown the opposite, namely that patients who had anovulatory cycles were less exposed to the risk of breast cancer than those with regular menstrual cycles. It is, in fact, the same argument that stated that female athletes do not suffer as often of breast cancer as the other women.

When discussing the age of first menstruation, the different standards and variations need to be taken into consideration: while in the USA the normal age of first menstruation is considered to be 12.8, in China, for example, the normal age of the menarche is considered to be 17 (7).

It has been estimated that in the last hundred years the age at which the menarche appears has decreased, especially in the developed countries of Western Europe, as a result of environmental, social and nutritional factors.

4. The association of an early menarche with a late menopause has been shown to further increase the risk of breast cancer, by increasing the exposure to high levels of endogenous sex hormones (8).

Women with menopause before the age of 45 are twice less likely to develop breast cancer as women with menopause after the age of 55. The risk for women with natural menopause before the age of 45 is 0.73%, while the risk associated with natural menopause after the age of 55 is 1.48% (9).

According to Pike's (1993) estrogen-progesterone breast carcinoma theory,

progesterone is an essential component for the proliferation of breast epithelium, and the risk depends on prolonged exposure to regular ovulatory cycles.

5. Short or irregular cycles are characteristic of women with breast tumors.

6. Nulliparity increases the risk of developing breast cancer by 30%, the single and nulliparous women having a calculated breast cancer risk 1.4 times higher than married women who gave birth to at least one child.

The age of the first pregnancy can increase the risk of developing breast cancer when the woman has the first birth after the age of 30 and especially after 35. Also, a low parity increases the risk of developing breast cancer in postmenopausal or at an older age, and a first pregnancy at an older age predisposes to the onset of breast neoplasm in premenopause (10).

The estrogen window - respectively the period between menarche and the age of the first pregnancy, intervenes in the increase of the breast neoplastic risk by the exclusive action of estrogens, without the counterbalance of progesterone, which increases the mitotic activity, favorable to the tumor induction (11).

It is estimated that women who carry the first pregnancy to term after the age of 25 have a 40% higher risk than women who gave birth before the age of 20.

7. The personal pathological history is important, most of the patients having a history of benign or malignant genital pathology, associated thyroid pathology or vesicular lithiasis.

8. The following exogenous factors favoring breast neoplasm were studied:

a) Obesity is closely correlated with an increased risk of breast cancer in menopausal women and does not influence the risk during the fertile period. The data from the specialized literature shows a percentage of 75% of patients with obesity of different degrees from I to III (12).

Another obesity-breast carcinoma correlation starts from the distribution of adipose tissue in the body, considering that the central, android distribution of fat is a potential factor of carcinogenesis. The idea starts from the association of the abdominal disposition of fat with the high levels of serum free testosterone

which causes a decrease of the serum protein for binding of the sex hormones, a decrease also of the insulin resistance through obesity, insulin being the main regulator of the hepatic synthesis of this protein and stimulates the production of androgen hormones. It appears that high serum triglyceride and insulin levels stimulate lipoprotein lipase, causing excessive accumulation of unsaturated fatty acids in the capillaries. Abdominal obesity can occur through an endocrine mechanism even in the absence of changes in hormone concentration at the systemic level.

b) Regarding smoking, an incidence of 22.36% was obtained within the studied group (13).

Recent data has shown some links between smoking and the development of breast neoplasm. Researchers at the University of Buffalo in collaboration with the National Cancer Institute conducted a study, published on November 13, 1996, in The Journal of the American Medical Association (14). The results showed that menopausal women born with a deficiency action of the gene encoding N-acetyltransferase (NAT2) - an enzyme that detoxifies the carcinogenic components of cigarette smoke and have smoked more than one pack of cigarettes a day for 20 years prior to diagnosis, present a risk 7 times greater to develop a breast neoplasm compared to women born with this gene. The risk was even higher if women started smoking before they were 18 years old (15).

c) In 1993, Hilakivi-Clarke issued three stress hypotheses:

- cancer can be preceded by significant stressful events;
- depression can influence the hormonal and immune system;
- personality type influences oncogenesis.

Regarding personality types it was considered in a study that a particular form, characterized by the inability to express emotion, especially anger, with a feeling of excessive cooperation, has an increased risk of developing breast cancer (16).

The research shows a relationship between depression and breast cancer incidence.

d) Studies have shown that during the use of oral contraceptives and in the 10 successive

years of discontinuation, there is a certain increase in the risk of developing breast cancer, which tends to decrease with the increase of the interruption years. A treatment started before the age of 20 significantly increases the risk of neoplasm compared to women who started using contraceptives after the age of 20.

e) It is worth noting the existence of risk factors such as electromagnetic fields in a patient with a telephone profession and ionizing radiation in a patient who performed MRF repeatedly at intervals between 6 months to 1 year for 10 years, as a caretaker profession in a nursery or as child caretaker.

Conclusions

In conclusion, the great differences on the globe of the incidence and prevalence of breast neoplasm, the geographical and economic particularities, the “borrowing” of regional pathology by the migrated population groups, are sufficient arguments to support the idea that breast neoplasm can be associated with a number of exogenous risk factors.

Throughout a person’s life, risk factors act differentially:

- during the prenatal period, twin pregnancy, advanced age of the mother, preeclampsia, increased birth weight can occur.

- during the neonatal period, the main element is breastfeeding, while in childhood and adolescence an important role as risk factors play the western diet, early menarche, menstrual disorders in the first years after menarche, stature, physical activity, ionizing radiation.

- during the fertile period of the woman, there are several risk factors influencing the occurrence of a breast neoplasm: pregnancy, twin pregnancies, number of pregnancies and abortions, oral contraceptives used, age at first birth, breastfeeding, physical activity, alcohol consumption, smoking, diet high in refined sugars and poor in whole plant foods, stress, mental illness, weight gain, some conditions such as sebum, acne, hirsutism, endometrial hyperplasia, infertility, benign breast pathology, ovariectomy or ovarian irradiation, environmental carcinogens.

- at the menopausal age, hormone replacement therapy, obesity, western diet and the

onset of menopause are factors to be considered.

From the multitude of factors analyzed from both the patients studied and the scientific data, it appears that the most frequent risk factors for the development of breast cancer are:

1. Obesity (37%)
2. Stress (29%)
3. Age category 41-60 years (55%)
4. Smoking (22.36%)
5. Late menopause (12.06%)
6. Early menarche (10.52%)
7. Oral contraceptives (11.84%)
8. Short or irregular menstrual cycles (7.35%)
9. Psychological disorders (7%)
10. Nulliparity (7.01%)
11. Family history of breast cancer (1st degree relatives - 3.94%; 2nd degree relatives - 1.31%)

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