BREAST CANCER RISK ASSESSMENT MODELS. OVARIAN ABLATION AND HORMONAL CHEMOPROPHYLAXIS

GEORGETA GÎNFĂLEAN[1]

[1] *"Lucian Blaga" University of Sibiu*

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Abstract: *Breast cancer is the most common form of cancer that affects females, during lifetime, 1 of 8, 1 in 12 <1: 8/1: 12> (1) develops this type of cancer. Breast cancer incidence is steadily rising; genetic studies show that over the last 80 years there has been a three-fold increase in incidence both in the general population and at high-risk population (those showing BRCA 1, BRCA2 gene mutations). The incidence of breast cancer newly diagnosed in women of all ages in Romania in 2018 according to Globocan is 21.5% (9269 new cases diagnosed).(3) The Gail and Claus models are the most commonly used prediction models regarding breast cancer risk due to the high predictive value in assessing estrogen-receptor-positive (ER+). Therefore, it is necessary not only to establish a degree of prediction of the disease through these assessment models, but also to apply hygienic-dietary measures, namely the initiation of prophylactic therapy, in order to prevent the disease. The interpretation of the Gail model, if the patient has a risk ≥ = 1.66%, is eligible for chemoprevention therapy with hormonal agents over the next 5 years.(4)*

Breast cancer is the most common form of cancer affecting the female sex (table no. 1), during lifetime, 1 out of 8, 1 in 12 women <1: 8/1: 12> (1) develops this type of cancer , being considered the second cause of death due to a karyokinetic process.(2)

Table no. 1. 2018 Globocan statistics on the most common cancers affecting the female sex in Romania

Summary statistic 2018

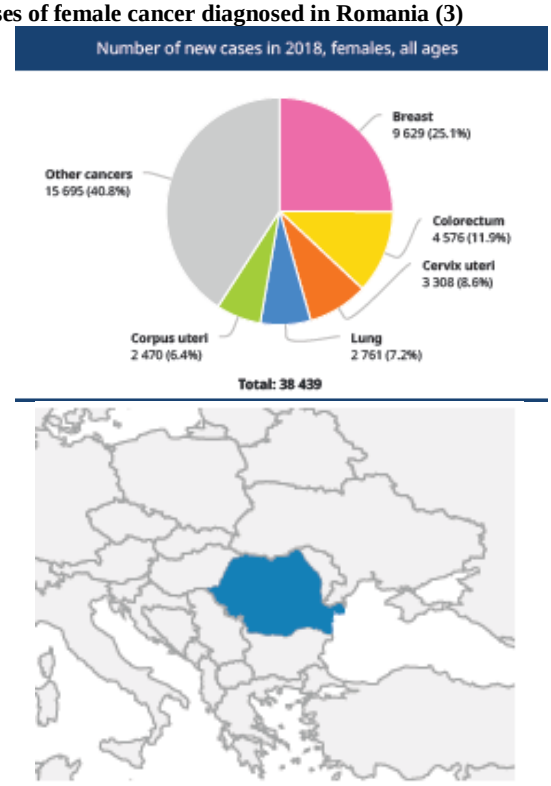
	Males	Females	Both sexes
Population	9 485 608	10 095 020	19 580 628
Number of new cancer cases	45 022	38 439	83 461
Age-standardized incidence rate (World)	264.7	192.3	222.4
Risk of developing cancer before the age of 75 years (%)	45.6	31.2	37.3
Number of cancer deaths	29 929	20 973	50 902
Age-standardized mortality rate (World)	167.6	88.9	123.3
Risk of dying from cancer before the age of 75 years (%)	35.9	20.4	27.0
5-year prevalent cases	97 511	104 719	202 230
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Prostate Bladder Stomach	Breast Colorectum Cervix uteri Lung Corpus uteri	Lung Colorectum Breast Prostate Bladder

In the developing countries, the incidence of breast cancer is increasing as a result of the absence of screening, and in the developed countries, due to changes in diet and reproductive pattern (first pregnancy at an old age, which defines an aging population). Approximately 80 years of genetic studies in the USA, Iceland, UK show the three-fold increase in incidence both in the general population and in the high-risk population (BRCA1-BRCA2 gene mutations).

The incidence of new cases of breast cancer in women of all ages in Romania in 2018 according to Globocan is 21.5% (9269 newly diagnosed cases).(3)

Therefore, it is considered necessary not only to establish a degree of prediction of the disease through these assessment models, but also to apply hygienic-dietary measures, namely the initiation of prophylactic therapy, in order to prevent the disease.

Figure no. 1. 2018 Globocan statistics on the number of new cases of female cancer diagnosed in Romania (3)



[1]Corresponding author: Georgeta Gînfălean, Str. Moreni, Nr. 19, Sibiu, România, E-mail: rezultatemedicina@yahoo.com, Phone: +04723 254897
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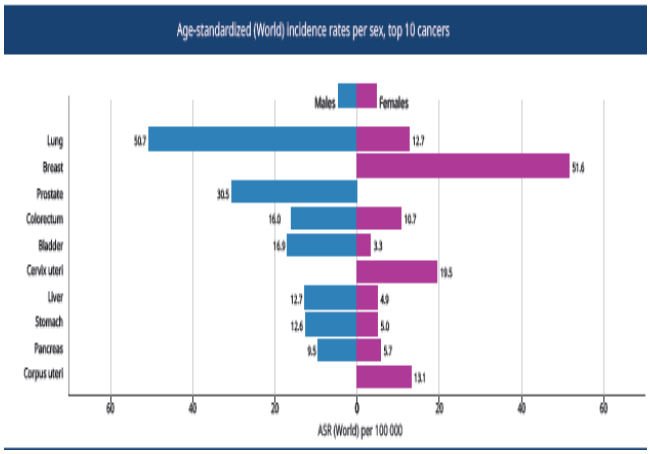

We mention that all women are at risk of developing a form of invasive breast cancer during their lifetime, so women without risk factors have a 3% risk in their lives and those with existing risk factors, respectively genetic mutations, present a risk higher than 80%.

The factors associated with the risk of developing breast cancer are: gender, age, ethnicity, estrogen exposure, pregnancy, breast density, family history, radiation exposure, benign breast disease, lifestyle (diet, physical activity) screening.

The risk factors are classified in:

- factors that cannot be changed (majority): age, gender, ethnicity, family medical history;
- factors that are difficult to change: age at first pregnancy, age at menopause.

Female gender is at a higher risk of developing breast cancer compared to male gender (1: 100) due to: precursor cells with cancer potential, changes in menstrual cycle, pregnancy or lactation, other effects of estrogen.

Age of diagnosis based on the increasing rate is 40 years. The average age of diagnosis of this disease is 60 years. The age probability of breast cancer incidence is the following: at the age of 30, the risk of developing breast cancer throughout life is 12.5%, at age 50 - 11.1%, and at the age 70, it is 6.6%.

Exposure to elevated estrogen levels leads to an increased risk of developing breast cancer throughout life. Estrogens increase the mitotic rate of breast cells, and by the increased mitotic stimulation, the risk of mutation also increases, thus becoming the promoter of carcinogenesis and disease progression.

The factors that reduce the risk of breast cancer are: late menarche, early menopause, oophorectomy, early pregnancy (between late adolescence and 20 years), multiple pregnancies, prolonged breastfeeding (it reduces the risk by 4.3% per year of breastfeeding), estrogen antagonist therapy (Tamoxifen), low estrogenic endogenous level, premenopausal obesity.

Factors that increase the risk of breast cancer: early menarche, late-onset menopause, nulliparity, age at first birth, postmenopausal obesity (due to an endogenous estrogenic level generated by peripheral aromatase), hormone replacement therapy in menopause.

Gestational status in correlation with patient age: for young women under 20 years old, pregnancy has a protective effect against the development of this disease and the risk of ER (+) breast cancer is reduced by 1/2. And an additional pregnancy in this context will lower the risk by 7%. Women older than 35 years of age, achieving a pregnancy, contrary to expectations, have an increased risk of developing breast cancer.

Regarding family history, 10-20% of breast cancer patients have first-degree relatives with breast cancer. 50% of cases are hereditary and the other half are sporadic. Thus, 5-10% of the mammary cancers are due to the genetic susceptibility inheritance, and these are due in 2/3 of cases to BRCA1 or BRCA2 gene mutation and the remaining 1/3 to other mutations (TP53, CHEK2, PTEN).

Two aspects are worth mentioning: > 85% of the women with positive family history will not develop breast cancer (thus underlining the phenotypic heterogeneity of this type of cancer); positive family history for relatives of first degree who develop postmenopausal cancer does not significantly alter the relative risk.

Radiation exposure of the chest area in puberty increases the risk of developing breast cancer. It also increases the number of cases of breast cancer in women treated with mantle radiation in Hodgkin's disease. For a young patient treated with radiation in the thoracic area> 40Gy, there is an estimated cumulative risk of developing breast cancer of 19.1% over the next 30 years.

There are ethnic groups with higher incidence of breast cancer, namely European women (132: 100,000), African (118: 100,000), Spanish and Asian (89: 100,000), the Asians are also noted for an incidence HER2-positive breast cancer.

Regarding the benign breast diseases, mention must be made of the fact that nonproliferative diseases of the breast (epithelial hyperplasia, duct ectasia and cysts) are not associated with an increased risk of developing cancer. In contrast, proliferative diseases with atypia are associated with a relative risk increase of 4-5 times.

Applying a risk assessment model will present the following implications:

- establishing a risk reduction method (e.g. chemoprevention, prophylactic surgical treatment - oophorectomy/ salpingectomy);
- establishing an optimal screening strategy;
- targeted genetic testing of a single gene: BRCA 1, BRCA2, TP 53, PTEN).

Next, we will analyze three risk assessment models for developing breast cancer: the Gail model, the Claus model, the BRCA PRO model.

The Gail and Claus models are the most commonly used models of breast cancer risk assessment, currently used due to the high predictive value in assessing hormone receptors for estrogen positive (ER +).

The Gail model is used for women with BRCA1 or BRCA2 mutation, calculating the individual risk for the next 5 years, respectively the lifetime risk. Conditions and items to be fulfilled within this model:

- age ≥ 35 years old;
- the risk assessment model does not apply if the patient has already been diagnosed with a form of breast cancer (ductal or lobular carcinoma in situ) or has been exposed to radiation in the thoracic area;
- items to be evaluated: ethnicity, age, menarche onset, age at first birth, number of grade 1 relatives who developed invasive breast cancer, number of previous breast biopsies, diagnosis of atypical hyperplasia.

Interpretation of the Gail model is the following: at a risk ≥ 1.66% the patient is eligible for chemoprevention therapy with hormonal agents over the next 5 years.(4)

The Claus model uses information about the family medical history, incorporating and analyzing the following items: the age of the patient, first and second-degree relatives with breast cancer, the age of onset of these cancers in first or

second degree relatives, a family history positive for ovarian cancer.

The BRCA PRO model incorporates and analyses information from the family medical history: the BRCA1 or BRCA2 mutation frequency, bearer's mutant penetrance, the phenotypic status of the patient (affection, unaffected or unknown), the age of the relatives of first or second degree presenting BRCA mutations. The model shows a 49% predictive value that will develop breast cancer.(5)

Hormonal treatment (table no. 2) is indicated in all cases of breast cancer with positive receptors, having a significant efficiency in decreasing disease progression and mortality. And also, according to Gail's model interpretation, if the risk is higher ≥ 1.66%, then the patient is eligible for hormonal chemoprevention therapy over the next 5 years.

Ovarian ablation will lead to eliminating an important source of endogenous estrogens.

Ovarian ablation is performed individually, according to the patient's menopausal status (pre / postmenopausal). It can be done by 3 methods:

a. chemically (GnRH analogs) - as an alternative to cases where patients are not eligible or do not accept surgical treatment. GnRH analogues achieve a profound inhibition of the pituitary-ovarian axis.
b. surgically (classical /laparoscopic - oophorectomy /salpingectomy). I mention that I opt for this type of intervention having the additional effect of this type of intervention, namely the reduction of the risk of developing ovarian cancer, especially in cases with BRCA 2 genetic mutations).
c. radiologically (indicated exceptionally).

Thus, we can draw the following therapeutic concepts:

- in pre-menopausal breast cancer patients, surgical ovarian ablation is preferred followed by anti-estrogen therapy (selective estrogen receptor modulator (SERM), especially Tamoxifen).
- in postmenopausal patients, first-line therapy is considered to be Tamoxifen selective anti-estrogen, with the second option of aromatase inhibitor therapy within the context in which tumour cells have developed secondary resistance to Tamoxifen therapy after a 5-year administration period. The mechanisms of action of the two above-mentioned therapy lines are:

a. Tamoxifen inhibits the growth of mammary tumour cells by a competitive mechanism at estrogen receptors level.
b. Aromatase inhibitors decrease the peripheral conversion of testosterone and androstenedione to estriol and estrone, thus lowering the level of circulating estrogens regardless of their origin (gonadal or extragonal).(6)

Table no. 2. Ovarian chemistry ablation - protocol for the administration of hormonal therapy (6)

Hormonal therapy			
Product	mg	Day	Interval/duration
Hormone therapy/ Premenopause			
Gn RH / LH RH analogue:	3,6	1	28 days / 2 years
Goserelin	3,6 mg s.c. at 28 days; 10,8 mgs.c. at 12 weeks		
Leuprorelin	3,7 mg s.c. at 28 days; 11,25 mg s.c. at 12 weeks		
SERM - Tamoxifen	20	daily	5 years
Hormone therapy/ Postmenopause			
SERM - Tamoxifen	20	daily	5 years
Aromatase inhibitors:			
- Anastrozole	1mg p.o. daily		
- Letrozole	2,5 mg p.o.daily		
- Exemstane	25 mg p.o. daily		

We conclude with the strengthening of the concept of the hormone-prophylactic therapeutic line in a risk context ≥ 1.66% according to the Gail model, the patient being eligible within the next 5 years for chemoprevention therapy with hormonal agents.

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