Analysis of odds ratio of increased relative risk of developing breast cancer in different groups of women

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Summary

Taking into account the large number and variety of factors of breast cancer there is constant need and necessity to monitor the risk of developing the disease. It is important to take preventive actions - health education concerning lifestyle and possible ways to modify unhealthy aspects. Quantitive assessment of risk of developing invasive breast carcinoma can be performed using the Gail model (GM). This method is designed to estimate relative and cumulative risk during the entire lifetime or at a certain age of a patient, considering risk factors. It is possible to identify women with increased risk of breast carcinoma and to choose a proper diagnostic path. The purpose of this study was to estimate the relative risk (RR) and to analyze the odds ratio (OR) of increased risk of developing breast cancer. The participants in the study were healthy women with no focal changes in mammary glands and women with diagnosed malignant or benign breast neoplasms. The total number of participants was 555 females aged 35-70 years. The study was carried on in the Great Poland and Lubuskie provinces between 2005 and 2006. High 5-year relative risk of developing breast cancer assessed by the Gail method, proved that this method was a useful tool in confronting reality. In classification of women to a group of increased risk of breast carcinoma, apart from assessment by the Gail method, factors like: BMI, education, medical interventions in puerperium and number of cases of familial invasive cancers should be taken into account.

Key words: Breast cancer; Risk factors.

Introduction

Taking into account a large number and variety of factors related to breast cancer there is constant need and necessity to monitor the risk of developing the disease.

According to Colditz *et al*. [1] identification and elimination of risk factors can significantly (up to 50%) reduce the morbidity of breast cancer.

It is necessary to take preventive action - health education concerning lifestyle and possible ways to modify it. Cancer preventive programs are also very crucial. Their aim is early diagnosis and as a result more effective and less deforming treatment can be achieved. Early diagnosis including regular self-examination, breast examination performed by general practitioners or specialists, and easy access to mammography is of great importance. A critical issue is to make patients conscious of the real threat of the disease [2].

Unfortunately in the Polish literature neither data concerning the number of women with increased risk of breast cancer nor epidemiological data are available.

Quantitive assessment of risk of developing invasive breast carcinoma can be performed using the Gail model (GM). This method is designed to estimate relative and cumulative risk throughout life or at a certain age of a patient, considering risk factors. It makes it possible to identify women with increased risk of breast carcinoma and to choose the proper diagnostic path.

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Material and Methods

The participants of the study were healthy women with no focal changes in mammary glands and women with diagnosed malignant or benign breast neoplasms. The total number of participants was 555 females aged 35-70 years. The study was carried on in Great Poland and Lubuskie province between 2005 and 2006.

The inclusion criteria for the first group (healthy; BZ) (n = 292) was an examination performed by a specialist which revealed no pathological changes and normal mammography and/or ultrasound (US) examination.

The second and third group consisted of patients who were according to histo-pathological examination of material gained by breast biopsy or operation: benign changes (D; n = 184) and malignant lesions (CA; n = 79).

Every patient voluntarily filled out an anonymous questionnaire consisting of 43 questions about socioeconomic conditions, menstrual and obstetric history, breastfeeding, puerperium and hereditary transmission. They also answered questions concerning their life-style and healthy behaviour (breast self-examination, attitude towards these exams, dietary habits, alcohol consumption and physical activity).

For every patient we estimated the risk of breast cancer using the Gail method. Two aspects of risk were considered: relative risk (RR) and prediction of absolute risk. RR is the ratio of risk of developing breast cancer in relation to age in women with risk factors compared to the risk of women of the same age but without risk factors.

Absolute risk is the probability that women with specified risk factors will develop breast cancer in a specified age range.

The Gail model takes into account factors like patient's current age, age at menarche, age of first live birth, number of previous breast biopsies, atypical hyperplasia, the number of first-degree relatives with breast cancer and race. On the basis

of these risk factors it is possible to calculate risk of developing breast cancer. To calculate relative and absolute risk an interactive computer program was used. A Gail score > 1 was estimated as the increased risk of developing breast cancer.

For each risk factor the odds the ratio (OR) was calculated.

Risk factor	Present	Absent	Total
Study group	a	b	a+b
Control group	c	d	c+d
Total	a+c	b+d	a+b+c+d

We assessed odds of developing breast cancer in cases with presence of a risk factor:

$$\text{Odds}^{yes} = \frac{\frac{a}{a+c}}{1-\frac{a}{a+c}}$$

and when a risk factor was not present:

$$\text{Odds}^{no} = \frac{\frac{b}{b+d}}{1-\frac{b}{b+d}}$$

We calculated OR with a 95% confidence interval (CI).

$$\text{OR} = \frac{a*d}{c*b}$$

Statistical analysis was performed using StatSoft, Inc. (2005), STATISTICA (data analysis software system), v 7.1 and Cytel Studio v 7.0.0 (2005).

For the study approval of the Bioethical Commision of K. Marcinkowski University in Poznan was obtained.

Results

Relative risk of developing breast cancer assessed by the Gail method

On the basis of the Gail method, taking into account risk factors, we estimated individual five-year risk of developing breast cancer for each patient as well as five-year risk for a population of the same age but without risk factors. The results of both groups (D - with benign changes and BZ - no changes in breast) were as follows: mean value of individual 5-year risk in group D was 1.2 and in group BZ - 0.7. The differences between these groups were statistically significant ($p < 0.001$). Estimated mean value of individual five-year risk for patients with malignant breast lesions (CA) was the highest of the three studied groups - 3.28. Mean values of five-year risk for the healthy population were: group D - 0.6 and group BZ - 0.5. The differences between groups were statistically significant ($p < 0.001$).

The above-mentioned results together with minimum and maximum values and median are presented in Tables 1 and 2.

OR of an increase in RR of development of breast carcinoma.

Among patients in the BZ group, 22.6% of women were at increased risk of developing breast cancer (RR > 1 estimated according to the Gail method); for the remaining 77.4% in this group the risk was decreased (RR ≤ 1). We analyzed risk factors in both subgroups, and parameters with statistically significant differences are shown in Table 3.

Table 1. — *Mean values of 5-year relative risk for studied groups*.

Groups	Mean ± SD	Range (min-max)	ANOVA $p < 0.05$
CA - group with breast cancer	3.28 ± 1.88	0.60-10.8	CA vs BZ
D - group with benign breast tumors	1.2 ± 0.9	0.1-7.4	D vs BZ
BZ - group with no changes	0.7 ± 0.5	0.1-4.7	

Table 2. — *Mean values of 5-year relative risk for the healthy population*.

Groups	Mean ± SD	Range (min-max)	ANOVA $p < 0.05$
D - group with benign breast tumors	0.6 ± 0.2	0.1-1.4	D vs BZ
BZ - group with no changes	0.5 ± 0.2	0.1-1.1	

Table 3. — *Risk factors with statistically significant differences in the BZ group in both subgroups with increased and decreased risks estimated by the Gail method*.

Parameter	*p* value
Age	0.001
BMI	0.03
Age at menarche	0.009
Age of first pregnancy	0.001
Number of deliveries	0.003
Age at first delivery	0.001
Fears concerning cancer	0.04
Familial cancer history	0.0003

BMI: Body mass index.

Among patients with neoplastic changes in the breast, 97.37% were at increased risk (RR > 1 estimated according to the Gail method) while in one patient (2.67%) risk was decreased.

In the BZ group we also assessed the OR of increased risk of developing breast cancer for chosen risk factors.

OR according to BMI

Odds ratio of an increased RR of developing breast cancer for women with a BMI ≥ 25 was OR = 2.094; 95% CI 1.16-3.77 in comparison to patients with a BMI within normal ranges (18.5-24.9).

OR according to menarche

Odds ratio of an increased RR of developing breast cancer for women who had menarche at the age of 12 was OR = 0.20; in comparison to those who experienced menarche at the age of 11; and at the age of 13, 14 and > 14 - OR = 0.16, OR = 0.13 and OR = 0.12, respectively (Table 4).

Table 4. — *OR according to age at menarche in patients with increased and decreased risk in the BZ group*.

Age at menarche	OR	CI 95%
12 years	0.20	0.05 - 0.83
13 years	0.16	0.04 - 0.62
14 years	0.13	0.03 - 0.50
> 14 years	0.12	0.02 - 0.49

OR according to education

Odds ratio of an increased relative risk of developing breast cancer for women with a secondary education was OR = 1.09; and for those with a university degree it was OR = 0.49, in comparison to women with only a technical education (Table 5).

Table 5. — *OR according to education for women with increased and decreased risk in BZ group*.

Education	OR	CI 95%
Secondary	1.09	0.57 - 2.06
University	0.49	0.24 - 1.00

OR for medical interventions in puerperium

Odds ratio of increased relative risk of developing breast cancer for women who had problems with lactation during puerperium requiring medical intervention was OR = 2.16 (95% CI 1.02-4.55), in comparison to those who did not experience problems with breastfeeding.

OR for positive familial cancer history

Odds ratio of increased relative risk of developing breast cancer for women who had one first-degree relative with cancer was OR = 1.47. When cancer occurred in more than one first-degree relative OR was 6.0 in comparison to women who had no cancer history in first-degree family members (Table 6).

Table 6. — *OR according to the number of cancers for women with increased and decreased risk in the BZ group*.

Number of familial cancers	OR	CI 95%
1	1.47	0.78 - 2.77
> 1	6.0	2.49 - 14.44

Discussion

In spite of the fact that breast cancer often seems to attack at random, for many years factors influencing this situation have been discovered. The majority of cases of breast cancer are probably connected with environmental factors and lifestyle. Studies carried out in the last three decades have made it possible to estimate the risk of developing breast cancer [3]. According to current knowledge, modification of risk factors may contribute to a reduction in breast cancer. Individual assessment performed by selecting a group of women with increased risk can help reduce mortality [4, 5].

Numerous clinical control and cohort studies have shown that obesity may increase the risk of developing breast cancer [6-8].

It has been confirmed in our studies that the majority of women suffering from breast carcinoma were characterized by increased BMI. We also observed a relation between increased BMI and risk of developing breast cancer in patients who were, according to the Gail method, classified to a group of patients with decreased risk (RR < 1).

In retrospective studies a strong positive correlation between BMI and development of breast cancer in postmenopausal women has been reported [9, 10]. According to epidemiological data concerning the Italian population, 20% of breast cancer in postmenopausal women and 27% in those older than 70 is due to overweight and obesity [11].

Time of exposure of breasts to ovarian hormones is considered as one of the more important and maybe even the most crucial factor among all known risk factors of breast cancer. A longer time of breast exposure to estrogens could be natural and result from early menarche and late menopause or could be caused by using contraceptive drugs or hormonal replacement therapy in the postmenopausal period.

According to Mazurkiewicz [12] the risk of breast cancer is three times greater in women who had menarche before they were 11 in comparison to those who experienced late onset – after the age of 16. Our results show that the OR of an increased RR of breast cancer significantly decreased in patients who had menarche after age 14 in comparison to patients who had menarche at the age of 11.

According to Budner *et al*. [13] relative risk for the age of menarche was RR = 1.2-1.5 for women with menarche before 12 years of age in comparison to women who experienced it after 12 years of age. The period between menarche and the first delivery also plays a crucial role. The shorter this time is the risk of breast cancer decreases. It is connected with the number of menstrual cycles within that period and shorter or longer exposure to carcinogens [14-16].

Godlewski [15], Tavani *et al*. [16] and Becher *et al*. [17], are of the opinion that the first delivery at earlier age and higher number of deliveries are protective factors against breast cancer. They also consider long-term breastfeeding to be protective.

Jernstromi *et al*. [18] revealed that the length of breastfeeding was connected with risk reduction and that for each month OR was 0.98 (95% CI 0.97-0.99). They also found that breastfeeding was protective and decreased risk among patients – carriers of mutated BRCA1 genes. In this group OR decreased in patients who breastfed longer that 12 months in comparison to those who did not breastfeed (OR = 0.55; 95% CI 0.38 - 0.80).

In our study we also calculated OR of breast cancer in women who during lactation experienced problems in which medical intervention was necessary. In this case OR was 2.25 (95% CI 1.20-4.19) in comparison to

women who had no such problems. OR concerning this parameter was significantly increased (more than two times greater) in patients who were classified to a group of decreased risk according to the Gail method (OR = 2.16; 95% CI 1.02-4.55). Although Gail did not take this parameter into account, our results suggest that medical intervention may be of great significance in selecting a group with increased risk, at least for breastfeeding women.

Women's education as well plays an important role. In the study of Graj and Grodecka-Gazdecka [19], among women suffering from breast cancer, the most numerous group had a secondary education (48.4%) while a university degree and technical education were 25.2% and 26.5%, respectively. In our study we observed a similar finding: 55.7% of patients had a secondary education, 21.52% a university degree and 22.78% a technical education. Nevertheless, after analyzing the OR of increased RR of breast cancer we found an opposite tendency in women with a university degree (OR = 0.49; 95% CI 0.24-1) in comparison to women with a technical education – which shows that better educated patients are less likely to have increased risk of breast cancer.

Studies carried out in highly developed countries reveal that breast cancer occurs more frequently in well-educated women – inhabitants of big cities. It could be connected with lifestyle which predisposes to breast cancer development (late first delivery, earlier menarche, childlessness, fewer pregnancies) or with higher health awareness and responsiveness to control examinations resulting in earlier diagnosis when the cancer is in early stage [15].

Hereditary transmission, especially when the mother and sister suffered from breast cancer, is a very crucial risk factor. In this group risk increases almost 14 times [20].

According to Budner and Przybylski [21] RR of developing breast cancer for women with first degree hereditary transmission is RR = 1.4-13.6 and second degree – RR = 1.5-2.0. Familial occurrence of breast cancer may be connected with similar lifestyle or have a genetic basis; 5-10% of all breast neoplasms are hereditarily predisposed. They are the result of impairment in BRCA1 and BRCA2 genes, which are also responsible for hereditary occurrence of ovarian cancer.

The Gail model is based on non-genetic factors and the majority of these result in development of invasive breast cancer, whose basis is endocrinological. Although in the Gail model the number of first-degree relatives suffering from cancer is taken into account, it considers neither the age of diagnosis nor concomitant cancers (e.g., ovarian cancer – its presence increases the possibility of discovering mutations in BRCA1 and BRCA2 genes). In our study we analyzed OR of increased RR of developing breast cancer in relation to familial cancer history (not only breast cancer) in a group of patients classified by the Gail method to a group at decreased risk (RR < 1). Odds ratio for women with one first-degree relative who suffered from cancer (breast, ovarian, colorectal or other) was: OR = 1.47 (95% CI 0.78-2.77) and if more than one first-degree relative – OR = 6.0 (95%CI 2,49-14,14). This would make it necessary to add to the Gail model questions concerning the number and type of cancers in a patient's family to assess relative risk more precisely.

Ostrowska *et al*. [22] revealed similar results – occurrence of breast, ovarian and other cancers together significantly differentiated compared groups. When analyzing only breast cancers no statistically significant difference among study groups was observed in their study.

It seems that recognition of intensity of individual risk factors of developing breast cancer makes it possible to prepare more effective educational and preventive programs as well as to spend money for prevention in a more rational way.

Conclusions

– High 5-year relative risk of developing breast cancer assessed by the Gail method proved that this method is a useful tool in confronting reality.

– In the classification of women to a group at increased risk of breast carcinoma, apart from assessment by the Gail method, factors like BMI, education, medical interventions in puerperium and number of cases of invasive familial cancers should be taken into account.

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