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The Applicability of the Gail Model in Iranian Population

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Abstract

Introduction: Gail model is one of the most important models for the evaluation of breast cancer risk between US white females. According to genetic diversity, there is a possibility of affecting the efficiency of the Gail model in risk assessment of breast cancer among Iranian populations. In this study, the Gail model efficiency in specifying the risk of breast cancer in Iranian population was evaluated.

Methods: This was a case-control study. The case group was formed of the referrals to Breast Cancer Research Center, Academic Center for Education Culture and Research (ACECR), who were affected by different types of aggressive cancer.

Results: A total of 416 patients with breast cancer and the same number in the control group were considered during the study. There were no meaningful statistical differences in age at menarche, age at first live birth, and nulliparous women between case and control groups. The average of five-year risk of breast cancer in the case and control groups had no statistically significant difference. Chemoprevention was only eligible for 7.2% of the patients based on 1.67% five-year risk. In addition, there was no statistically meaningful difference between comparative risk and breast cancer risk in a lifetime.

Conclusions: The low risks estimated by the Gail model among patients with breast cancer as well as the absence of meaningful statistical difference in the estimated risks by this model between the case and control groups showed that the Gail model had insufficient efficiency in determining breast cancer risk in the Iranian society.

INTRODUCTION

During the past two decades, clinical studies on breast cancer majorly focused on finding effective diagnosis methods and standardization of the treatment procedure. Despite noteworthy advances in this field, breast cancer still remains the most widespread malignant cancer and the second leading cause of death among women [1]. Considering the widespread nature of breast cancer, preventive strategies merit more attention.

The first step in preventing breast cancer is identifying the risk factors. The most important risk factors are 1- aging [2], 2- reproduction-related factors such as early menarche, late menopause, nuliparity, and advanced maternal age [3], 3- benign lesions of breast [4], 4- lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) [5], 5- previous history of breast cancer [6], 6- positive family history of breast cancer [7], and 7- environmental factors such as radiation, hormone replacement therapy (HRT) and oral contraceptives [8, 9].

Using statistical models, the risk of breast cancer is quantitatively calculated based on analyzing all the risk factors. In fact, breast cancer risk assessment model is a statistical model which calculates the probability of the occurrence of cancer in a person based on assessing all the related risk factors. Therefore, it is possible to provide each patient with necessary recommendations to prevent breast cancer or detect it early in primary phases. Breast cancer risk assessment models are mostly used to identify people that have a high risk of developing this type of cancer. This will help provide the identified people with preventive

medicines or mastectomy [10, 11].

The most accepted models of breast cancer risk assessment are the Gail, the Claus and the BRCA PRO Models. The Claus model calculates the risk of breast cancer based on age and family history, including first- and second-degree relatives with breast cancer. BRCAPRO is a statistical model to assess the probability of an individual to carry a germline deleterious mutation of the BRCA1 and BRCA2 genes, based on family history of breast and ovarian cancer [10].

The Gail model can quantitatively calculate the risk of breast cancer in a patient based on personal characteristics; however, family history has little relevance [11]. This model has been developed based on the BCCDP (Breast Cancer Detection Demonstration Project) study, which included 280,000 females in 28 states of America. Risk factors in this model include age of menarche, first-live-birth age, number of first-degree relatives with breast cancer, and the number of previous biopsies and the results. In order to assess the overall risk, first, the relative risk of each factor is calculated; then, the scores of relative risks are combined to calculate the five-year risk of breast cancer [12].

Some professionals question the efficiency of the Gail Model in assessing the risks of breast cancer in individuals, since the model does not consider the age of menopause. Furthermore, incorporating the total number of biopsies regardless of the results may seem unreasonable. This model was developed before the emergence of genetic examining; therefore, it is not recommended for patients whose family history reveals an inheritance pattern of breast cancer. Nonetheless, the Gail Model remains the most used tools in clinics for assessing the risk of breast cancer, and its efficiency continues to be assessed and studied [13].

Despite possible differences in genetic background, environmental conditions and possibly a different risk pattern in Iran [14], no study has been conducted on the applicability of the Gail Model in the Iranian population.

Under the light of this, the Breast Cancer Research Center (BCRC) team intends to assess the risk of breast cancer in Iranian females based on the Gail Model and compare the results with the control group. The result of the study will help to determine the applicability of the Gail Model in Iranian females and will prepare the ground for further research on evaluation and management of the risk of breast cancer.

METHODS

In this case-control study, 832 women referred to BCRC were enrolled. The examined cases comprised women who were confirmed with breast cancer based on histopathology reports and the matched control population was selected from women who had been referred for routine annual checkups with no histories of breast cancer and the results of all their screening procedures including mammography were normal. Considering that the risk of breast cancer increases with age, the control and case groups were matched based on age. All the participants were asked to sign a written consent prior to the study. All the gathered information was treated as confidential.

The clinical data of patients were studied and the required information was collected by means of structured questionnaires. In addition, the requested information about control groups was assembled via interviews. The risk of breast cancer was calculated using CA.Gen 4.3.2 software based on the gathered information on the control and case groups, and SPSS version 13 were used to analyze the data. T-test was used to analyze the relation between the two quantitative variables, and the chi-squared test was applied to analyze the relation between the qualitative variables.

RESULTS

During the study, a total number of 416 women in each group of case and control were studied and information about the risk factors in the Gail model was gathered from them. The average age of the patients was 46.12 (95% CI, 45.15-47.09) and they were categorized in five-year age groups. The age group of 46-50 had the highest frequency (Table 1).

Based on the pathology report, 85.5% of the patients had invasive ductal carcinoma and the rest of them were categorized in other groups such as the invasive lobular carcinoma and medullary cancer groups (Table 2).

Comparison of Risk Factors in the Gail Model in Case and Control Groups

Menarche Age

The menarche age of the study population varied from 9 to 18 years old. The menarche age of 13 had the highest frequency in both case and control groups, which included 34.4% and 31.5% of the individuals in control and case groups, respectively. There was no significant difference between the age of menarche in the case and control groups.

Number of Previous Biopsies

In the case group, 26 individuals (6.3%) had undergone biopsy for at least one time. Of this number, 21 patients had undergone biopsy once, three for two times and two of them for three times. The result of the biopsy in five patients (23.8% of the biopsy results) was atypical ductal hyperplasia. In the control group, nine patients (2.2%) had undergone breast biopsy for at least one

Table 1: Number and Percent of Women in Control and Case Groups

	Number of Patients in Case Group	Number of Patients in Control Group	Percent
26-30	18	18	4.32
31-35	50	50	12.01
36-40	66	66	15.86
41-45	75	75	18.02
46-50	81	81	19.47
51-55	42	42	10.09
56-60	47	47	11.29
61-65	24	24	5.76
66-70	9	9	2.16
71-75	9	9	0.96
Total	416	416	100

Table 2: Average of 5-Year, Lifelong and Relative Risks of Breast Cancer Based on the Tumor Pathology

	Number of Patients	Average 5 Year Risk (%)	Average Lifelong Risk (%)	Average Risk
Invasive Ductal Carcinoma	356	0.8	9.54	1.48
Invasive Lobular Carcinoma	24	1.39	11.18	1.92
Medullary Carcinoma	10	0.64	9.17	1.47
Squamous Cell Carcinoma	1	0.96	11.01	1.6
Adenocarcinoma	1	0.36	6.94	0.94
No Pathology Report	24	0.90	8.44	1.32
Total	416	0.84	9.56	1.49

time. However, atypical ductal hyperplasia was not reported in any of them. There was a meaningful relation between the percentage of patients who had undergone biopsy in the control and case groups (P = 0.003).

First Live Birth Age

Of the patients with cancer 12.5% (52 individuals), and 11.5% (48 individuals) in the control group were nullipara. Among the individuals who had at least one childbirth, the average age at the birth of the first child in the case group was 21.22 years old (95% CI, 20.7-21.74) and it was 22.01 (95% CI, 21.53–22.49) in the control group; the difference between the two figures was statistically meaningful (P = 0.029).

History of Breast Cancer among First-Degree Relatives

There was a family history of breast cancer among first-degree relatives in 6.7% (28 patients) of the case group. From them, 26 patients had a history of breast cancer in one of their first-degree relatives, one of them had a history of breast cancer in two of her first-degree relatives and one of them had the history of breast cancer in three members of his first-degree relatives. Among the members of the control group, there was a history of breast cancer among first-degree relatives in 11.8% (49 women). There was a meaningful relation between patients with family history of breast cancer in the case and control groups (P = 0.012)

Five-Year Risk of Breast Cancer

The average of five-year risk of breast cancer in the case group was 0.84% (95% CI, 0.77-0.91%) (Table 2). In 85.9% of the case group, the calculated risk for the patient was lower than that of the normal population of the same age and race. The risk was higher in 58 patients (14.1%). However, the five-year risk of breast cancer in 30 patients (7.2%) was higher than 1.67%.

The average of five-year breast cancer risk in the control group was calculated to be 0.85% (95% CI, 0.79%-0.92%). The risk was lower in 84.46% (351 patients) than that of the population of the same age and race. No significant difference was observed in the average five-year breast cancer risk between the members of case and control groups (P = 0.74).

Lifetime Risk of Breast Cancer

The average lifetime risk of breast cancer was calculated to be 9.56% (95% CI, 9.18%-9.94%). Patients with invasive lobular carcinoma had the highest risk of breast cancer (Table 2). The average lifetime risk of breast cancer in the control group was calculated to be 9.81% (95% CI, 9.42%-10.2%). No meaningful difference was observed in the average lifetime risk of breast cancer between the members of case and control groups (P = 0.37).

Relative Risk of Breast Cancer

The average of the relative risk of breast cancer in the case group was calculated to be 1.49 (95% CI, 1.41%-1.57%). The highest risk belonged to patients with invasive lobular carcinoma (Table 2). The average risk of breast cancer in the control group was 1.50. No statistically significant difference was observed in the average risk of breast cancer between the members of case and control groups. The average of the relative risk of breast cancer based on the age of menarche (group A) was calculated to be 1.069 in the case group and 1.063 in the control group. The difference was not statistically significant (Table 3).

The average relative risk based on age and number of biopsies (group B) was 1.05 in the case group and 1.01 in the control group. The difference was statistically meaningful (P = 0.002) (Table 4).

The relative risk of breast cancer based on first-degree relatives with a history of breast cancer and age of first childbirth (group C) was 1.35 in the case group and 1.46 in the control group. The difference was statistically meaningful (P = 0.016) (Table 5).

DISCUSSION

Gail model was originally developed to assess breast cancer risk in white females in the United States and it seems necessary to be studied in other countries. Various studies have indicated its inapplicability in the Republic of Czech [15], Spain [16], Italy [17], and among African-American females of the United States [18]. In the present study, breast cancer risk for the patient was calculated and the results were compared with females of similar age who had attended BCRC with normal screening mammography in the Iranian population. No significant difference was observed between breast cancer patients and the control group regarding the age of menarche. This result disagrees with those of two large-scale studies which indicated that premature menarche is associated with breast cancer [19, 20], and concurs with those of Mckarem et al. which studied 124 patients with invasive breast cancer and found that the

Table 3: Comparison of Relative Risk of Breast Cancer Based on Age of Menarche in Control and Experiment Groups

	Number and Percentage of Experiment Group Members	Number and Percentage of Control Group Members
Relative Risk of Group A = 1	167 (40.1)	184 (44.2)
Relative Risk of Group A = 1.1	210 (50.5)	200 (48.1)
Relative Risk of Group A = 1.2	39 (9.4)	32 (7.7)

Data in table are presented as No. (%)

Table 4: Comparison of Relative Risk of Breast Cancer Based on Age and Biopsies in Control and Experiment Group

	Number and Percentage of Experiment Group Members	Number and Percentage of Control Group Members
Relative Risk of Group B=1	390 (93.8)	407 (97.8)
Relative Risk of Group B=1.3	7 (1.7)	3 (0.7)
Relative Risk of Group B=1.6	-	1 (0.2)
Relative Risk of Group B=1.7	14 (3.4)	5 (1.2)
Relative Risk of Group B=1.9	5 (1.2)	-

Data in table are presented as No. (%)

Table 5: Comparison of Relative Risk of Breast Cancer in Control and Experiment Group

	Number of Experiment Group Members	Number of Control Group Members
Relative Risk of Group C = 1	133	103
Relative Risk of Group C = 1.1	1	0
Relative Risk of Group C = 1.2	123	141
Relative Risk of Group C = 1.5	114	106
Relative Risk of Group C = 1.9	19	22
Relative Risk of Group C = 2.6	12	8
Relative Risk of Group C = 2.7	4	13
Relative Risk of Group C = 2.8	8	19
Relative Risk of Group C = 4.9	1	1
Relative Risk of Group C = 6.8	1	3

age of menarche was less than 12 in 18% of them [21].
The results of the present study confirm the four case studies by Mahouri et al. in south of Iran [22], Naini et al. In Mazandaran Province [23], Yavari et al. in Tehran Province [24], and Ebrahimi et al. in BCRC [25].
Higher first-birth age and nulliparity are associated with increased risk of breast cancer in the Gail model, but the results of studies do not indicate any significant relation between the mentioned factors and breast cancer risk. No significant difference was observed between the percentage of nullipara patients in the case and control groups in this study. Furthermore, contrary to the initial assumptions, the average age of first live birth in patients with breast cancer was 1.2 years less than the control group, which was statistically significant. However, this difference had no remarkable effect in calculation of breast cancer risk using the Gail model. There are four groups in terms of first-birth age in the Gail model: < 20, 20-24, 25-29 and ≤ 30. In the present study, no significant difference was observed between the number of members in the case and control age groups. Considering the rather lower average of first-birth age in the case group in comparison with the control group, the difference had no significant effect on the calculation of the risk of breast cancer in the case and control groups. This finding agrees with the reports of Novotny et al. and Mckarem et al. [15, 21].
The results of the studies conducted on the Iranian population confirm the present findings and indicate that there is no significant relation between nulliparity and breast cancer risk in Iran [22, 25].
In the present study, the number of breast biopsies in the patients with breast cancer was three times more than the control group; there was a statistically significant difference. This indicated that the increased number of breast biopsies is associated with increased breast cancer risk. It is worth mentioning that the previous biopsy showed atypical ductal hyperplasia in five persons in the case group, while it did not show atypical ductal hyperplasia for anyone in the control group. This study indicated that atypical ductal hyperplasia was associated with the increased risk of breast cancer, as demonstrated in previous studies.
Our result was confirmed by Mackarem et al. [21] and Novotny et al. [15]. In addition, in a study conducted by Mahouri et al., 4.2% of patients with breast cancer and 2.4% of the control group had a history of benign breast diseases and the difference was not statistically meaningful [22].
In the Gail model, only the number of first-degree relatives with breast cancer has been considered, but it fails to mention the number of second-degree relatives who have breast cancer as well as the family history of ovarian cancer. Therefore, the risk of breast cancer among individuals with a highly positive family history of breast cancer might stand below the expected figure [26]. As in the present study, three first-degree members of a patient's family were diagnosed with breast cancer at the ages of 32, 37 and 44. Genetic testing for BRCA 1/2 mutation has been indicated according to BRCAPRO model. The five-year mean and lifelong risks of breast cancer are 6.2% and 43.7%, respectively, according to the Claus model. However, the five-year and lifelong risks of breast cancer were equal to 0.56% and 32.4%, respectively, according to the Gail model. These results showed that the Claus estimates were lower than the Gail estimates. This finding agrees with the reports of Anne McTiernan et al. [26] and Mohammadbeigi et al. [27]. Mohammadbeigi et al. showed that the Gail model overestimated the risk of breast cancer in Iranian females. They also indicated the factors most affecting the difference in risk estimates.
The present study showed that there was a history of breast cancer among first-degree relatives in 6.7% of the patients with breast cancer. Two studies carried out on the Iranian population by Ebrahimi et al. and Mahuri et al. showed that there was a history of breast cancer among first-degree relatives in 6.6% and 8.3% of patients with breast cancer, respectively. In these two studies, there was a direct relationship between history of breast cancer among first-degree relatives and risk of breast cancer [22, 25].
In the present study, contrary to expectations, the history of breast cancer among first-degree relatives in the control group was relatively higher compared to the group of patients with breast cancer (P = 0.012, 6.7% versus 11.8%). This was probably because people with the history of breast cancer in their families are more concerned with the diseases associated with breasts and therefore refer to medical centers for mammography screening more often.
As mentioned earlier, no meaningful difference in relative risk of breast cancer with five-year and lifelong risks of breast cancer was established in case and control groups. This indicates that Gail model has low efficiency in predicting individuals with risk of breast cancer and cannot produce a reliable estimate of risk of breast cancer among the Iranian population. The fact that the average five-year risk of breast cancer in the case group was pretty low (0.84%), and that based on the lifelong risk of breast cancer risk of 10% of the case group could be predicted, confirms this. Furthermore, based on the 1.67% five-year risk, only 7.2% of the breast cancer patients were placed in the high risk group and preventive medications were indicated for them. Only in 14.1% of the patients, the estimated risk by the Gail model was higher than the risk for individuals matched for age and gender. This also confirms the Gail model's low efficiency in making estimates of breast cancer risk in the Iranian population and its failure to identify those at high risks.
The inefficiency of the Gail model in the Iranian population can be due to different breast cancer risk factors in this population and in the United States population,

based on which the Gail model has been defined. In the above mentioned study, the number of previously performed breast biopsies was considered as the only underlying factor for breast cancer and there was no meaningful difference between the age of menarche, nulliparity, and age of first childbirth among those in case and control groups. This was also confirmed by four other case-control studies conducted over the Iranian population. Therefore, it is possible that some factors considered in the Gail model for determining the relative risk of breast cancer play no role for risk estimation among Iranians. Therefore, the Gail model will not produce a reliable estimate of breast cancer risk in the Iranian population. Conducting further studies for determining breast cancer risk factors in the Iranian population and developing a local model for risk estimation of breast cancer seems necessary.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

The ethics committee of breast cancer research center of ACECR approved the study.

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