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Original Article

Identify Breast Cancer Risk Factors Using the Gail Assessment Model in Iraq

Abdulhussain Fadhil, A[1*], Abdul Hussein, H[2], Jawad, M[3], Khaled Younis Albahadly, W[4], Hussein, A. S[5], Abed Jawad, M[6], Hamza Samein, L[7], Mihdi Mohammed, N[8], Kasim Sherif, B[9], Jalil Obaid, A[10]

1. College of Medical Technology, Medical Lab Techniques, Al-Farahidi University, Baghdad, Iraq
2. College of MLT, Ahl Al Bayt University, Kerbala, Iraq
3. Al-Manara College for Medical Sciences, Maysan, Iraq
4. University of Al-Ameed, College of Pharmacy, Kerbala, Iraq
5. Radiological Techniques Department, Al-Mustaqbal University College, Babylon, Iraq
6. Al-Nisour University College, Baghdad, Iraq
7. The University of Mashreq, Baghdad, Iraq
8. Department of Pharmacy, Mazaya University College Dhi Qar, Iraq
9. Department of Pharmacy, Ashur University College, Baghdad, Iraq
10. Medical Laboratory Techniques Department, Hilla University College, Babylon, Iraq

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Corresponding Author: alialshamary412@yahoo.com

Abstract

The prevalence of breast cancer (BC) has increased significantly in the last 50 years worldwide. This increase may be because more women today have mammograms and, as a result, are more known to have cancers. At the same time, the theory is growing that many other factors contribute to the increase in cancer rates. The current study tried applying the Gail assessment model to identify hormonal and familial risk factors that may be important for BC in Iraq. Patients aged 30 years and over with all known risk factors for BC were selected for the study group. The selected patients were divided into two groups. Group 1: Patients diagnosed with non-proliferative lesions who have had a breast biopsy performed at least three years before; Group 2: Controlled patients. The individual risk of BC for patients in groups 1 and 2 was calculated using the Gale model. In addition to groups 1 and 2, we identified two other groups. Group 3: Groups 1 and 2 of patients without BC at the end of the 3-year follow-up period; Group 4: Patients who have undergone BC surgery. Multiple regression tests assessed all known risk factors in groups 3 and 4 to determine the risk factors for the development of BC in Iraq. The results show that Gail's assessment model is a reliable example of calculating the risk of developing BC. The model results show that the significant risk factor for BC in Iraq is not hormonal but genetic or familial. Current research also shows that the risk of developing BC increases significantly with age. It was concluded that there are genetic factors, and the risk of developing BC increases with age, but hormonal features do not cause a significant increase in risk. Identifying risk factors in causing disease in the community makes it possible to prepare codified plans to control and treat the disease.

Keywords: Gail Model, Breast cancer, Risk factors of BC, Iraq

1. Introduction

Breast cancer is one of the most common cancers, caused by various factors such as genetics, environment, and lifestyle, which have a global distribution. Its prevalence, mortality, and survival rates are significant (1). Understanding that most breast

tumors are benign, not cancerous or malignant, is essential. Non-cancerous breast tumors grow abnormally but do not spread to another organ (2). These tumors are not considered a severe threat, but some benign breast tumors increase the risk of developing malignant BV in women. To determine whether the cancer is benign or malignant, a medical professional must examine any tumors or changes in the appearance of the breast (3-5).

Although BC is not the leading cause of cancer mortality in women, it is the most common type of cancer (6). A study showed that among the newly diagnosed cancers in the USA, BC takes the lead with a rate of 32%, followed by lung cancer with 12% and colon cancer with 9% (7). Previous studies emphasized that BC ranks second among the causes of death due to cancer in women. A woman's risk of developing invasive BC during a lifetime is 13.3%, known in society as "BC develops in one of every eight women" (8). This ratio indicates the cumulative lifetime risk for BC. For a 30-year-old woman, the absolute risk of being diagnosed with BC in the next ten years is 0.4%, 1.85% for 20 years, and 4.54% for 30 years (8, 9).

Today, epidemiological studies have determined many hormonal and genetic risk factors for BC development. However, these risks may vary between different communities. The region of residence, the factors the person is exposed to, and even dietary habits can impact risk rates (10).

In recent years, society's awareness of breast cancer and the ability to provide protective and preventive treatments, especially in some high-risk patient groups, have increased the importance of BC risk determination methods (11, 12). The Gail Model (GM) has frequently been used among the methods developed for this purpose. The GM is a model created using the data of a study conducted on 284,780 women who underwent screening mammography. Because the GM determines the risk of both non-invasive and invasive BC, this model was named “Model 1” and “Model 2”, which were modified to determine the exact risk of invasive BC only, was developed (13). One of the essential changes made in Model 2 was the addition of breast biopsies with and without atypical hyperplasia among the risk factors. In this model, by registering high-risk factors, the probability of developing breast cancer in 5 years can be calculated, and women with a risk value of at least 1.66% are defined as the high-risk group for the 5-year BC development. Many clinical studies have proved the validity of both models. However, it should be emphasized that GM is not suitable for determining risk in women under 35 years, those with a previous history of BC, lobular carcinoma, ductal carcinoma, or women who do not have annual mammograms (14-16). This study was planned to reveal the hormonal and familial risk factors that may be important for BC to evaluate the reliability of GM in Iraqi society.

2. Materials and Methods

2.1. Sampling and Design of the Study

In the first phase of this study, all breast patients who underwent annual examination and follow-up at Oncology Teaching Hospital (Baghdad, Iraq) between 2017 and 2020 were evaluated retrospectively. All known risk factor data were included in the study among patients over 30 years of age, with at least five years of follow-up. It should be noted that age, age at first menstruation, age at first childbirth, presence and the number of childbirth, and presence duration of breastfeeding were evaluated. Also, family history of BC in first- and second-degree relatives, age at menopause, history, and the number of previous breast biopsies were evaluated. The selected patients were divided into two groups. Group 1 included patients diagnosed with non-proliferative lesions with breast biopsy performed at least three years before, and Group 2 was a Controlled group.

The age of each patient in Groups 1 and 2, age at first menstruation, pregnancy, age of first childbirth, history of BC in first-degree relatives, and breast biopsy history were evaluated with the GM program. Women with a GM score of at least 1.66% were considered high-risk, and those below were considered low-risk. Patients who developed BC during the 3-year follow-up period were identified in each group. It was tried to determine the suitability of the GM for Iraqi society by

correlating the risk groups of these patients with the development of BC.

In addition to the risk factors included in the GM, the effect of all other risk factors obtained from patient files on the development of BC was performed in both Group 1 and Group 2 patients, and a 3-year risk analysis was performed. Among these patient groups, patients who developed BC at the end of 3 years were excluded from the study, and patients who were shown to be free of BC at the end of 3 years under imaging and physical examination findings constituted Group 3.

The GM we used to determine risk in our study is a computer program developed by the National Cancer Institute in the USA using Model 2 and distributed to all healthcare professionals in the country. The questions in the program are the person's age, the age of the first menstruation, and the age of first childbirth. It included the history of BC in first-degree relatives, the history of breast biopsy, and the person's ethnicity (17).

2.2. Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 19.0 program was used for statistical analysis. Data for intergroup significance were evaluated with Chi-square, t-student, multiple Cox regression, and multiple logistic regression tests. The analyses considered a p-value of 0.05 (P<0.05) statistically significant.

3. Results

In Group 1, BC was detected in 13 patients after three years of follow-up, while in Group 2, 38 patients were found to have BC. There was no statistically significant difference in the development of BC between the groups (P>0.05) (Table 1).

Table 1. Evaluation of Group 1 and Group 2 in terms of BC development after three years of follow-up (Chi-square test)

	No follow-up	BC patients
Group 1 (n=223)	210 (94.17%)	13 (5.83%)
Group 2 (n=406)	368 (90.64%)	38 (9.36%)

*P>0.05, relative ratio (RR)=0.870, confidence interval (CI)=0.47-1.61

In Group 1 (n=223), who had previously been diagnosed with a benign, non-proliferative lesion by biopsy, BC developed in a total of 13 (5.83%) patients in the follow-up. In the history of these patients, 1~3 (mean=1.22±0.42) breast biopsies were obtained. The previous biopsy of patients showed 9 fibrocystic diseases, one ductal ectasia, two squamous hyperplasias, and one fibroadenoma. In 9 of these patients (70%), there was a family history of BC; BC developed in 1st-degree relatives of 5 patients, both 1st and 2nd-degree relatives of 1 patient, and 2nd-degree relatives of 3 patients.

Among 223 patients of group 1, 159 patients (71.3%) were considered low-risk, according to the GM. In comparison, 5 out of 64 (223-159=64) patients were considered high-risk. It should be noted that 10 (15.6%) BCs were detected during the year (RR=5, P<0.002) (Table 2).

Table 2. Evaluation of patients in Group 1 (n=223) who were considered low and high risk for the development of 3-year BC according to the GM (Chi-square test)

GM	No follow-up	BC patients
low-risk group	148 (93.1%)	11 (6.9%)
high-risk group	57 (89%)	7 (11%)

*P<0.002, relative ratio (RR)=5.08, confidence interval (CI)=1.82-14.15

In Group 2, which consisted of people who were examined and followed up in the breast polyclinic, who were found to be expected and did not have a biopsy history, BC developed in 19 (4.68%) patients out of 406 patients. Notably, 10 (52.63%) of these patients had BC in their family history. First-degree relatives of three patients, first- and second-degree relatives of one patient and second-degree relatives of six patients were diagnosed with BC. Also, the results indicated that 32 of 406 people in group 2 were considered as high risk, and six patients (11.7%) in this group developed BC during follow-up, while 26 (4.7%) BC was detected among 374 patients who were calculated as low risk (RR=2.6, P<0.045) (Table 3).

Table 3. Evaluation of patients in Group 2 (n=406) who were considered low and high risk for the development of 3-year BC according to the GM (Chi-square test)

GM	No follow-up	BC patients
low-risk group	349 (93.3%)	25 (6.7%)
high-risk group	25 (78.1%)	7 (11.9%)

P<0.045, relative ratio (RR)=2.68, confidence interval (CI)=1.05-6.86

When Groups 1 and 2 were evaluated (n=629), BC developed in 50 patients at the end of 3 years, while 579 patients were regular according to physical examination and imaging methods. When the effects of all known risk factors of these patients on the development of BC were evaluated, the history of BC in the first-degree relatives, the history of BC in the second-degree relatives, nulliparity, not breastfeeding, and age were determined as significant risk factors (Table 4). In this patient population, 528 of 579 patients who did not develop BC and 36 of 50 patients who developed BC had a history of childbirth. The risk factors of patients who had childbirth only (n=564) were evaluated. Age was a significant risk factor; no significant relationship was found between age and duration of breastfeeding, the number of first- childbirth, age at menarche and menopause, and cancer risk (Table 5).

Table 4. Evaluation of all risk factors in 3-year BC development in Groups 1 and 2 (Multiple Cox regression tests)

Risk factors	*P*-value	RR	CI
Age	<0.0001	1.69	1.03-2.06
1st-degree family history	<0.0001	8.48	3.73-18.92
2st degree family history	<0.0001	6.71	2.95-13.58
nulliparity	<0.0001	3.98	1.86-9.35
Not breastfeeding	0.0001	3.76	1.72-8.73
Age of the first menarche	-	0.97	0.81-1.23
Age of menopause	-	0.84	0.92-1.15

Table 5. Evaluation of risk factors for 3-year BC development in patients with a history of childbirth in Groups 1 and 2 (Multiple Cox regression tests)

Risk factors	*P*-value	RR	CI
age	<0.0001	1.77	1.05-2.10
1st-degree family history	<0.0001	8.78	3.44-22.92
2st degree family history	<0.0001	7.51	3.23-16.85
first childbirth age	-	1.02	0.92-1.09
Number of childbirth	-	1.23	0.86-1.65
not breastfeeding	-	0.96	0.98-1.11
age of the first menarche	-	1.19	0.81-1.43
age of menopause	-	0.81	0.92-1.32

In the last stage of the study, all individual risk analyses were performed after excluding 48 patients diagnosed with BC during follow-up. The patients who did not develop BC in the 3-year follow-up period are considered Group 3. Group 4 was formed with patients operated on for BC in our clinic whose risk factors were evaluated retrospectively. The risk factors of both groups were compared; in Group 4, which includes patients with BC, we found that age at menopause was high. The presence of BC in 1st degree 2nd-degree relatives, the number of births, duration of breastfeeding, age at first birth, and age at first menarche were statistically significantly lower (*P*<0.05) (Table 6). When the effect of risk factors in the development of BC in both groups was evaluated with multiple logistic regression tests, it was found that nulliparity, not breastfeeding, and age were significant risk factors. Also, no significant correlation was found between age and cancer risk.

Table 6. Distribution and comparison of risk factors according to groups (t-Student and Chi-Square tests) of the patients who did not develop BC in the three-year follow-up (Group 3) and those diagnosed with BC at the first admission (Group 4)

Risk factors	Group 3	Group 4	*P*-value
Age	41.8±7.4	46.2±10.6	<0.001
1st-degree family history	4.9%	10.3%	<0.001
2st degree family history	5.3%	12.6%	0.0048
nulliparity	9.8%	15.3%	0.0055
Number of childbirth	4.8±2.6	3.8±2.9	<0.001
first childbirth age	16.6±3.9	18.6±4.3	<0.001
age of the first menarche	12.6±1.3	11.9±2.2	<0.001
age of menopause	47.6±4.9	50.9±3.8	<0.001
breastfeeding presence	93%	84%	0.0023
Breastfeeding duration (months)	39.3±12.2	22.8±14.4	<0.001

4. Discussion

Breast cancer has become a scary dream for women due to its high prevalence. As society became more aware of this issue, more women began checking their breasts regularly (1). The fact that treatment is possible when diagnosed in the early stages and that some preventive treatment methods can be recommended in high-risk women has increased the importance of screening and identifying high-risk patients with this

disease (6). Various tools have been developed for risk determination, among which the GM has become a frequently used risk determination tool. This study was planned to determine whether the GM is a reliable model for the development of BC for the Iraq population in calculating the individual risk and other risk factors (12, 15). In this way, it is possible to inform patients who come for breast examination in a short time, provided they have appropriate criteria, by calculating the risk level for BC and arranging the subsequent follow-up and treatment. The main issue is identifying patients at high risk of developing BC (6). However, the fact that many factors determine the risk and that different combinations of these factors are present in the individual are the reasons that make risk calculation difficult. Established risk is given as the relative risk (RR) or odds ratio (OR) based on whether data are drawn from a prospective or retrospective case-controlled study (8). While giving the relative risk or probability ratio for a specific feature as a risk factor, a figure greater than 1 indicates that the risk of developing BC is higher in people with that feature. Women with BC are 1.7 times more likely to develop BC. An even more meaningful explanation is to tell the patient their risk of developing BC in a given time frame (6).

The epidemiological studies have determined many internal and external factors that increase the risk of developing BC. Endogenous hormonal factors, familial and genetic predisposition, and the presence of benign breast lesions that are known to carry a pathologically high risk can be counted as internal, that is, self-existing risk factors. External factors, on the other hand, are external hormonal factors, the region where the person lives, external factors exposed, and nutrition. Factors with a relative risk greater than four are considered high-risk factors for developing BC, with 2-4 describing moderate risk and 1-2 describing low-risk factors. However, there is no definite consensus on which risk level is sufficient to define the individual as at high risk and at which risk level BC preventive treatment methods should be recommended to the individual (14, 15).

Patients with a history of benign breast biopsy non-proliferative lesion as a result of pathology were evaluated with the GM, and 52 (26%) of 223 patients were considered high-risk with a score above 1.66. It was determined that the rate of BC development in the low-risk group was five times higher than in the low-risk group. Then, 406 patients who had normal controls and did not have a history of breast biopsy were evaluated with the GM, and 32 of them were found to have a high-risk score compared to the GM, and the rate of developing BC within three years in the high-risk group was 2.6 times higher. These results were interpreted as the GM can also be a reliable method for BC risk determination in the Iraq population.

In the second stage of the study, the effects of all risk factors on the development of BC in the Iraq population were evaluated by adding other known risk factors that were not included in the calculation of the GM. For this purpose, patients who developed BC during follow-up and t did not were compared in terms of risk factors. The most important risk factor was the history of BC in first-degree relatives, which increased the probability rate 8.6 times. Family history is a widely recognized and accepted risk factor for BC. The cumulative risk of developing BC in women with a family history rarely exceeds 30%.

Other risk factors found to be important in our study were, in addition to advanced age, not having given birth and not breastfeeding. Many studies have shown a relationship between exposure to endogenous hormones and the risk of developing BC. As age increases, the BC diagnosis rate also increases, and the disease is more common in the postmenopausal period than before. These data suggest that ovarian activity plays a role in the development of BC (18). The correlation between the development of BC and early menarche, late menarche, non-delivery, and giving birth at an advanced age in various studies has supported estrogen's role in the disease's development (19).

Increasing the number of ovulatory cycles is the primary mechanism that increases the risk. In our study, after three years of follow-up of 629 patients (Group 1+2), no statistically significant relationship was found between early menarche and late menopause and the risk of developing BC. This result suggests that hormonal factors may differ between societies regarding BC risk. In order to eliminate the factors of not childbirth and therefore not breastfeeding, which were found to be significant risk factors at this stage of our study, women who never had childbirth in both groups were excluded, and then the statistical analysis was repeated. It was concluded that the number of births and the duration of breastfeeding were not statistically significant risk factors for BC. These results are important because they contradict many studies in the literature, and as mentioned above, it is necessary to conduct more extensive studies with more significant numbers of patients.

The current study showed that GM is a reliable model for calculating individual risk for the development of BC in Iraqi society; the risk factors in our society were also determined. History of BC in first-degree relatives, BC in second-degree relatives, not breastfeeding, not having given birth, and age is the risk factors found to be significant for the development of BC, respectively. However, childbirth was evaluated, and it was concluded that the number of first childbirth, age, and the duration of breastfeeding did not increase the risk of BC, such as age at menarche and menopause. It was concluded that there are genetic factors, and the risk of developing BC increases with age, but hormonal factors do not cause a significant increase in risk in Iraq society.

Authors' Contribution

Study concept and design: A. A. F. and H. A. H.
Acquisition of data: A. A. F. and H. A. H.
Analysis and interpretation of data: M. J., W. K. Y. A.
Drafting of the manuscript: A. S. H. and A. J. O.
Critical revision of the manuscript for important intellectual content: M. A. J., L. H. S. and N. M. M.
Statistical analysis: B. K. S.
Administrative, technical, and material support: A. A. F. and H. A. H.

Ethics

This retrospective study was approved by Al-Farahidi University of Iraq and written informed consent of penitents.

Conflict of Interest

The authors declare that they have no conflict of interest.

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