Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20152127-31

Performance of the Gail Model for Breast Cancer Risk Assessment in Iranian Women

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ARTICLE INFO

Received:
16 November 2014
Revised:
25 December 2014
Accepted:
10 February 2015

Keywords:
Gail model,
validation,
Iran

ABSTRACT

Background: The Gail model has been widely used for estimation of absolute risk of breast cancer development. The original model and most of the validation studies have been performed among western populations and controversial results have been reported regarding the applicability of this model in Asian populations. Our aim was to investigate the performance of this model in Iranian women.

Methods: In a cross-sectional study, a total of 280 patients with breast cancer and 280 participants with normal screening results were enrolled as case and control groups, respectively. Risk factors used in the latest version of the Gail model were compared between the two study groups. Gail score was calculated by using Breast Cancer Risk Assessment Tool and based on the cut-off point of 1.67, patients were categorized in order to assess model performance.

Results: In total, 560 patients with a mean age of 43.07±8.60 years were enrolled. Comparison of different risk factors between the two groups revealed significant associations of patients' age ($P < 0.001$), age at first pregnancy ($P = 0.022$), previous history of breast biopsy ($P < 0.001$) and atypical hyperplasia ($P = 0.002$) with risk of breast cancer. No association was found between age at menarche ($P = 0.115$) or first-degree family history ($P = 0.117$) and increased risk. Considering the Gail score for 5-year risk of breast cancer development, the difference between the two groups failed to reach significance ($P = 0.052$). The sensitivity and specificity of the model were 13.9% and 94%, respectively.

Conclusions: Based on the current findings, it can be suggested that employing the current version of the Gail model for breast cancer risk assessment will underestimate the risk of cancer development in Iranian women.

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Introduction

In the recent years, investigators have tried to design statistical models that predict the risk of breast cancer development.[1] The aim is to select high risk women for risk reduction strategies based on the status of multiple risk factors that are associated

with increased risk of breast cancer.[1] There are two main types of models; the first type estimates the risk of developing breast cancer in a defined period and the second assesses the probability of BRCA mutation.[1-4] The most commonly used models of the first category are Gail model, that incorporates several known risk factors of breast cancer, and Claus model in which all predictions are only based on family history .[5,6]

The Gail model was designed to predict 5-year absolute risk of development of invasive breast cancer in women.[6] In this model, clinical characteristics and family history are used to predict the risk of breast cancer development over a specific period of time.[6] Those who are at high risk for breast cancer (Gail score ≥ 1.67%) are candidates for more invasive approaches, while women who are categorized as low risk are followed-up through the routine screening program to avoid complications and high costs.[7,8] The first version of the model was used to predict both invasive and *in situ* carcinoma; but the model was further modified to only predict the risk of invasive breast cancer.[6,9] The latest modification is generally known as "Gail Model 2".[9] Considering the impact of ethnicity on breast cancer incidence and characteristics, the Gail model has been validated in different countries to assess the performance of the model in various ethnicities.[10-13]

In Iranian women, breast cancer is diagnosed in a relatively younger age and higher stage compared to their western counterparts.[14,15] These differences might affect the applicability of the Gail model in Iran. To the best of our knowledge, previous studies have not validated this model in Iran. Therefore the aim of the current study was to investigate the performance of the Gail model in a sample of the Iranian female population.

Methods

A cross-sectional study was conducted in a referral hospital affiliated with Tehran University of Medical Sciences between 2011 and 2013. Study protocol was in accordance with the latest Declaration of Helsinki for investigations on human subjects and approved by the local ethics committee.

Study population consisted of patients with histologically confirmed breast cancer, as group A, and women who attended the breast clinic and had normal mammographic results as group B. Those with previous history of ductal or lobular carcinoma *in situ* were not enrolled in the study as controls. Only patients aged between 35 and 85 years were included.

The Gail model was used to predict 5-year risk of breast cancer by employing the Breast Cancer Risk Assessment Tool (available at http://www.cancer.gov/bcrisktool/). Risk factors were categorized according to the relevant instructions and included age at menarche (7-11, 12-13, 45 14 years), age at first pregnancy (no birth, 20 to 24, 25 to 29, ≥ 30 years), family history of malignancy in first-degree relative(s) (no family history, positive family history in one relative, positive family history in > 1 relative), and the issue that whether the subject has previously underwent breast biopsy and the related result was atypical hyperplasia or not.

Statistical analysis

The statistical package for the social sciences (SPSS) software version 20.0 (IBM Inc., NY, US) was used to perform statistical analyses. Descriptive results are presented as mean and standard deviation, while categorical variables are shown as percentages. Risk factors were compared between the two groups by employing independent t-test and chi-square test, as applicable. Mann-Whitney U test was used for comparison of continuous variables that did not meet the assumption of normality. Based on the recommendations of previous studies, the cut-off value of 1.67 in Gail score was used to define low and high risk groups for breast cancer development. Additionally, the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the model were calculated. The area under the receiver operating characteristic (ROC) curve was used to define a cut-off value of model score among study participants. P value less than 0.05 was considered as statistically significant in all analyses.

Results

A total of 560 participants (280 cases and 280 controls) with a mean age of 43.07±8.60 years were enrolled in the study. Demographic characteristics of study population are presented in Table 1.

Patients with breast cancer, who were considered collectively as group A, were significantly older than those in group B, *i.e.* healthy controls. Mean age of subjects in each group was 44.35±9.35 and 41.79±7.58 years, respectively ($P < 0.001$). Distribution of participants in different categories of age at menarche was almost similar in both groups and no differences were observed between the two groups ($P = 0.115$). Forty percent of women in group A gave birth to their first child when they were younger than 20 years, while the corresponding figure was 33% in group B (healthy subjects). Comparing the different categories of age at first pregnancy in terms of percentage of patients in each category, a significant difference was observed between the two groups ($P = 0.022$). Positive family history of breast cancer in first-degree relatives was more commonly observed among healthy individuals in group B (23.92%) than in group A patients (17.14%) ($P = 0.117$). Higher frequencies of previous breast biopsy and atypical hyperplasia pathology results were recorded in patients with breast cancer compared to healthy women ($P < 0.001$ and $P = 0.002$, respectively).

Table 1. Comparing components and final score of Gail model between the two study groups

	Total (N = 560)	Case (N = 280)	Control (N = 280)	P-value
Mean Age	43.07±8.60	44.35±9.35	41.79±7.58	<0.001
Age at menarche				0.115
7 – 11	54 (9.64%)	34 (12.14%)	20 (7.14%)	
12 – 13	213 (38.03%)	104 (37.14%)	109 (38.93%)	
≥ 14	244 (43.57%)	116 (41.43%)	128 (45.72%)	
Unknown	40 (8.76%)	26 (9.29%)	23 (8.21%)	
Age at first pregnancy				0.022
< 20	207 (36.96%)	114 (40.71%)	93 (33.21%)	
20 – 24	180 (32.14%)	96 (34.28%)	84 (30.0%)	
25 – 29	75 (13.39%)	27 (9.65%)	48 (17.15%)	
≥ 30	38 (6.79%)	20 (7.15%)	18 (6.43%)	
Nulliparous	58 (10.36%)	23 (8.21%)	35 (12.5%)	
Unknown	2 (0.36%)	0 (0.0%)	2 (0.71%)	
Family history of breast cancer (number of relatives positive for breast cancer)				0.117
Negative	441 (78.75%)	230 (82.15%)	211 (75.37%)	
1	98 (17.50%)	42 (15.0%)	56 (20.0%)	
> 1	17 (3.04%)	6 (2.14%)	11 (3.92%)	
Unknown	4 (0.71%)	2 (0.71%)	2 (0.71%)	
Previous breast biopsy (number of biopsies)				<0.001
No	493 (88.04%)	235 (83.92%)	208 (74.29%)	
1	64 (11.43%)	45 (16.08%)	19 (6.79%)	
> 1	3 (0.53%)	0 (0.0%)	3 (1.07%)	
Unknown	0 (0.0%)	0 (0.0%)	50 (17.85%)	
Atypical hyperplasia	*(N = 67)*	*(N = 45)*	*(N = 22)*	0.002
Negative	32 (47.76%)	23 (51.11%)	9 (40.90%)	
Positive	12 (17.92%)	10 (22.22%)	2 (9.09%)	
Unknown	23 (34.32%)	12 (26.66%)	11 (50.0%)	
Gail score	N/A	0.910±0.86	0.808±0.82	0.052

Abbreviation: N/A: not applicable

Gail model scores, that predict 5-year risk of invasive breast cancer, in group A and B were 0.910±0.86 and 0.808±0.82, respectively and no statistically significant difference existed between them (P = 0.052). Using the cut-off value of 1.67 in Gail score, subjects were categorized into high and low risk groups. The model was able to correctly characterize 256 participants in the healthy group as having low risk of breast cancer (Specificity = 91.4%). The sensitivity, NPV and PPV of the Gail model were 13.9%, 51.5%, and 61.9%, respectively. According to ROC curve analysis, a cut-off point could not be defined.

Discussion

The aim of this study was to assess the applicability of the Gail model among a sample of Iranian women who were treated or visited in a tertiary referral center. Different components of the Gail model were compared between patients with pathologically confirmed breast cancer and healthy participants who had normal screening tests. In this study, the two groups differed significantly in terms of age, age at first pregnancy, number of previous breast biopsies and atypical hyperplasia.

Several studies evaluated the performance of this model in various populations. Gail model was not reliable in predicting the risk of breast cancer development in Czech, Italian, Spanish, African-American and Indian women.[16-20]

Several reports focused on the performance of the Gail model in Asian populations and the results of these reports were in agreement with findings of the current study. A study of Gail model in Turkish women compared 650 breast cancer patients with 640 healthy women as control group.[11] In this study, age and first live birth (≥30) were statistically significant between case and control groups but other risk factors used in Gail model were not different between two groups. They concluded that Gail model is not appropriate for risk estimation in Turkish population.[11] Similar to the results of the current study that indicated very low sensitivity (13.9%) and high specificity (91.4%) of the Gail model in Iranian population, that study recorded the sensitivity and specificity of 13.3% and 92%, respectively for Gail model .[11] It is worth noting that the relatively small number of patients that were recruited in the study by Ulusoy *et al.* and the current study, may hinder detection of significant association between the variables and risk of breast cancer and limit proper interpretation of results.

In a prospective study of more 28,104 women in Singapore, Chay and his collogues assessed the incidence of breast cancer among study participants in a 10-year follow up. They demonstrated that

estimation of breast cancer risk development employing the Gail model, overestimated the population risk of breast cancer, especially in women aged 60-64.[10] This overestimation might be due to additional risk factors running in the population which are not included in the Gail model.

In Iran, a few studies evaluated the performance of Gail model in limited populations.[21-23] A case-control study performed by Behboudi *et al.* in the north of Iran revealed that the Gail model is not sufficiently capable of predicting the risk of breast cancer in that population and they suggested the cut-off point of 1.25 to segregate the high risk women.[22] Other studies on the Gail model in Iran either estimated breast cancer risk in a population of healthy women or calculated the risk in a group of breast cancer patients without comparing it to a control group.[21,23]

Although it did not show a statistically significant difference, higher frequency of family history of breast cancer was observed among healthy participants. In total, 17.14% of the people in patient group and 23.92% of the members of control group had positive family history of breast cancer. This finding might result from the fact that control group mostly consisted of healthy relatives of breast cancer patients treated in this center. Similarly, in a study reported by Shojamoradi *et al*., a higher rate of positive family history of breast cancer in first-degree relatives was found in control group compared to case group (11.8% vs. 6.7%, respectively).[24] There was no significant relationship between age at menarche and the risk of breast cancer in this study. Two other studies from Iran and a study from Czech Republic showed similar results.[16,25,26]

Several points should be noted regarding the limitations of the current study. Most importantly, it should be kept in mind that a sample of patients selected from a referral center in Tehran might not be representative of Iranian female population. Larger studies including women from different parts of country should be conducted in order to obtain an accurate assessment of the Gail model performance in Iranian women. Cross-sectional nature of the study and lack of patients follow-up, do not allow researchers to assess absolute risk of cancer development among study population.

Based on the results of the current study, it could be suggested that current version of Gail model should be modified to make it applicable for breast cancer risk estimation in Iranian women.

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