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Original Article

Assessment of common risk factors and validation of the Gail model for breast cancer: A hospital-based study from Western India

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Abstract

Objective: Modified Gail Model is a noninvasive, easy to implement risk estimation tool for absolute breast cancer risk. It was developed with data collected from non African American females and further modified for African-American, the Hispanic, and Native American populations. The use of this model for population outside the US and European country is not yet validated. We evaluated the prevalent risk factors and the effectiveness of the Gail model for risk assessment in our local Indian population. **Materials and Methods:** A retrospective analysis of a prospectively maintained database was conducted on patients treated between 2008 and 2013. Six hundred and fifty patients were included in each group. Six questions were taken as per the breast cancer risk assessment tool calculator. A value of over 1.67% was taken as a high risk for breast cancer development. **Results:** The mean age of the participant was 50 ± 21.3 years in cases and 41 ± 16.4 years in controls. Age and age at first childbirth >30 years were found to be significant and associated with increased risk of breast carcinoma, but the age at menarche, family history, previous breast biopsy, and atypical hyperplasia was no significant. The Gail model was assessed, and sensitivity was 10.30% and 96.30% specificity for our population. Positive and negative predictive values were 73.62% and 51.77%. **Conclusion:** Our study concluded that the Gail model is not an appropriate risk assessment tool for the population in its present form. For the future application of this model, we need to perform a bigger study with a higher sample size representing a maximum number of local variabilities in the Indian population.

Keywords: *Breast cancer, Gail model, Risk factors*

Introduction

Breast cancer is common cancer for which preventive interventions have been implemented widely. It has been the leading cause of mortality and morbidity for the patients in India with an incidence at an age-adjusted rate of 26/100,000 women and mortality of 12.7/100,000 women [1]. Recent advances in the understanding of cancer pathogenesis have helped us to develop various risk assessment algorithms to assist the clinicians in evaluating the risk factors and estimating future breast cancer risk. These models also help in screening and suggesting early intervention such as chemoprevention or prophylactic oophorectomy or mastectomy for lowering estrogen exposure and hence lowering the breast cancer risk [2].

Gail model, one of the several models, developed by Gail *et al*. at the National Cancer Institute to estimate the probability of the occurrence of breast cancer over 5 years [3]. The model was derived using data from 4496 matched pairs of cases and controls in the Breast Cancer Detection demonstration project, using primarily nongenetic factors to predict breast cancer risk for women with no personal history of breast cancer [Table 1]. After the success of breast cancer prevention trial, the U.S. Food and Drug Administration has approved the use of tamoxifen for breast cancer chemoprevention in a patient with Gail score >1.6% [4,5].

One of the limitations of the model was that the data used for developing this model was from white females, which had limited applicability in another ethnic group. The authors consequently try to answer this limitation by extending this model for African-American, Hispanic, Asian, and Pacific Islander women in further studies [6]. Still, these modifications shave the limitation of a lesser number of the patient sample used for prediction tool development and generalizability of this knowledge to the worldwide population.

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Table 1: Risk factors included in breast cancer risk assessment tool based on modified Gail Model

Age
Age of menarche
Age at first live birth
First-degree relative with breast cancer
Previous breast biopsy
Race/ethnicity

Wide variation has been seen in the incidence of breast cancer, and the highest has been seen in the more developed regions of the world and the lowest observed in the least developed regions. Recently, low-income countries have shown an increased incidence of breast carcinoma. According to the recent data, over the next 20 years, the majority of the increase in the worldwide burden of the disease will be due to rising incidences in these countries. In India, there has been a recent increase in breast cancer cases. Changing lifestyle, prosperity, and increased efficiency of cancer care might have led to these findings. There are multiple risk factors for breast cancer in which some are more prevalent in western countries, and some are in the Indian population. Along with that, individual contribution of each risk factor might be different according to ethnicity and changing circumstances. Hence, risk factors that are more prevalent in Western countries cannot be applied to the population as such.

As a result of these differences, the incidence and risk factors of breast carcinoma may change in different populations. Hence, the Gail model should be validated before the application in this population. This model has to be applied systematically for validation in the local population. The primary objective of this study is to evaluate the performance of the Gail model to estimate the risk for the development of breast carcinoma in the local population.

Materials and Methods

A retrospective analysis of a prospectively maintained database was conducted on patients treated between 2008 and 2013. The analysis included 650 patients with invasive breast carcinoma of more than 35 years of age and 650 women with negative results who had undergone screening on visiting a breast cancer clinic of the center. Two groups were compared for individual risk factors included in the breast cancer risk assessment tool (BCRAT). Six questions were taken as per BCRAT calculator like the history of any breast cancer or of ductal carcinoma *in situ* or lobular carcinoma *in situ*, age, age at the time of the first menstrual period, age at the time of first live birth of a child, number of first-degree relatives with breast cancer, breast biopsies (number of biopsies and atypical hyperplasia). This risk assessment tool is available on http://www.cancer.gov/bcrisktool/. Five-year risk of having breast cancer was calculated using BCRAT. A value of over 1.67% was taken as a high risk for breast cancer development. This study has been exempted from review by the IRB because it was a retrospective study from the database.

Statistical analysis

Categorical variables were expressed in percentages and frequencies, and the Gail score in the median. A Chi-square test was used for group comparison of categorical variables. Receiver operating characteristic was used to determine a cutoff value of the Gail score for the female population. Software packages SPSS version 16 (IBM corp, Chicago, Illinois, USA) and EP info version 6.1 (Centers for disease control and prevention, city-Atlanta, Georgia, USA) were used for the statistical analysis. All values of $P < 0.05$ were taken as statistical significance.

Results

The mean age of the participant was 50 ± 21.3 years in cases and 41 ± 16.4 years in controls. Women in cases were older than women in controls, which was statistically significant. A maximum number of cases were observed in 41–50 years (33.07%). In this study, the risk of breast carcinoma increases as the age of patient increases ($P < 0.00001$) and by bivariate logistic regression analysis, for each year increase in the age, Gail score increased by 0.04 ($P < 0.00001$ and 95% confidence interval [CI] =0.037–0.048). In this study, the range of menarche is from 11 to 19 years. Most of the patients had aged at menarche >13 years (77.23%). No differences were found among the groups regarding age at menarche ($P = 0.226$ and 95% CI = 0.008–0.035) which does not show normal regression, and hence, this factor is not found to be significant for the assessment of breast cancer in this local population. In this study, we found that the increased age at first childbirth increases the risk of cancer ($P < 0.01$). It is also proven by bivariate logistic regression analysis ($P < 0.00001$ and 95% CI = 0.020–0,035). We also found that only 76 patients (10.13%) had a history of breast carcinoma in relatives, which is equal to 10% seen in developed nations. In this study, only a small number of women underwent more than one biopsy, and hence, it was investigated separately. In this group, a response was performed as YES or NO. A history of previous breast biopsy was 11.84% in Group 1 and 8.33% in Group 2. Only six had atypical hyperplasia in biopsies among those who underwent a previous biopsy examination. As compared to Group 2, Group 1 found to have few more women with a history of previous breast biopsies ($P < 0.012$), but statistically no significant difference was found among these groups considering atypical hyperplasia ($P < 0.68$). Probably, a larger sample size might have helped us make a better estimate for this factor [Table 2].

For a definition of high risk (Gail score), 1.67% was taken as cutoff point for the population, and only 10.30% of the women had a high risk for developing breast carcinoma. In this study, the Gail score did not follow a normal distribution (Kolmogorov–Smirnov test statistic, 0.204, $P < 0.0001$, Shapiro–Wilk, 0.629, $P < 0.0001$) [Figure 1]. The calculated Gail risk score was 0.97 ± 0.83 (median = 1.6) in cases, and 0.58 ± 0.46 (median = 0.90) in controls and difference was statistically significant, higher in cases compared with controls ($P < 0.001$). According to the Gail model, those women were classified as high risk (calculated risk score ≥1.67), found only 10.30% of women from cases and 3.6% of women from

Table 2: Distribution of breast cancer patient according to the risk factors suggested in the Gail model for breast cancer risk assessment

Risk factors	Cases (*n*)	Controls (*n*)	Chi-square test	*P*	Degree of freedom
Age group					
≤40	169	442	243.92	<0.00001	3
41-50	220	130			
51-60	156	46			
>60	105	32			
Age at menarche					
<12	24	15	2.97	0.226	2
12-13	124	139			
>13	502	496			
Age at first live birth					
≤20	348	308	10.12	0.01	3
21-24	157	209			
25-29	114	107			
≥30	28	26			
Number of relatives with breast cancer					
0	574	592	4.46	0.107	2
1	67	55			
>1	9	3			
Biopsies					
Yes	578	604	6.3	0.012	1
No	72	46			
Atypical hyperplasia					
Yes	4	2	Yat's corrected-0.17	0.682	1
No	646	648			

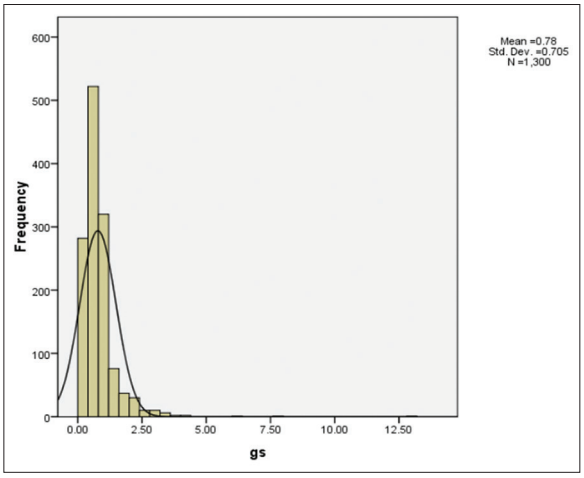

Figure 1: Normal distribution curve for Gail score

controls. The difference was statistically significant ($P < 0.001$). This study demonstrated that the Gail model had 10.30% sensitivity and 96.30% specificity with positive predictive value of 73.62% and negative predictive value of 51.77% for the risk assessment of breast carcinoma development. It showed positive skewness (6.175) and the standard deviation (0.705) were more with respect to mean (0.78).

Discussion

The exponential rise in breast cancer incidence requires strategies for identifying the responsible risk factors and attributable risk of these factors for breast carcinoma in this population. We analyzed the effect of age, age at menarche, age at first live birth, family history, number of biopsies, and biopsy status.

We found that the incidence of breast cancer increases as age advances. In this study, the maximum number of cases were observed in premenopausal women. The findings of our study were similar to previously reported Indian reports of early incidence of breast cancer compared to Western counterparts where the majority of patients belonged to >50 years of age group[7].

Age at menarche is another reproductive risk factor for breast cancer. Our study did not show any relation between age at menarche and breast cancer. There are conflicting reports on the relationship between age at menarche and the incidence of cancer. There are several Western and Indian study which states that there is no relationship between age at menarche and breast cancer incidence. Whereas others support the relationship between the early age of menarche and increase breast cancer incidence [8,9]. We would be conservative about our result in this case as the patients in control were mainly of <40 years and longer follow-up would be required for making any conclusion regarding the relationship between menarche and breast cancer from this study.

Age at first live birth is also an important factor affecting breast cancer incidence. Delay of first childbirth increases the chance of breast cancer in the latter part of life. In this study, we found that a higher age at first childbirth increases the risk of cancer. Similar results were reported in many studies reported from both the Western and Indian population [8-11]. Although clear pathogenesis is not clearly explained, the

benefit of early pregnancy has been attributed to decreased exposure to estrogen and permanent changes in breast oncogenesis after pregnancy independent of the estrogen exposure [12,13].

We also found that patient with a family history of breast carcinoma in first degree relatives has increased risk of breast cancer. This finding is in line with the previous reports from other studies from India and abroad [14-16]. Atypical hyperplasia is a premalignant condition for breast carcinoma and leads to an increased incidence of breast cancer. We were not able to evaluate the relationship between atypical hyperplasia and breast cancer because of the limited number of cases with atypical hyperplasia in our study. In previous studies, it has been suggested that the Gail model significantly underestimates the effect of these findings on breast cancer incidence [17].

Although the above-discussed risk factors may be the same, their relative contribution varies across the population depending on the family history, ethnicity, and geographies. There are few quantitative risk assessment models that work by combining the relative risk of risk factors to formulate the future risk of cancer [2,3]. Among all these risk assessment tools, the Gail model has been used commonly in primary care practice because of its simplicity and easy implementation [18]. Clinical datasets can be acquired easily from the clinical history and used with Internet-based or electronic health record-based BCARTs.

In Gail's original work, the selection of risk factors and the estimation of relative risk for risk factor combination was very important. In his original work, only five risk factors were taken in the white ethnic group which was further enhanced by two more studies which included data from the African-American, Hispanic, Asian, and Pacific islander's population in the united states [6,19]. These studies have led to a wider acceptability of this model as a BCART. Two of the limitation of the study on the Asian population was the limited number and the geographic location of the patients. Both of these limitations will affect the prediction accuracy of this tool for the Indian population.

In this study, we also analyzed the effectiveness of the Gail model for breast cancer prediction. We evaluated the performance of the modified Gail model to estimate the risk of breast cancer in the local population. If we apply the usual cutoff of >1.67% for Gail model, the 5-year prediction, only 10.3% of patients with breast cancer were found to be in the cancer risk group. We found that the Gail model in its current form significantly underestimates the risk of breast cancer. One of the important factors for this finding is the variation of breast cancer risk factors from the Western population or Asian population present in the Western country [20].

Along with this, very wide regional variation is seen in the incidence of breast cancer all around the country, with the highest incidence reported from the cities. This increased incidence in cities can be attributed to increased risk factors for breast cancer or better health facility and increased awareness about the cancer symptoms in cities [21,22]. These two factors do not affect the incidence directly but influence the data collection capabilities for studies that form the basis for these kinds of risk assessment models.

Many studies have suggested the use of the Gail model as a risk assessment tool in low-income and minority populations where socio-economic factors usually led to lesser utilization of screening and preventive services [23]. It has also been reported that the Gail model can stratify the risk for breast cancer further in women with suspicious breast imaging reports [24]. Gail model, modified for the Indian population, holds a lot of promise as noninvasive and easy to implement the tool for generating immediate breast cancer risk data for socioeconomically underprivileged population.

Limitation and future perspective

There were some limitations in our study which can be dealt with in detail in future. Since we had collected data retrospectively, further studies shall be performed to establish our findings and to see the strength of association between breast carcinoma and risk factors in this population. Few risk factors such as the number of biopsies and biopsy status were present only in small numbers of subjects to make any definitive conclusion.

Conclusion

Finally, our study concluded that the Gail model is not an appropriate risk assessment tool for the population in its present form. For the future application of this model, we need to perform a bigger study with a higher sample size representing a maximum number of local variabilities in the Indian population. A bigger study will help in developing the Indian version of BCRAT as developed for African-American, Hispanic, Asian, and Pacific Islander populations in the United States.

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Conflicts of interest

There are no conflicts of interest.

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