BioCore Exploring Scientific Community

International Journal of Cancer Epidemiology and Research

Research Article ISSN 2572 -7664

Can we apply the guidelines derived from western database to other ethnic groups? A Gail model based evaluation of geo-ethnic variations in breast cancer

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Abstract

Purpose

Breast cancer is a multi-factorial disease with marked geographical and ethnic variation in epidemiology and risk factors. However most of the literature that defines screening and management guidelines of breast cancer is derived from large prospective trials on western population, the applicability of which to other ethnic groups with possibly different disease biology is questionable. The purpose of this study is to analyze the applicability of the Gail model to Indian females.

Methods

The case records of 688 patients, ≥40 years old diagnosed at our institute with invasive breast cancer in 2012-2013 were retrospectively analyzed. Breast cancer risk estimates of these patients in the 5-year period prior to their diagnosis were calculated using the Breast Cancer Risk Assessment Tool (BCRAT).

Results

The median estimated 5-year risk using BCRAT was 0.7%. Since all these patients were diagnosed in 2012-2013, a significant proportion (at least 95%, assuming significance at $p < 0.05$) of them were supposed to be in the high-risk group in the 5- year period prior to their diagnosis. However, only 2.9% of the studied population was in the high-risk group as calculated using the BCRAT ($p < 0.0001$). Even after including the other factors defined by the NCCN that categorize the patients as high risk, only 4.1 % of the population fell into this group.

Conclusion

Gail model does not accurately predict the risk of breast cancer in Indian females. This study highlights the need for development of independent databases for each ethnic group rather than universally adopting protocols designed from western databases.

Keywords: Gail Model, Applicability, Geo-Ethnic Variations, Breast Cancer

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Citation: Ankita Gupta et al. (2018), Can we apply the guidelines derived from western database to other ethnic groups? A Gail model based evaluation of geo-ethnic variations in breast cancer. Int J Cancer Epid & Res.2:2,9-12

Received: December 10, 2018

Accepted: December 20, 2018

Published: December 31, 2018

Introduction

Breast cancer is a multifactorial disease with marked geographical and ethnic variation as evidenced by diversity in epidemiology and risk factors. Risk factors for breast cancer have been extensively investigated in western population, and it has been suggested that genetic, reproductive and life-style related factors are strongly associated with an increased incidence.[1] Risk-assessment tools estimating the individual's absolute risk for developing breast cancer and identifying women at high level of risk are crucial for decision-making about prevention and screening.

Various risk assessment models such as Gail, Clause and BRACPRO have been developed and validated in white women. They are used to recruit women for breast cancer screening protocols.[2]

Modified Gail model (Breast Cancer Risk Assessment Tool, BCRAT) is a statistical tool that estimates the 5-year and lifetime-risk of developing breast cancer in women

>35years of age. This model was developed using the North American database and has been validated in large prospective trials on the western population.[3] The latest breast cancer screening guidelines by the NCCN categorize females over 35 years with a BCRAT estimated 5-year risk of ≥ 1.7% as high-risk population.[4]

However, owing to differences in cancer biology across various racial and ethnic groups, there lies considerable diversity in epidemiology and risk factors. Hence, applicability of such screening and manage-

ment guidelines to other ethnic groups with possibly different disease biology is questionable. A number of studies have been conducted to validate the Gail model in American [5-7], European [8, 9], Asian [2, 10, 11] and Oceanian [12] women with inconsistent results. Moreover, limited data is available from studies conducted on the Indian population and the diagnostic accuracy of the Gail model has not been fully evaluated.The purpose of this study is to analyze the applicability of this model to Indian ethnic groups.

Material And Methods

The case records of 688 patients, ≥40 years old diagnosed at our institute with invasive breast cancer in 2012-2013 were retrospectively analyzed. Breast cancer risk estimates of these patients in the 5-year period prior to their diagnosis were calculated using the BCRAT. All five factors, which have been shown to be significant predictors of lifetime risk of breast cancer, were analyzed. These included: (1) current age, (2) age at menarche, (3) number of benign breast biopsies, (4) age at first live birth or nulliparity, and (5) family history of breast cancer in first-degree relatives. Biopsies (incision, excision, or fineneedle aspirations, but not cyst aspirations) for benign breast disease were considered, and a biopsy showing atypical hyperplasia carried twice the risk of a biopsy showing no benign disease.

Statistical analysis

Breast cancer risk estimates of these patients in the 5-year period prior to their diagnosis were calculated using the BCRAT. Pearson's Chi-square test was used to correlate the risk associated with each of the above factors and was then compared with the actual 5-year risk of developing breast cancer in these patients

Results

A total of 655 patients were included for analysis. Patient characteristics are listed in Table I.

Study patients	n = 688
Median age at menarche	13 years
Median age at first childbirth	20 years
Median parity	3 (0-9)
Nulliparity	32 (4.7%)
Positive breast feeding history	655 (95.3%)
Significant family history	28 (4.1%)
History of benign breast biopsies	19 (2.3%)

Table I: Patient characteristics

The median estimated 5-year risk of developing breast cancer using the BCRAT was 0.7%. Since all these patients were diagnosed in the years 2012-2013, a significant proportion (at least 95%, assuming significance at $p < 0.05$) of them were supposed to be in the high-risk group in the 5-year period prior to their diagnosis. However, only 2.9% of the studied population was in the high-risk group as calculated using the BCRAT ($p < 0.0001$). Patients with previous history of breast biopsies ($p < 0.0001$) or positive family history ($p < 0.0001$) or nulliparity ($p = 0.04$) had a significantly greater chance of being in the high-risk group. (Table II) Even after including other factors defined by the NCCN that categorize the patients as high risk, like previous history of breast cancer or of lobular carcinoma in situ, only 4.1 % of the population was at high risk according to the NCCN guidelines, which is significantly different from reality ($p < 0.0001$). There was no significant variation among rural and urban women, or with occupation.

Significant risk factors	**P value**
Previous history of breast biopsy	< 0.0001
Positive family history	< 0.0001
Nulliparity	0.004
5-year risk using BCRAT	**0.7%**

Table II. Significant risk factors and calculated 5-year breast cancer risk using BCRAT

Discussion

The original model of Gail et al (model 1), developed in 1989 among a case–control study subsample of regularly screened women participating in the Breast Cancer Detection and Demonstration Project (BCDDP), estimates the absolute-risk (probability) that a woman in a program of annual screening will develop invasive or in situ breast cancer over a defined age interval.[3] Statisticians modified the original Gail model to predict specifically the risk of developing invasive breast cancer. This modified model, referred to as "model 2", (7) was used to determine eligibility for the Breast Cancer Prevention Trial (BCPT). [13] The modification of model 1 to model 2 was accomplished by substituting age-specific invasive breast cancer rates for white women from the Surveillance, Epidemiology, and End Results (SEER). This model is incorporated in the Breast Cancer Risk Assessment Tool of the NCI.

However, the applicability of this model to define screening and management guidelines to other ethnic groups with possibly different disease biology is questionable, as evidenced by considerable variation in epidemiology and risk factors. This disparity can be accounted for by differences in distributions of age at menarche, age at menopause, age at first birth, number of children, weight, use of hormone replacement therapy, or alcohol consumption and other lifestyle-related factors amongst women across the world.

A number of studies including four meta-analyses with variable results have been conducted in the past to validate different versions of the Gail model across various ethnic groups.

This study was carried out to determine the applicability of the Gail model to the Indian population. On analysis of risk factors it was noted that, in contrast to a high prevalence of various reproductive factors in women in the west, there was a low prevalence in our study. Almost similar trend has been observed in other reports from India. [14, 15] The median age at menarche in our and other studies had been reported to be around 13 years. Median age at first live birth was 20 years and nulliparity was seen only in 4.7% of the cases. A majority of the study patients had a positive breast- feeding history (95.3%). Other studies too report a high rate of breast-feeding practice in Indian women. [16] In our study, patients with previous history of breast biopsies ($p < 0.0001$) or positive family history ($p < 0.0001$) or nulliparity ($p = 0.04$) had a significantly greater chance of being in the high-risk group.

To determine the usefulness of Gail model Breast cancer risk assessment tool in identifying women at high risk for breast cancer in an India, a retrospective analysis was conducted on patients with breast cancer and benign breast disease, in which the Gail score was calculated for 104 breast cancer patients, 100 patients with confirmed benign breast disease and 100 patients attendants. In their study, they found that the median Gail score was lower in patients with breast cancer when compared to normal people and concluded that Gail Model cannot be used to predict high risk of breast cancer amongst Indian women. [17]

The median estimated 5-year risk using BCRAT in our study population was 0.7%. On comparing with the actuarial risk, we found that only 2.9% of the studied population was in the high-risk group. Our observation is in agreement with other studies that have been carried out to examine the applicability of the Gail model on different ethnic groups.

Using the data from the Women's Contraceptive and Reproductive Experiences (CARE) Study, Mitchell H. Gail et al developed a model for projecting the absolute risk of invasive breast cancer in African American women and compared its projections with those from the BCRAT. They found that the number of cancers predicted for African American women by the CARE model were higher than those predicted by the BCRAT and agreed well with the numbers of cancers observed among African-American women in the Women's Health Initiative (WHI).[18]

Matsuno et al developed a model, known as the Asian American Breast Cancer Study model (AABCS model) for projecting the absolute invasive breast cancer risk in Asian and Pacific Islander American (APA) women and compared its projections to those from BCRAT. They found that the relative and attributable risks for APA women were comparable to those in BCRAT, but the AABCS model usually estimated lower-risk projections than BCRAT in Chinese and Filipino and not in every age and ethnic subgroup. The AABCS model underestimated absolute risk by 17% (95% confidence interval = 1% to 38%) in independent data from the WHI, but APA women in the WHI had incidence rates approximately 18% higher than those estimated from the SEER program. They concluded that the AABCS model is preferable to BCRAT for counseling APA women. [19]

In a case control study by Leila Farahmand et al, the Gail model efficiency in specifying the risk of breast cancer in Iranian population was evaluated. They found that the average 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. They concluded that the Gail model had insufficient efficiency in determining breast cancer risk in the Iranian society. [20]

Similarly, in another study that evaluated the sensitivities of Gail model and its modifications, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the National Cancer Institute (NCI) models in Turkish women, the Gail model identified 32.52% of the patients as being at high risk. The NSABP model identified 15.48% as being at high risk and the NCI identified 19.39%. It concluded that these three models are not applicable to Turkish women due to their low sensitivity and poor concordance.

In a recent systematic review and meta-analysis assessing the performance of different versions of the Gail model in predicting breast cancer risk, it was concluded that although the original Gail model 1 and the Caucasian-American Gail model were appropriate for predicting the incidence of breast cancer in American and European women, these were not suitable for use in Asian women. However, it was noted in that the Caucasian-American and Asian-American Gail models might overestimate the risk in Asian females about two times, in contrast to the results obtained from our study. Moreover, the discrimination and diagnostic accuracy of the Gail model was not satisfactory overall or stratified by geographic region and different versions of the Gail model.[21]

The current study showed that the BCRAT model underpredicted the risk for developing breast cancer in Indian women. Gail model 1 was designed for white women who were being screened annually [3]. The current version of Gail model 2 used Surveillance Epidemiology and End Results (SEER) breast cancer rates for Asian-American women and the relative and attributable risks were derived from Asian-American females [8]. The Breast Cancer Risk Assessment Tool program specifically warns against the use of the Gail model in Asian women, where breast cancer rates are lower than those in Asian-American women [1]. Accordingly, the risk prediction of the Gail model should be explained with caution when applying it to Asian women and it is necessary to modify the Gail model based on the special risk factors and incidence of breast cancer in Asia as well as by integrating newer genetic variants.

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