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Original Article

Evaluation of risk assessment tools for breast cancer screening in Chinese population

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Abstract: Background: There are many models for screening breast cancer, but not all of them were suitable for all women worldwide including the most famous Gail model. There is no independent risk prediction model in China and no verification of the Gail model in Chinese female population. To evaluate the Gail model for screening breast cancer in Chinese population and compare it with the health risk appraisal (HRA) model. Methods: A total of 3030 Chinese females between 45-70 years were randomly selected for five years follow-up from 2008 to 2014. Gail model and HRA model were compared based on the screening database for breast cancer screening in Chinese female population. Other potential risk factors were also analyzed. Results: The sensitivity of the Gail model was 5.0% and specificity was 97.1%. For the HRA model, the sensitivity was 70.0% and the specificity was 60.6%. The AUC of the Gail model was 0.542 (95% CI, 0.426, 0.658) and the Youden index was 2.1%. The AUC and Youden index of the HRA model was more reliable than the Gail model (AUC, 0.734 (95% CI, 0.643, 0.825); Youden index, 30.6%). In addition, non-menopausal women had a higher risk of developing breast cancer than menopausal women (*P*=0.000). The age of menarche was statistically associated with the risk of developing breast cancer (*P*=0.000). Conclusions: The HRA model is more suitable for Chinese females than the classic risk assessment tool. However, the HRA model needs to be updated to increase its sensitivity and specificity.

Keywords: Risk assessment tool, gail model, health risk appraisal model, breast cancer, Chinese female population

Introduction

Breast cancer is the most common female cancer worldwide, and the sixth leading cause of death in Chinese women [1, 2]. Mammography is the only efficacious screening method that can decrease the mortality rate by 20% as compared to no-screening [3-5]. However, it is not readily available in the developing countries and some remote rural areas of China [6]. With growing public awareness and the discovery of several risk factors of breast cancer, women are paying more attention to the risk of breast cancer. Several risk assessment tools for breast cancer screening, based on the analysis of epidemiological risk factors and genetic mutations, have been developed in the last two decades [7]. These models can estimate a woman's relative risk for breast cancer. Some of them have been applied to surveillance, prevention and decision-making for further clinical invasive examination or operation [8]. Although nearly 30 models have been developed since the first model reported by Gail in 1989, the Gail model remains the most frequently used [9]. The Gail statistical analytic model was established using a database of case-control studies and validated by several epidemiological data. With the gradual improvement of this tool, it was approved by the US Food and Drug Association (FDA) in 2001 and is widely used. However, the Gail model was developed in USA, where the etiological risk factors of breast cancer are different from other countries [10]. Novotny et al. [11] tested the validity of the Gail model in Czech female population and found that the original model is not an accurate breast cancer risk assessment tool for Czech females. Matsuno et al. [12] created an Asian American Breast Cancer Study model (AABCS model) using the data from 589 patients with breast cancer and 952 control subjects, and this model showed different results when compared with the Gail model. Therefore, the Gail model is not suitable for all women worldwide. There is no independent risk prediction model in China and no verification of the Gail model in Chinese female population. Wang et al. [13] developed a health risk appraisal (HRA) model based on the meta-analysis of epidemiological studies on risk factors of breast cancer in Chinese females. It was established by case-control studies with large sample sizes and originally developed using database of Chinese population. Thus, the HRA model seems to basically have advantages in the performance over classic Gail model for Chinese female population. Therefore, we conducted this study to evaluate the Gail model in Chinese population and compare it with the HRA model.

Patients and methods

Patients

The population data was obtained from breast cancer screening in Feicheng of Shandong province in China. We enrolled women between 45-70 years, permanent residents living for > three years in Feicheng, with no history of malignant breast tumor, voluntary participation and acceptable inspection. Finally, 3030 women were randomly selected for five years follow-up from 2008 to 2014. The screening details included medical history of any breast cancer and benign breast diseases, family history of breast cancer and the number of first-degree relatives (mother, sisters, daughters) with breast cancer, history of breast biopsy, the age of the woman when first screened, the age of menarche, the age of first live birth of a child, history of breast-feeding, and history of induced abortion. Patients who were highly suspected to have malignant breast tumor by physical examination, breast ultrasonography or mammography were recommended to undergo biopsy or operation. The result of pathological examination was also obtained.

Risk assessment tool

Risk assessment tool for individualized probabilities of breast cancer was searched from the Pubmed database. Two risk assessment tools were finally selected. Gail model remains the most frequently used and classic model for breast cancer screening. It is most widely used for projecting individualized probabilities of breast cancer. It includes the following eight questions: a medical history of any breast cancer; a mutation in either the *BRCA1* or *BRCA2* gene, or a diagnosis of genetic syndrome that may be associated with elevated risk of breast cancer; the age of the woman; the age at her first menstrual period; the age at her first live birth of a child; how many of her first-degree relatives-mother, sisters, daughters-had breast cancer; any history of breast biopsy, the number of breast biopsies (positive or negative), and any history of at least one breast biopsy with atypical hyperplasia; the race/ethnicity and sub-race/ethnicity of the woman. Each survey data was entered in the system (http://www.cancer.gov/bcrisktool/) and the percentage of 5-year risk of developing breast cancer was recorded. The HRA model was originally developed using database of Chinese population by meta-analysis. It contained six main risk factors for breast cancer in Chinese females: the age of menarche (≤12 years); the age of first birth (≥35 years); history of benign breast diseases; family history of breast cancer; history of breast feeding; and history of induced abortion (≥3 times).

ROC curve and youden index

The receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC) were applied to evaluate the discriminatory power of these two risk assessment tools. The degree of accuracy was divided by the level of AUC as follows: 0.5-0.7, lower accuracy; 0.7-0.9, moderate accuracy; >0.9, higher accuracy. The percentage of females predicted to be at risk of breast cancer among the total females with breast cancer is the sensitivity of the tool. The specificity is the percentage of females predicted to not be at risk of breast cancer among the total females without breast cancer. Youden index is the difference between sensitivity and (1 minus specificity) and shows the diagnostic capability and ability of disease elimination. The value scope of Youden index is 0 to 1. Values close to 1 indicate higher reliability of the diagnostic indicator.

Summary of risk factors

The risk of developing breast cancer in the subgroup of risk factors in this screening was ana-

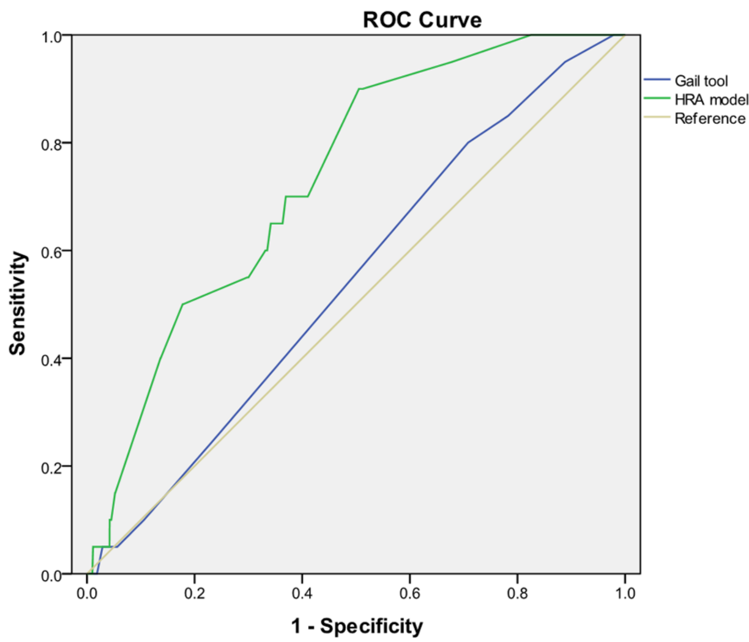

Figure 1. ROC curves for Gail and HRA models. The ROC curve was calculated and the results are shown in this figure. The AUC was 0.542 (95% CI, 0.426, 0.658) in the Gail model and 0.734 (95% CI, 0.643, 0.825) in the HRA model, which suggesting that HRA model was more reliable than the Gail model in our population.

lyzed. Characteristics that were not included in the two risk assessment tools (Gail and HRA models) were also obtained, including body mass index (BMI), the status and age of menopause, history of pregnancy, time of breast feeding, history and duration of oral contraceptives, history of estrogen replacement therapy, history and age of sterilization operation, smoking (both active and passive smoking) and drinking.

Statistical analysis

The calculations of the HRA model were based on the formula established by Wang et al. in 2014 [13]. ROC curve was used to evaluate the sensitivity and specificity of various risk assessment tools for breast cancer screening in Chinese female population. The values of various risk assessment tools were assessed by AUC. Data were expressed as means (range). The normality of the variables was assessed by the Shapiro-Wilk test (for sample size <2000) or Kolmogorov-Smirnov test (for sample size ≥2000). The Mann-Whitney U test (two samples) was applied to compare the differences between continuous variables that were not normally distributed. The x^2 test was used for categorical variables. All tests were two-sided, and statistical significance was defined as $P<0.05$. Data analysis was performed using SPSS version 19.0.

Results

ROC curve and youden index

A total of 3030 females were screened with a 5-year follow-up. Twenty patients (0.66%) developed breast cancer since their first screening within five years. Females, whose estimated risk for developing breast cancer over the next five years was higher than the risk for a woman of the same age (Gail model) or median risks (HRA model), were predicted to have a risk of breast cancer. Each screening data was applied to these two risk assessment tools. The sensitivity of the Gail model was 5.0% and the specificity was 97.1%. The sensitivity of the HRA model was 70.0% and its specificity was 60.6%. The ROC curve was calculated and the results are shown in **Figure 1**. The AUC of the Gail model was 0.542 (95% CI, 0.426, 0.658) and the Youden index was 2.1%, suggesting that it was less reliable. Meanwhile, the AUC and Youden index of the HRA model were more reliable than the Gail model (AUC, 0.734 (95% CI, 0.643, 0.825); Youden index, 30.6%).

Summary of other risk factors

Characteristics that were not included above were further analyzed and are shown in **Table 1**. In this screening population, the risk of developing breast cancer was significantly higher in non-menopausal women than in menopausal women ($P=0.000$). Meanwhile, the mean age of menarche in the patients with breast cancer was significantly higher than that in women without breast cancer ($P=0.000$). However, no association was found between the age of menopause and the risk of developing breast cancer ($P=0.284$). No potential relationship was found between the other risk fac-

Table 1. Characteristics summary by other risk factors

Characteristic	Case (n=20)	Control (n=3010)	*P*
BMI, kg/m^2			
Mean (range)	24.79 (19.53-35.16)	25.12 (16.02-50.78)	0.383
Age of menarche, years			
Mean (range)	16.70 (12-22)	16.34 (10-30)	0.011*
Menopause			
Yes/No	4/16	1920/1090	0.000*
Age of menopause, years			
Mean (range)	48.13 (38-53)	49.05 (23-65)	0.284
History of pregnancy, times			
Mean (range)	2.80 (1-5)	2.66 (1-21)	0.536
Time of breast feeding, months			
Mean (range)	30.21 (10-90)	32.13 (1-384)	0.967
History of oral contraceptives			
Yes/No	2/18	263/2747	1.000
History of estrogen replacement therapy			
Yes/No	0/20	45/2965	1.000
History of sterilization operation			
Yes/No	3/17	273/2737	0.597
Smoking (active and passive)			
Yes/No	9/11	1383/1627	0.930
Drinking			
Yes/No	1/19	97/2913	1.000

Footnotes: BMI, body mass index. *P<0.05.

tors and breast cancer development in this population.

Discussion

We evaluated the Gail and HRA models for breast cancer screening in Chinese female population. The individual consistency between observed cancer status and 5-year predictions of the two models was poor. However, the HRA 5-year risk estimates were more reliable than the Gail model in our population. The status of menopause and the age of menarche were statistically associated with the risk of developing breast cancer. This may be helpful for the development of risk assessment tools for breast cancer screening.

Nowadays, there are several risk assessment tools for breast cancer screening based on the related risk factors. Gail, Couch, Frank, Cuzick-Tyrer, and Claus are commonly used models in different races and countries. The effectiveness of the different models reported in their original literatures was not achieved when they were applied to different populations. The Gail model, which is the first and most frequently used model for breast cancer screening, is mainly based on the family history of breast cancer. Its effectiveness is verified by many studies in different populations, but not all results showed good reliability [11, 12, 14]. This may be due to different population characteristics, such as race (genetic background), lifestyle, environment, etc. that could influence the contribution of risk factors to breast cancer development. So the Gail model is not suitable for all females worldwide and an independent risk prediction model is needed in China.

Last year, Wang et al. [13] developed a breast cancer risk assessment model based on a meta-analysis of epidemiological studies that included 98 published studies on risk factors of breast cancer in Chinese women. The risk score of each risk factor was estimated and those with pooled odds ratio >1.5 or <0.7 was chosen as the input data for calculating the 5-year risk of breast cancer. Finally, six predictors, age of menarche (≤12 years), age at first birth (≥35 years), history of benign breast diseases, family history of breast cancer, history of breast feeding and history of induced abortion (≥3 times), were included in this HRA model. Due to limited large epidemiological data in China, the results of this meta-analysis can be generalized for a larger Chinese population and we hypothesized that the HRA model may be more reliable than others.

This study evaluated the Gail and HRA models for breast cancer screening and found that both the AUC and Youden index are higher in the HRA model than in the Gail model. Therefore, the HRA model may be more applicable to Chinese population than the Gail model because all the analyzed data are from Chinese population. However, the individual consistency of the HRA 5-year predictions was not optimal due to the following reasons: A patient was suggested to have an operation or biopsy only when she was highly suspected to have breast cancer in our population, and not all suspects opted for surgery or biopsy, which may induce misdiagnoses and thus influence the evaluation of these two models. Secondly, the Gail model may be unsuitable for Chinese population due to racial differences. The HRA model is based on a meta-analysis, and heterogeneity and publication bias may have existed between the original epidemiological studies. Lastly, the risk factors included in the HRA model had pooled odds ratio >1.5 or <0.7, and thus some may be over-estimated while others may be missed. Hence, new risk factors associated with the development of breast cancer can also be incorporated into the HRA model.

In our screening population, we also found that older age at menarche and menopausal status were related to the risk of developing breast cancer because of prolonged exposure to endogenous estrogen [15]. The risk of breast cancer was reported to increase with the level of estrogen [16], which may be because estrogen can promote the occurrence and growth of breast cancer by stimulating the mitosis of breast cells. The level of estrogen both in urine and blood is associated with breast cancer [17]. Secondly, breast density was found to be highly associated with the risk of breast cancer, and the risk is higher in patients with high breast density [18]. Moreover, the breast density is related to the level of estrogen. The level of estrogen and progesterone decreases in postmenopausal population, which can lead to the involution of breast tissue with more fatty tissue in the breast, and thus lower the density of the breast [19]. The current HRA model needs to be updated, so that the age of menarche and menopausal status are considered in the risk assessment for breast cancer screening. No association between the age of menopause and the risk of breast cancer was found in this population. As the subjects were in different phases of their menstrual cycles, the comparison of hormone levels was not reliable. So, the hormone analysis should be performed in the same phase of the menstrual cycle with large sample size in the future.

Taken together, the HRA model showed better discriminatory power than the Gail model in this Chinese female population, and was more suitable for Chinese females than the classic risk assessment tool. But it needs to be updated to increase its sensitivity and specificity. Well-designed case-control studies with larger sample size will be helpful for developing risk assessment tools for breast cancer screening in Chinese female population.

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Disclosure of conflict of interest

None.

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