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Sensitivities of the Gail, NSABP and NCI Risk Analysis Models for Turkish Women for Breast Cancer Risk Assessment

Türk Kadınlarında Meme Kanseri Risk Değerlendirmesi için Gail, NSABP ve NCI Risk Analiz Modellerinin Duyarlılıkları

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Abstract
Objectives: The best protection against breast cancer, the most common cancer in women, is early detection. The most commonly used risk assessment tools, identifying women at high risk of developing breast cancer, are the Gail model and its modifications, National Surgical Adjuvant Breast and Bowel Project (NSABP) and National Cancer Institute (NCI) models. We aimed to evaluate the sensitivities of these models.
Materials and Methods: We retrospectively evaluated 1333 patients who had been diagnosed with breast cancer at Ankara Numune Education and Research Hospital and Ankara University Medical Faculty between April 1998 and December 2014.
Results: The Gail model identified 32.52% of the patients as being at high risk. The model NSABP identified 15.48% as being at high risk and the NCI identified 19.39 %.
Conclusion: Comparison of the sensitivity of three models revealed Gail model as the most sensitive one, but it only identified 32.52 % of the patients who developed breast cancer as being at high risk. There was a correlation between the results, but results were significantly different. We conclude that these three models are not applicable to Turkish women due to their low sensitivity and poor concordance. There is a need to develop a new risk assessment model with the addition of different parameters for Turkish women.
Key words: Breast cancer, risk assessment, Turkey

Öz
Giriş: Kadınlarda en sık görülen kanser olan meme kanserine karşı en iyi koruma erken tanıdır. Meme kanseri gelişimi için yüksek riskli bireyleri tanımlamak için en sık kullanılan risk değerlendirme yöntemleri Gail ve modifikasyonları olan National Surgical Adjuvant Breast and Bowel Project (NSABP) ve National Cancer Institute NCI modelleridir. Araştırmamızda bu modellerin duyarlılıklarını değerlendirmeyi amaçladık.
Materyal ve Metot: Ankara Numune Eğitim ve Araştırma Hastanesi ve Ankara Üniversitesi Tıp Fakültesi'nde, Nisan 1998 ile Aralık 2014 tarihleri arasında, meme kanseri tanısı almış 1333 hastayı retrospektif olarak değerlendirdik.
Bulgular: Gail modeli hastaların %32,52' sini yüksek riskli olarak tanımladı. NSABP %15,48 ve NCI modeli %19,39 hastayı yüksek riskli olarak tanımladı.
Sonuç: Üç modelin duyarlılığını karşılaştırdığımızda Gail modeli en duyarlısıdır; fakat zaten meme kanseri gelişmiş olan hastaların sadece %32,52' sini yüksek riskli olarak tanımlayabilmiştir. Sonuçlar arasında korelasyon vardı; ama anlamlı derecede farklı idi. Biz, bu üç modelin, düşük duyarlılık ve zayıf uyuşmalarına bağlı olarak, Türk kadınlarına uygun olmadığına karar verdik. Türk kadınları için, farklı parametreler eklenerek yeni bir risk değerlendirme modeli geliştirilmesine ihtiyaç vardır.
Anahtar kelimeler: Meme kanseri, risk değerlendirme, Türkiye

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Introduction

Breast cancer, about which we got the very first information in Edwin Smith's original Papyrus found in the Egypt between the years 3000 - 2500 BC, ranks first among the malignant tumors in women and second in deaths due to cancer after lung cancer worldwide.[1,4] One of every eight women has breast cancer during their lifetimes and each year 450000 women have lost their lives worldwide because of this illness.[3,5]

The incidence of breast cancer has risen from 31.9 in 100000 in 2002 to 40.6 in 2009 in Turkey and breast cancer ranks first among cancers in women with a rate of 23.4%.[6]

Although a wide range of risk factors are considered in breast cancer; any risk factors cannot be recognized in 75% of the cases. Many risk analysis methods have been identified to determine the risk of breast cancer. Currently, the most common ones are Gail and its modifications named National Surgical Adjuvant Breast and Bowel Project (NSABP) and National Cancer Institute (NCI). These models have been found to be valid in various European racial and ethnic groups.[7,12] And they can be accessed via internet.[13]

The Gail and NSABP models calculate the risk of the individual by taking into account the age, menarche age, the number of breast biopsies and presence of atypical hyperplasia, first live birth age, race, and the history of breast cancer in first-degree relatives. They provide a score according to the same age group without any risk factors. If the calculated risk is higher than 1.67, the subject is considered to have a high risk of breast cancer in the next 5 years.[7]

In addition to the Gail and NSABP models, NCI queries the presence of the BRCA1 and 2 gene mutations or any genetic syndrome that increases the risk of breast cancer for the groups aged 35 to 85 years. This model calculates risks both for the next 5 years and lifetime. Patients can be classified as 'high risk' compared to the average risk of the population of the same age.[14]

In our study we started with the question "Can we predict the patients' high risks for breast cancer". Our study group had been diagnosed with breast cancer. But by ignoring this fact, could we predict their high risks by using the data of the time they were presented to the clinic? We aimed to determine the sensitivity of the Gail, NSABP and NCI risk analysis methods commonly used throughout the world for Turkish women that had actually been diagnosed with breast cancer.

Materials and Methods

We retrospectively evaluated the data of 1333 patients for this study. The group included 903 patients who had a breast cancer diagnosis and have been followed-up at the 2nd

General Surgery Department of the Ankara Numune Education and Research Hospital between April 1998 and December 2014 and 430 patients from the Breast Surgery Unit of the Ankara University Medical Faculty who have been diagnosed with breast cancer and have been followed-up between September 1990 and April 2006.

We evaluated the patient parameters necessary for the Gail, NSABP and NCI risk analysis methods. We collected data from patient files and breast cancer follow-up forms. To investigate each model, we included only the cases providing all the data for that model in the study. Patients with incomplete data were excluded.

The breast cancer risks of all patients were calculated separately using the “Gail Model Risk Calculator”, “NSABP Model Risk Calculator” and “NCI Model Risk Calculator” via internet using data from the day of the diagnosis.

We analyzed the high-risk patients for each model using the statistics program "SPSS for Windows, version 18". After defining the characteristics of the patients, we determined how many patients were at high-risk and how many were not for each model by using the SPSS frequencies table. We used the Chi-Square Test to determine the difference between the models and Pearson Correlation analysis to determine the correlation between models. We calculated Kappa coefficients to check the agreement between the models. $P < 0.001$ was considered as statistically significant.

Results

The mean age of the patients was 50.60 ± 12.30 years, the mean age at menarche was 13.37 ± 1.32 years and mean age at first live birth was 18.38 ± 9.41 years. The percentage of patients with a history of benign biopsy previously was 10.13% (n = 135) and a breast cancer history in the first-degree relatives was present in 3.15% (n = 42).

The Gail and NSABP models could not assess the data in 4.50% (n = 60) of the patients as these models are not available for patients under 20 and over 75 of age. The NCI model could not calculate risks in 0.60% of the patients (n = 8) as they had a diagnosis for another kind of breast cancer previously. Another limitation of the NCI model is that; it cannot evaluate patients under 35 or over 85 years of age, preventing the assessment of 8.48% (n = 113) of the patients.

All three risk assessment models reported 5-year increased risk rates of 32.52% or less. The sensitivities of the Gail, NSABP and NCI models for assessing breast cancer risk were; 32.52%, 15.48% and 19.39%, respectively (Table 1).

Table 1. Risk Increase Status of Patients by Risk Assessment Model

	Increased risk exists	**No increased risk**	**Total**
Gail	414 (32.52%)	859 (67.48%)	1273
NSABP	197 (15.48%)	1076 (84.52%)	1273
NCI	235 (19.39%)	977 (80.61%)	1212

Table 2 shows 5-year risks for breast cancer with the Gail, NSABP and NCI risk assessment models.

Table 2. Results of Evaluation with Risk assessment of the Models

	Mean + s	**min.**	**max.**	**Total**
Gail 5-year risk	1.50 ± 0.96	0.2	10.10	1273
NSABP 5-year risk	1.06 ± 0.74	0.2	7.30	1273
NCI 5-year risk	1.11 ± 0.70	0.2	7	1212

The NCI model reported “No increased risk” for 59% of the patients where the Gail model reported "Increased risk exists" during the 5-year risk assessment. There was a statistically significant difference between the NCI and Gail risk assessment models (P<0,001, Table 3).

Table 3. Comparison of the Gail and NCI Models at 5 years for Increased Risk Existence

			NCI Risk Existence		**Total**
			No	**Yes**	
Gail Risk Existence	No	n	695	59	754
		%	92.18	7.82	100
	Yes	n	242	168	410
		%	59.02	40.98	100
Total		n	937	227	1,164
		%	80.50	19.50	100
P value			<0.001		

When we compared the Gail and NSABP models, NSABP reported “No increased risk” for 54% of the patients where Gail reported "Increased risk exists". There was a statistically significant difference between these models (P < 0,001, Table 4).

While determining the difference between NCI and NSABP models, we saw that NSABP reported “No increased risk” for 50.66 % of patients where NCI reported as "Increased risk exists". We found a statistically significant difference between NCI and NSABP models. (P < 0,001, Table 5).

There were positive correlations between the Gail and NSABP models (r = 0.585, P < 0.001), Gail and NCI (r = 0.400, P < 0.001) and also NCI and NSABP (r = 0.431, P < 0.001) for 5-year risk assessments.

The degree of agreement between the models was 52% (κ = 0.52, P < 0.001) for the Gail and NSABP models, 36% (κ = 0.37, P < 0.001) for Gail and NCI, and 42% (κ = 0.42, P < 0.001) for NCI and NSABP.

Discussion

We found that the commonly used Gail, NSABP and NCI risk assessment models were not suitable for Turkish women. The sensitivities of the models were; 32.52%, 15.48% and 19.39%, respectively.

Table 4. Comparison of Gail and NSABP Models for the existence of 5-year Increased Risk

			NSABP Risk Existence		Total
			No	Yes	
Gail Risk Existence	No	n	856	7	863
		%	99.19	0.81	100
	Yes	n	223	190	413
		%	54.00	46.00	100
Total		n	1079	197	1,276
		%	84.56	15.44	100
p value			<0.001		

Table 5. Comparison of NCI and NSABP Models for 5-year Increased Risk Existence

			NSABP Risk Existence		Total
			No	Yes	
NCI Risk Existence	No	n	854	82	936
		%	91.24	8.76	100
	Yes	n	115	112	227
		%	50.66	49.34	100
Total		n	969	194	1,163
		%	83.32	16.68	100
p value			<0.001		

Euhus et al. found the Gail model adequate for the majority of women, with 87% sensitivity on 213 patients. They claim that the addition of other risk calculation models increased the risk estimate by only 13%.[10] Anne et al. found Gail to be a good method to calculate the risk of breast cancer in their study on 491 women aged 18 to 74 years with family history of breast cancer in 2001.[11] Abu-Rustum et al. suggested Gail for risk estimation with their study on a population with low socio-cultural status.[9] In our study, the Gail risk calculation method was applied to 1273 women aged 19 to 87 years and we found increased risk in only 32.52% of the patients. Considering that all of our patients had been diagnosed with breast cancer, the Gail risk analysis method could not detect 67.48% of the patients with a breast cancer risk. Our results contradict the results of the

above studies and we could not prove the applicability of this model in a larger number of patients.

Mackarem et al. randomly selected 107 women and 129 nurses aged under 40 with a history of breast biopsy for benign reasons and found that Gail was not adequate in this age group.[12] Kaur et al. reported that the Gail model was an inadequate method of risk assessment for breast cancer in 1458 women of Indian American or Alaska origin.[15] Our study differed from others as it was conducted on patients diagnosed with breast cancer and we believe this decreased Gail's applicability. Gail could not foresee the breast cancer risks of our patients who had a breast cancer diagnosis. Gail used patients participating in the "Breast Cancer Detection Demonstration Project" while creating his models and all his subjects were Caucasian and had come for annual mammography follow-up. Other limitations of this model, which does not include African-Americans, are that Gail does not include the age of relatives when they had cancer and does not assess second-degree relatives or the father's relatives with breast cancer. Therefore the risk calculated by Gail is lower than expected.[7,16]

In the Pastor et al. study on 685 patients with breast cancer, NSABP was used for breast cancer risk estimation. They found only 40% of patients to have high risk and concluded that NSABP is not suitable for Spanish population.[17] The NSABP model, which is an upgraded version of Gail with the addition of African-Americans to the assessment and can only accept invasive ductal carcinoma as cancer, could only report "increased risk exists" for 15.48% of our patients in our study. We can also say that the NSABP model is not suitable for our population as we did not find increased risk in 84.52 % of our patients.

NCI, the latest version of Gail, showed insufficiency for estimating the risk of breast cancer for Turkish population by defining only 19.39% of patients as at 'increased risk'. In the literature, we could not find any study evaluating the adequacy and sensitivity of the NCI model. The NCI model cannot evaluate patients who have been diagnosed with any type of breast cancer or ductal carcinoma in situ or lobular carcinoma in situ or who have received radiation therapy due to Hodgkin's lymphoma disease to the chest area.

Adams et al. accepted the threshold value of Gail as 1.7% for their study on 725 breast cancer patients and 725 control patients conducted on African-American women in June 2007. The results of the 5-year risk with Gail were; 0.2% - 15.4% in the breast cancer group and 0.2% - 13.6% in the control group. For the NSABP model, the 5-year risk results were 0.2% - 8.7% and 0.2% - 7.2% in the cancer and control groups, respectively. In this study, the sensitivities of the Gail and NSABP models were 17.9% and 4.1%, respectively.[18] In another study conducted in Turkey, the researchers declared that Gail model can be used to estimate an individual's probability for developing breast cancer. In their study, the average 5-year risk for all women was 0.88±0.91%, and 7.4% of women had a 5-year breast cancer risk >1.66%. Mean lifetime breast cancer risk up to age 90 years was 9.3±5.2% .[19] In another study according to Gail model, as to 5-year breast cancer risk score, 22.4% (n = 140) of the women were defined as in "increased-high risk" group with a median risk score of 2.00 (Range: 1.70-4.20) and 77.6% (n = 484) were in "average risk" group with median Gail score 1.20 (Range: 0.50-1.60).[20] We calculated the average 5-year risk as 1.5 (0.2% -

10.1%) with Gail and 1.06 (0.2 % - 7.3 %) with NSABP (Table 2). According to our results, the Gail model had a sensitivity of 32.52% for the Turkish woman groups while the sensitivity of the NSABP model was 15.48%. In a study conducted in Turkey for the applicability of the Gail model for breast cancer risk assessment for Turkish female population, they concluded that the Gail model was not appropriate breast cancer risk assessment tool for Turkish females with the sensitivity of 13.3% and specificity of 92%.[21]

When compared with the NSABP model, the Gail results were better, but were still inadequate to detect the high-risk cancer patients in our study. Considering that NSABP is the upgraded version of Gail, we expected NSABP to be more sensitive but the NSABP model detected fewer patients and showed lower sensitivity.

We could not find any studies that compared these three methods in terms of sensitivity and evaluated their correlation in the literature. In our study, Gail was the most sensitive method with 32.52%, NCI was second and NSABP was the least sensitive one. When we compared these three methods in terms of sensitivity and correlation, there was a statistically significant difference between the models despite the high degree of correlation between the absolute values with significant positive correlations. We consider this as an expected result.

According to the magnitude guidelines, κ values < 0 were characterized as indicating no agreement, 0 – 0.20 as slight, 0.21 – 0.40 as fair, 0.41 – 0.60 as moderate, 0.61 – 0.80 as substantial and 0.81 – 1 as almost perfect agreement.[22] We found the agreement between the Gail and NSABP models and the NCI and NSABP models as fair, and the agreement between the Gail and NCI models as moderate.

Considering the lack of a significant correlation between the models and that the NSABP, NCI were developed as models to correct deficits seen in Gail, it is interesting that they detected different patients with high risk and low risk.

We did not come across any study evaluating the suitability and sensitivity of these three models for the Turkish society and investigating the ideal risk analysis method in the literature.

The limitation of our study was that; we did not have a control group. We only investigated the risk for certain groups of patients with a definite diagnosis of breast cancer and could therefore only calculate the sensitivity. The results could have been different with a control group. Therefore, another study querying the usability of the models on the normal population with 5-year follow-up is needed.

The strengths of our study are that; we evaluated 1333 patients, the largest number for such studies so far, and compared the Gail, NSABP and NCI models, making the study unique.

Currently there is no method that is adequate by itself to calculate the effect of each variable such as family history, reproductive history and benign breast diseases of the individuals and the histopathology of the disorder, etc. Another issue is to determine the effect of each risk factor for evaluation risk in the population. Inclusion of additional risk parameters should also be investigated. For an extensive and comprehensive analysis, it is

required to fully understand the strengths and weaknesses of the individual methods. It is necessary to develop a risk assessment model for each community by working on a large number of cases.

The Gail, NSABP, and NCI methods will not be appropriate for use in the Turkish society and we believe that they would not detect many patients' actual cancer risk as a result of their low sensitivity as well as the low concordance with each other. Risk calculation models should be developed for the Turkish population.

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