RESEARCH ARTICLE

Breast Cancer Risk Based on the Gail Model and its Predictors in Iranian Women

Mojgan Mirghafourvand[1], Sakineh Mohammad-Alizadeh-Charandabi[2], Parivash Ahmadpour[3]*, Pari Rahi[3]

Abstract

Background: This study was carried out to examine breast cancer risk and its fertility predictors in women aged ≥35. Materials and Methods: This cross-sectional study was conducted on 560 healthy women referred to health centers of Tabriz-Iran, 2013-2014. Five-year and lifetime risk of developing breast cancer were determined using the Gail model. General linear modeling was applied to determine breast cancer predictors. Results: The mean age of the subjects was 42.7 (SD: 7.7) years. Mean 5-year and lifetime risks of developing breast cancer were determined to be 0.6% (SD: 0.2%) and 8.9% (SD: 2.5%), respectively. Variables of family history of breast cancer, age, age at menarche, parity, age at first childbirth, breastfeeding history, frequency of breastfeeding, method of contraception, marital status and education were all found to be predictors of breast cancer risk. Conclusions: According to the results of this study, screening programs based on the Gail model should be implemented for Iranian people who have a high risk for breast cancer in order to facilitate early detection and better plan for possible malignancies.

Keywords: Gail model - breast cancer - risk factors - five year - lifetime - Iran

Asian Pac J Cancer Prev, **17 (8)**, 3741-3745

Introduction

Breast cancer is the most prevalent type of cancer ever diagnosed in women (DeSantis et al., 2014). At the time, %40 all cancers diagnosed among women is breast cancer (Clarke and Glaser, 2007; Anders et al., 2009). About 7% of women suffering from breast cancer are <40 years of age (Sasco, 2001; Siegel et al., 2013). There is a wide variety of breast cancer prevalence across the world (Yankaskas, 2005). It has relatively increased among African and American women and decreased among Hispanic women. The prevalence has been constant among white American and Asian women; especially, Icelandic women and indigenous Americans of Alaska and India between 2006 and 2010 (DeSantis et al., 2014).

Based on the last report by Iranian Cancer Research Center, the updated age-standardized breast cancer incidence rate was 28.89/1000 for East Azerbaijan Province, in 2009. Its prevalence and mortality in Iranian women have been reported respectively 17.7 and 5.2 in every 1000 women (Report, 2012). Mean cancer age has been reported between 47.1 and 48.8 in Iranian women. It is a decade lower than mean breast cancer age in advanced countries (Harirchi et al., 2004).

Cancer risk factors are related to women's fertility issues including premature menstruation, infertility, giving the first birth at higher ages, prolonged menopause, diet, physical activity, and endogenous (the high level of free estrogen versus estrogen attached to serum proteins) or exogenous (the long term use of contraceptive pills or alternative hormone therapy in menopausal women) hormonal factors (Sasco, 2001; Mohammadbeigi et al., 2015). Geographical differences affect the prevalence and risk factors of cancers. It is impossible to generalize criteria and risk factors to other populations (Shantakumar et al., 2007, Ulusoy et al., 2010).

There are various ways to estimate breast cancer risk. Among them, Gail model is the most well-known. This model comprises seven criteria including age, age at the start of menstruation, age at first live birth, at least one breast biopsy with atypical hyperplasia, number of previous breast biopsies (whether positive or negative, number of first-degree relatives (mother, sisters, daughters) with breast cancer, and race. The probability of breast cancer is estimated based on these seven measures (Vacek et al., 2011). Breast cancer screening plan and the secondary treatments have been reported to reduce the rate of mortality (Berry et al., 2005). This study aimed to determine the 5-year and the general lifetiume risk of breast cancer and also to determine breast cancer predictors in women referred to a healthcare center in Tabriz-Iran.

*[1]Midwifery Department, [2]Social Determinants of Health (SDH) Research Center, Midwifery Department, [3]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran *For correspondence: parivash.ahmadpor@yahoo.com.*

Materials and Methods

Study design, participants and setting

This cross-sectional study was conducted on 560 healthy women referred to health centers of Tabriz during 2013- 2014. Inclusion criteria were women ≥35 years old and who expressed a willingness to participate in the present study.

Sample Size

The sample size of this study was calculated 280 subject based on a study by Hosseinpour et al (Hosseinpour et al., 2012) and confidence level %95, SD:0.47, D=0.05, M=0.55. Yet, with respect to cluster sampling and considering the design effect equal 2, the final sample size was set 560.

Sampling

Two-stage cluster sampling was conducted. Using website www.random.org computer, first, 27 health centers and bases were randomly selected among 27 health centers and 53 health bases in Tabriz. Then, based on the information existing in each health center and base, suitable sample size for each center was computed and set based on the main sample size (i.e. n=560). The list of all women under the coverage of each unit was extracted. They were aligned in the list by number. Using computer, about 1.5 times the quota of each center were randomly selected. Now, if any participant did not meet the inclusion criteria or was not accessible and/or reluctant to participate in the study, the next individual would be randomly selected and substituted for her in the list. In all sampling stages, people who were among the main individuals in the list based on the center quota were prioritized.

Those who eligible to enter the study were asked to participate in the study during phone call. They were asked to attend the health center in given date and time for completing questionnaires. In this meeting, the objectives, methods and necessary explanations on content of the study were given to the subjects. The subjects were assured that all information would remain confidential. After obtaining informed consent forms, questionnaires were completed by the researcher via interview from participants.

The data collection tool

Data collection tools included the form of socio-demographic characteristics, reproductive characteristics questionnaire and Breast Cancer Detection Demonstration Project (BCDP).

The socio-demographic characteristics including: age, educational level, job, economic status, marital status and BMI (Body Mass Index).

The reproductive characteristics questionnaire including: gravidity, parity, number of children, age at first live birth, breastfeeding history, breastfeeding frequency, duration of breastfeeding, history of infertility, duration of infertility, contraception, duration of oral contraceptives usage, age at menarche, mammogram history, mammogram number, age at first mammogram, family history of breast cancer, and menopause status.

Breast Cancer Detection Demonstration Project (BCDP) is a model for annual mammography screening plan to estimate the risk of breast cancer in women (Costantino et al., 1999). In this model, the 7 criteria including age, age at menarche, age at first birth, previous history of carcinoma in situ , history of breast biopsy, family history of breast cancer and race. The probability of breast cancer is estimated based on these criteria. This is an on-line computer program. It is developed for the providers of the basic health care to present advice to women. Early Gail model estimate the absolute risk of invasive cancer in situ (Yankaskas, 2005). The model was modified later by Constantion et al., It is used for intervention plans in women to prevent from cancer. Gail

Table 1. Socio-demographic and Reproductive Characteristics of the Participants (n=560)

Characteristics	n (%)
Age (years) *	42.7 (7.7)
Monarch age (years) *	13.1 (1.3)
Gravida*	3.2 (2.1)
Parity*	2.6 (1.6)
age at first live birth	21.3 (6.4)
Body mass index (kg/m2) *	28.3 (4.4)
<18.5	2 (0.4)
18.5-24.9	133 (23.8)
25-29.9	247 (44.1)
≤30	178 (31.8)
Sufficiency of income for expenses	
Completely	19 (3.4)
To some extent	499 (89.1)
Absolutely not	42 (7.5)
Education	
Illiterate	97 (17.3)
Elementary	154 (27.5)
Secondary	102 (18.2)
High school & Diploma	139 (24.8)
University	68 (12.1)
Marital status	
Single	7 (1.3)
Married	535 (95.5)
Widow	17 (3)
Menopause	
Yes	94 (83.2)
No	466 (16.8)
History of infertility	
Yes	25 (4.5)
No	535 (95.5)
History of breastfeeding	
Yes	532 (95)
No	28 (5)
mammography	
Yes	56 (10)
No	504 (90)
Family history of breast cancer	
Yes	12 (2.1)
No	548 (97.9)

Data indicate number (%) unless it has a *; There was a divorced woman among participants

model 2 is a tool for examining the risk of breast cancer in National Cancer institute. It is accessible through site http://www.cancer.gov/bcrisktool (Costantino et al., 1999). The sensitivity and specificity of this model have been reported over %90, in the recent studies (Pohls et al., 2004).

Validity of questionnaires was determined using content validity and based on the comments of ten different experts.

Data analysis

After filling out on-line forms through site http://www.cancer.gor/bcrisktool/, the 5-year and lifetime risk of developing breast cancer were determined.

The data was analyzed using SPSS ver 21. The descriptive studies including mean, standard deviation, frequency and percentage were used for description of reproductive and socio-demographic characteristics. To determine the relationship between the socio-demographic and reproductive characteristics and the 5-year and lifetime risk of developing breast cancer, first bivariate tests including one-way ANOVA, independent t-test and Pearson correlation test were used. Then, to control confounder factors, variables with p<0.05 in bivariate tests were entered in general linear model to determine the predictors of breast cancer risk.

Results

Based on the findings of the socio-demographic information, age of the participants was 35 to 74 years with the majority of patients (90.9%) in the age group 35 to 55 years. The mean age of subjects at menarche was 42.7 (SD: 7.7) years old.16.8% of the subjects were postmenopausal. Most women (91.6%) were housekeeper. The majority (89.1%) stated that their monthly income for life costs is somewhat adequate. More than a quarter (27.5%) had elementary and 1.12% had university education. The majority of women (95.5%) were married.

About a half of participants (50.4%) had taken hormonal contraceptive pills during their lives. The age of the first childbirth was between 14 and 43. Most participants (11.8%) gave the first birth at age of 20. Most women (95%) had a history of breastfeeding. About 4.5% of women had a history of infertility. About 10% had gone under at least one mammography and 12 women had a familial history of breast cancer; mother in five cases, sister in four cases, cousin in a case, aunt in a case, and grandmother in a case (Table 1).

5 -Year Risk of Developing Breast Cancer

Results of this study showed that average breast cancer risk in the next five years is 0.6% (SD: 0.23%). Results of bivariate tests demonstrated that there was a relationship between the risk of breast cancer in the next five years and variables of a ge, job, education, age at menarche, gravidity, parity, marital status, BMI, history of breastfeeding, breastfeeding frequency, infertility history, duration of infertility, menopause age, the number of mammography, woman's age in the first mammography, a positive familial history of breast cancer, the number of people with positive breast cancer in a family, the type of birth control and duration of taking contraceptive pills (P<0.005).

These variables were entered in general linear model. Finally, the variables of having age, age at menarche, education, parity, positive familial history of breast cancer are among the predictors of breast cancer risk in the next five years. These variables predict 79.9% of variance of the five-year risk (Table 2).

Lifetime Risk of Developing Breast Cancer

Mean breast cancer risk in whole-life was 8.9% (SD: 2.5%). Results of bivariate tests showed that there is a relationship between lifetime risk of breast cancer and variables of age, job, education, age at menarche, gravidity, parity, marital status, BMI, age at first childbirth, breastfeeding history, breastfeeding frequency, infertility history, duration of infertility, menopause age, positive familial history of breast cancer, the number of people with positive breast cancer in a family, the type of birth control and duration of taking contraceptive pills (P<0.005).

These variables were placed in general linear model. Finally, the variables of age, age at menarche, marital status, education, parity, age at first childbirth, breastfeeding history, breastfeeding frequency, positive familial history of breast cancer and the type of birth control are among the predictors of breast cancer risk in Lifetime. These variables predicted 77.3% of the variance of the lifetime risk (Table 3).

Table 2. Socio-demographic and Reproductive Predictors of 5-Year Risk of Developing Breast Cancer in Women 35 Years and over in Tabriz Based on the General Linear Model

Socio-demographic and reproductive characteristics	5 Year Risk of Developing Breast Cancer	
	B (CI 95%)	P
Age (years)	0.04 (0.04 to 0.05)	<0.001
Monarch age (years)	-0.02 (-0.03 to -0.01)	<0.001
Parity	-0.04 (-0.08 to -0.01)	0.007
Education (Reference: University)		
Illiterate	-0.05 (-0.11 to 0.01)	0.121
Elementary	-0.03 (-0.08 to 0.02)	0.201
Secondary	-0.06 (-0.11 to -0.01)	0.028
High school	-0.03 (-0.11 to 0.04)	0.387
Diploma	-0.03 (-0.08 to 0.02)	0.174
Family history of breast cancer (Reference: Yes)		
No	-0.59 (-0.68 to -0.50)	<0.001

Table 3. Socio-demographic and Reproductive Predictors of Lifetime Risk of Developing Breast Cancer in Women 35 Years and over in Tabriz Based on the General Linear Model

Socio-demographic and reproductive characteristics	Lifetime Risk of Developing Breast Cancer	
	B (CI 95%)	P
Age (years)	0.07 (-0.1 to -0.05)	< 0.001
Monarch age (years)	-0.33 (-0.41 to -0.25)	< 0.001
Parity	-0.51 (-0.77 to -0.25)	< 0.001
Frequency of Breastfeeding	-0.31 (0.07 to 0.56)	0.013
Age at first live birth	0.23 (0.21 to 0.25)	< 0.001
Education(Reference: University)		
Illiterate	-0.68 (-1.17 to -0.17)	0.009
Elementary	-0.64 (-1.1 to -0.21)	0.003
Secondary	-0.81 (-1.2 to -0.37)	< 0.001
High school	-0.42 (-1.1 to 0.22)	0.196
Diploma	-0.51 (-0.91 to -0.10)	0.014
Marital status(Reference: Widow)		
Single	2.17 (0.92 to 3.41)	0.001
Married	-0.1 (-0.70 to 0.50)	0.744
Divorced	-0.69 (-3.10 to 1.70)	0.574
History of breastfeeding (Reference: Yes)		
No	2.91 (2.19 to 3.64)	< 0.001
Family history of breast cancer (Reference: Yes)		
No	-5.93 (-6.62 to -5.24)	< 0.001
Contraceptive method(Reference: LD With other methods of contraception)		
Non-use of contraception	0.80 (0.28 to 1.32)	0.003
Only contraceptive pills	0.44 (-0.01 to 0.89)	0.055
Other contraceptives except pills	-0.06 (0.29 to -0.18)	0.643

Discussion

In this study, all women underwent breast examination by a researcher trained in this area. Here, 560 women lived in Tabriz were examined. In individuals with any abnormal finding and those with high breast cancer risk factors including people mentioning the first and second degree positive familial histories were further examined using sonography or mammography. Fibrocystic masses were reported in 59 cases. Yet, no abnormal result was observed in the further examinations. Proper breast self-examination was also taught to all individuals.

Based on Gail model, mean breast cancer risk in the next five years was computed 0.6% for Iranian women resident in Tabriz city and 8.9% for whole life. It correlates with studies done in other cities, in Iran. For instance, in a study carried out in Rasht (Seyednoori, Pakseresht et al., 2012) in 2008, 314 women were evaluated using Gail model. In this study, mean participants' age was 45.8. Mean five-year risk of breast cancer was reported 0.8% and 9% for whole life. Hosseinpour et al (Hosseinpour et al., 2012) (2011) examined 513 women in a study in Yasuj. Mean participants' age was 41.8. In these women, the five-year risk of breast cancer was reported 0.55% and 8.2% for whole life. Low risk of breast cancer in Yasuji women is attributed to low age of marriage, having children, and breastfeeding. In another study by Mohammadbeigi et al. (2015), 296 women aged more than 34-year-old in Qom, center of Iran were examined using Gail model. The mean age of the participants was 47.8 ± 8.8-year-old and 47% have Fars ethnicity. The 5 years and lifetime risk was 0.37±0.18 and 4.48 ± 0.925%, respectively. It was lower than the average risk in same race and age (P<0.001).

In a study by Lee et al. (2014), 15582 women between 35 and 85 were examined using Gail model. Mean five-year breast cancer was reported 1.16% and 1.12% for urban and non-urban women, respectively. Similarly, general cancer risk was reported 8.94% and 8.85% for urban and non-urban women, respectively. The level of risk was lower for non-urban women as compared to urban women. In this study, age, menstruation age, breast biopsy history, and the age of the first childbirth were reported as breast cancer risk factors. These are in accordance with the results of the present study. In a study by Erbil et al. (2015), 231 women 35 years or older were examined using Gail model. The mean five-year breast cancer risk for all women was 0.88±0.91%, and 7.4% of women had a five-year breast cancer risk >1.66% in this study. Mean lifetime breast cancer risk up to age 90 years was 9.3±5.2%.

Based on the results of the present study, average five-year risk of breast cancer increases with age. Maximum five-year risk was seen in educated people. That is, as the education level increased, the presence of the positive familial history of breast cancer was also among the main five-year risk factors. Again, low menstruation age increased the risk.

The general risk of breast cancer was high in single individuals, people with a positive familial history of breast cancer, and individuals with no history of breastfeeding. It increased with the reduction of menstruation age, higher level of education, and higher women's age in the first childbirth. The risk was lower in individuals with no history of taking contraceptive pills and using birth control methods. The increase of the number of parity and breastfeeding history reduced respective risk. These results approve the results of previous studies regarding breast cancer risk factors (McPherson et al., 2000; Hosseinpour et al., 2012). Premature menstruation and prolonged menopause increase breast cancer risk. The risk of breast cancer in women with menopauses after

55 is twice the risk in women with menopauses before 45. Again, breast cancer risk was twice in women gave birth after 30 as compared to women gave birth before 20 (McPherson et al., 2000). In the present study similar to mentioned studies, the risk of breast cancer was associated with higher age, early age at menarche and higher age at first birth.

Since 1990, breast cancer morality has annually decreased about 2.2% in the US and other industrial countries. This reduction is attributed to the advance of secondary treatment and the use of mammography and screening (Berry et al., 2005). Despite the reduction of breast cancer morality in developed countries, it is still a health challenge for developing countries like Iran. Based on studies done in Iran, breast cancer morality has an increasing trend in this country (Taheri et al., 2012). There is a need to plans for women's awareness of breast cancer symptoms and the administration of screening plans (Taghavi et al., 2012). Women must be educated about breast cancer screening methods and early diagnosis. The women in the high risk group should be informed on their risk status which may increase their attendance at breast cancer screening (Acikgoz and Ergor, 2013).

In addition to the above mentioned risk factors, factors like diet, gene, and race have effect on breast cancer (Shaukat et al., 2013). Accordingly, it is suggested that breast cancer risk is assessed in various populations and areas using Gail model. Screening plans are developed in the area based on the determined risk, and policies are made based on cost-benefit equation.

One of the limitations of this study is its cross-sectional nature. Yet, the relationships shown do not exactly indicate the cause-and-effect relationship.

In conclusion, Based on the results of this study, the main risk factors of breast cancer include the history of breastfeeding, the age of first childbirth, and the number of parity. Regarding the lack of an extensive screening plan in Iran, it seems that screening must be emphasized for people with a high risk of cancer incidence.

Acknowledgements

This article is written based on a research proposal approved by Student Research Center of Tabriz Medical School. It is funded by the research deputy of this university. We thank all the participants in this research.

References

Acikgoz A, Ergor G (2013). Compliance with screening recommendations according to breast cancer risk levels in Izmir, Turkey, *Asian Pac J Cancer Prev*, **14**, 1737-42.

Anders CK, Johnson R, Litton J, et al (2009). Breast cancer before age 40 years. *Seminars Oncol*, **36**, 237-49.

Berry DA, Cronin KA, Plevritis SK, et al (2005). Effect of screening and adjuvant therapy on mortality from breast cancer, *N Engl J Med*, **353**, 1784-92.

Clarke CA, Glaser SL (2007). Declines in breast cancer after the WHI: apparent impact of hormone therapy. *Cancer Causes Control*, **18**, 847-52.

Costantino JP, Gail MH, Pee D, Anderson S, et al (1999). Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst*, **91**, 1541-8.

DeSantis C, Ma J, Bryan L, et al (2014). Breast cancer statistics, 2013. *CA Cancer J*, **64**, 52-62.

Erbil N, Dundar N, Inan C , et al (2015). Breast cancer risk assessment using the Gail model: a Turkish study, *Asian Pac J Cancer Prev*, **16**, 303-6.

Harirchi I, Karbakhsh M, Kashefi A, et al (2004). Breast cancer in Iran: results of a multi-center study, *Asian Pac J Cancer Prev*, **5**, 24-7.

Hossainpour R, Haji Nasrolah E, Rangpour F, et al (2012). Evaluation of the risk of breast cancer, based on the Gail model, in women of more than 35 years old: at health centers of Yasouj during 2010-2011. *Iranian J Sergical*, **20**, 13-20.

Lee C, Lee J C, Park B, et al (2015). Computational discrimination of breast cancer for korean women based on epidemiologic data only. *J Korean Med Sci*, **30**, 1025-34.

Lee JY, Klimberg S, Bondurant KL, et al (2014). Cross-sectional study to assess the association of population density with predicted breast cancer risk. *Breast J*, **20**, 615-621.

McPherson K, Steel CM, Dixon JM (2000). ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *BMJ*, **321**, 624-8.

Mohammadbeigi A, Mohammadsalehi N, Valizadeh R, et al (2015). Lifetime and 5 years risk of breast cancer and attributable risk factor according to Gail model in Iranian women. *J Pharm Bioallied Sci*, **7**, 207-11.

Pohls UG, Renner S, Fasching P, Lux M, et al (2004). Awareness of breast cancer incidence and risk factors among healthy women. *Eur J Cancer Prev*, **13**, 249-56.

Iran Cancer Report (2012). Iran cancer report 2009, from (http://ircancer.ir/Portals/0/CancerBooks/Iran%20Cancer%20Report%201388.pdf).

Sasco AJ (2001), Epidemiology of breast cancer: an environmental disease. *APMIS*, **109**, 321-32.

Seyednoori T, Pakseresht S, Roushan Z (2012). Risk of developing breast cancer by utilizing Gail model. *Women Health*, **52**, 391-402.

Shantakumar S, Terry MB, Teitelbaum SL, et al (2007). Reproductive factors and breast cancer risk among older women. *Breast Cancer Res Treat*, **102**, 365-74.

Shaukat U, Ismail M, Mehmood N (2013). Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. *Asian Pac J Cancer Prev*, **14**, 5625-9.

Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013, *CA Cancer J Clin*, **63**, 11-30.

Taghavi A, Fazeli Z, Vahedi M, et al (2012). Increased trend of breast cancer mortality in Iran. *Asian Pac J Cancer Prev*, **13**, 367-70.

Taheri NS, Bakhshandehnosrat S, Tabiei M, et al (2012). Epidemiological pattern of breast cancer in Iranian women: is there an ethnic disparity. *Asian Pac J Cancer Prev*, **13**, 4517-20.

Ulusoy C, Kepenekci I, Kose K, et al (2010). Applicability of the Gail model for breast cancer risk assessment in Turkish female population and evaluation of breastfeeding as a risk factor. *Breast Cancer Res Treat*, **120**, 419-24.

Vacek PM, Skelly JM, Geller BM (2011). Breast cancer risk assessment in women aged 70 and older. *Breast Cancer Res Treat*, **130**, 291-9.

Yankaskas BC (2005). Epidemiology of breast cancer in young women. *Breast Dis*, **23**, 3-8.