

Risk Factors of Breast Cancer in Bahrain

Suhair Al-Saad, MBChB, FRCS I, CABS* Hamdi Al-Shinnawi, MBBS, FRCS I**
Najla Mahmood Shamsi, MD***

Background: Breast cancer is the most common cancer in females worldwide, and the second leading cause of cancer deaths in women. It is accounting for 32% of all cancers. It is well known that gender, age, past history of malignancy, family history of malignancy, prolonged uninterrupted exposure to estrogen are recognized risk factors of breast cancer. Few studies on risk factors in Bahrain were performed.

Objective: To assess the primary risk factors of breast cancer in patients living in Bahrain.

Setting: All patients operated by the two senior authors in Salmaniya Medical Complex and Ibn Al-Nafees hospitals in Bahrain.

Design: Prospective study.

Method: A clinical review of 105 breast cancer patients performed from August 1999 to September 2008. Bahraini and non-Bahraini patients are included. Presentation, diagnostic approach, and management were evaluated. Characteristic data included were age at presentation, age at menarche and menopause. Other factors age at first full term pregnancy, history of lactation, history of using hormonal replacement therapy, history of using oral contraceptive pills, past personal history of malignancy and, type of malignancy, family history of breast cancer.

Result: One hundred and five patients, all were females. The age of patients at diagnosis was categorized as follows: less than 35 years old were 10 patients (9.5%), 35-45 years were 33 patients (31.4%), 46-55 years were 30 patients (28.6%) and more than 55 years old were 32 patients (30.5%).

Twenty patients had early menarche (19%), 3 patients (2.8%) had late menopause. Twenty patients were nulliparous (19%). Six patients (5.7%) had their first delivery at an age of more than 30 years while those who had their first delivery at less than

* Consultant Surgeon and Assistant Professor
** Consultant Surgeon and Assistant Professor
College of Medicine, Arabian Gulf University
*** Surgical Intern
Surgical Department
Salmaniya Medical Complex
Kingdom of Bahrain

30 years of age were 79 patients (75.2%). Lactation history was negative in 27 patients (25.7%). Twenty-one patients (20%) used Oral Contraceptive Pills (OCP) for long periods. Two patients (1.9%) only were on Hormonal Replacement Therapy (HRT). Two patients (1.9%) had positive past personal history of malignancy (breast and ovaries). Twenty-two patients (20.9%) had positive family history of breast cancer.

Conclusion: Almost 70% of our patients were below or equal to 55 years at presentation. Family history was found significantly higher in our patients (20.9%).

Bahrain Med Bull 2009; 31(2):

Breast cancer is unlike lung cancer, in which smoking is the primary cause. Breast cancer has large number of epidemiological factors which will increase the risk.

These risk factors could provide important clues to the etiology of breast cancer.

Advancing age is one of the most important factors. It was found that breast cancer incidence and death rates generally increase with age. From 2001-2005, the median age at diagnosis for breast cancer in US females was 61 years of age. Approximately 0.0% was diagnosed under age 20, 1.9% between 20 and 34, 10.6% between 35 and 44, 22.4% between 45 and 54, 23.3% between 55 and 64, 19.8% between 65 and 74, 16.5% between 75 and 84 and finally 5.5% in 85 years of age and above¹.

Personal history of previous breast cancer is a risk factor for cancer recurrence or the development of a new primary breast cancer, the risk is 19% according to the study by Hiranek².

The probability of a woman aged 20 years to develop breast cancer by the age of 80 with no affected relatives is 7.8%, with one affected relative is 13.3% and with two affected relatives is 21.1%^{3,4}.

The prolonged uninterrupted exposure to estrogens such as early menarche, late menopause, nulliparity, late pregnancy (after the age of 30), absence of history of lactation, the use of hormonal replacement therapy (HRT), the use of oral contraceptive pills (OCPs) are considered risk factors⁵.

Other environmental factors such as alcohol intake and exposure to radiation may play a role⁵.

Aetiology is unknown in 95% of breast cancer cases, while approximately 5% of new breast cancers are attributable to hereditary factors. Carriers of the breast cancer susceptibility genes (BRCA1 and BRCA2) are at 30-40% increased risk for breast and ovarian cancer^{6,7,8}.

Another study confirmed that increased risk of developing breast cancer at an earlier age was seen in those who are having family history of breast cancer. The mutation in BRCA1 and BRCA2 might explain these findings^{9,10}.

The aim of this study is to assess the primary risk factors of breast cancer.

METHOD

During the last nine years (August 1999 and September 2008) one hundred and five breast cancer patients were diagnosed, operated and followed up by the senior authors.

Presentation, diagnostic approach, and management were evaluated. Age at presentation, age at menarche and menopause were recorded. The risk factors, such as parity, age at first full term pregnancy, history of lactation, history of using hormonal replacement therapy, history of using oral contraceptive pills, past personal history of malignancy and type of malignancy, family history of breast cancer or other related malignancy were recorded.

This data was recorded prospectively for almost all of our patients.

This study is continuation and follow up to a previous similar study which was conducted on fifty two patients and published in 2006. Those patients were included in this study with the addition of 53 new patients⁸.

The data was entered and analyzed using SPSS program.

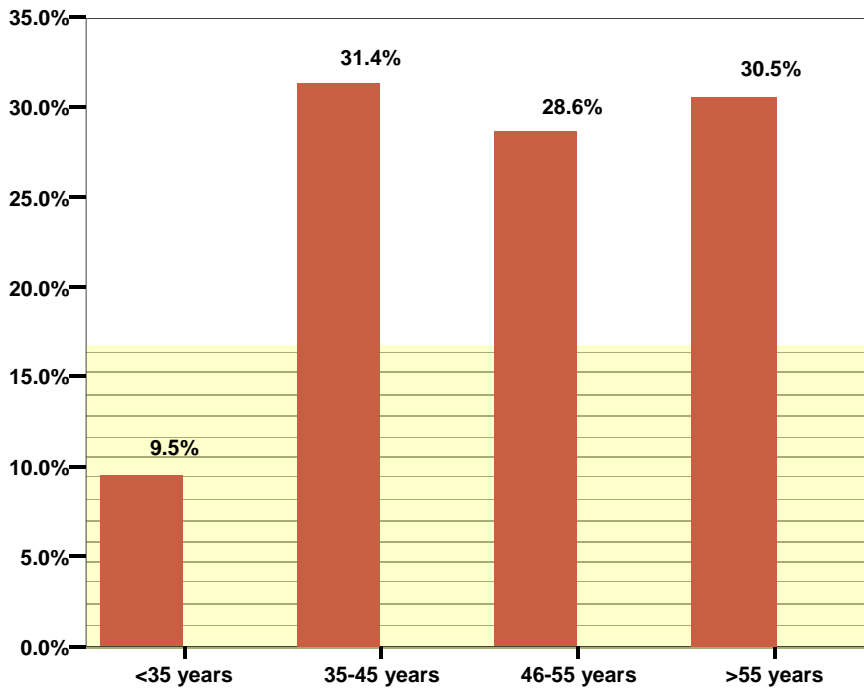
In a previous study, we revised the risk factors in 52 breast cancer patients. The study revealed that more than half of the cases (67.3%) were below 50 years at presentation, compared to 85% above 50 years in other studies. There was a significant high incidence of positive family history (35.3%) compared to other studies (5-15%)⁸.

RESULT

One hundred and five patients, all were females. Age at diagnosis of these women was ranging from 26 to 75 years old. Ten patients (9.5%) were diagnosed at an age less than 35 years old, 33 patients (31.4%) were 35-45 years, 30 patients (28.6%) were 46-55 years and 32 patients (30.5%) were more than 55 years old, see Table 1 and Graph 1.

Table 1: Age and Breast Cancer

	Count	Percent
Age at diagnosis		
<35 years	10	9.5%
35-45 years	33	31.4%
46-55 years	30	28.6%
>55 years	32	30.5%



Graph 1: Age at Diagnosis

Age of menarche of these women was ranging between 9-18 years, see Table 2 (a) and 2 (b). Twenty patients (19%) were Patients with early menarche (defined as less than 12 years old)⁵. Seventy-one patients (67.6%) had menarche at 12 years or above. Fourteen patients failed to remember their age of menarche. Forty-eight patients (45.7%) attained menopause, Table 3. The age of menopause ranged between 35-59 years. Three patients (2.8%) had late menopause (defined as more than 55 years old)⁵. Fifty-seven (54.3%) patients of the study group did attain menopause, Table 4.

Table 2 (a): Age of Menarche

	Number of Patients	Mean of Age	Std. Deviation	Minimum	Maximum
Age of menarche (Years)	91	12.70	1.742	9	18

Table 2(b): Age at Menarche

Age	Frequency	Valid percent
9	2	2.2
10	3	3.3
11	15	16.5
12	31	34.1
13	12	13.2
14	15	16.5
15	8	8.8
16	2	2.2
17	1	1.1
18	2	2.2
Total	91	100.0

Table 3: Age at Menopause

	Number of Patients	Mean of Age	Std. Deviation	Minimum	Maximum
Age of menopause (Years)	48	48.63	4.475	35	59

Twenty patients (19%) were nulliparous, see Table 4 and Graph 2. Eighty-five (81%) patients had childbirth. Six patients (5.7%) had their first delivery at an age of more than 30 years, while 79 patients (75.2%) had their first delivery at less than 30 years of age, Table 4, Graph 2.

Table 4: Risk Factors of Breast Cancer II

	Yes		No		No. of patients not included
	No.	%	No.	%*	
Early menarche ^a	20	19.6%	71	67.6%	14**
Late menopause ^b	3	2.8%	45	42.8%	57***
Nulliparous	20	19.0%	85	81%	0
Late first full-term pregnancy & delivery ^c	6	5.7%	79	75.2%	20****
History of lactation	78	74.3%	27	25.7%	0
Used OCPs	21	20.0%	79	75.2%	5
Used HRT	2	1.9%	100	95.2%	3
Past history of breast cancer	2	1.9%	103	98.1%	0
Family history of breast cancer	22	20.9%	83	79.1%	0

*Percentage is calculated from total 105 patients included in the study

** No. of patients who fail to remember age of menarche

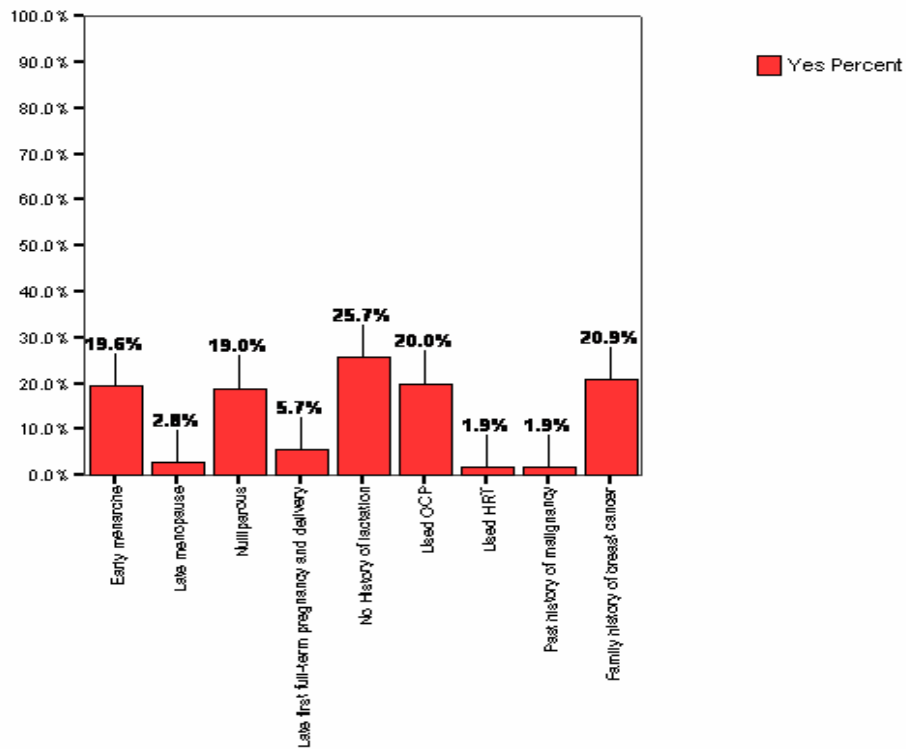
*** No. of patients who didn't attain menopause

****No. of patients who are nulliparous

^a Menarche at age less than 12 years old

^b Menopause at age more than 55 years old

^c First delivery at age more than 30 years old



Graph 2: Risk Factors in Our Study Group

Lactation history was positive in 78 patients (74.3%) and was negative in 27 patients (25.7%), Table 4. Twenty-one patients (20%) used oral contraceptive pills (OCP) for long period and two patients (1.9%) were on hormonal replacement therapy (HRT). Two patients (1.9%) had positive past personal history of malignancy (breast and ovaries). Twenty-two patients (20.9%) had positive family history for breast cancer, Table 4.

DISCUSSION

Breast cancer has no single etiological factor like smoking in lung cancer but multiple risk factors. The most important factors are advancing age, family history and past history of breast cancer.

Advancing age is one of the most powerful risk factors of breast cancer in women; however, both our current and previous studies are showing different results^{1,5}. In US patients, the incidence of breast cancer is at an age group less than 35 years was 1.9% while in this study it is 9.5% (N=10), this was similar to a study by Azzena A et al. At an age of 35-44 years, in US patients, it was 10.6% and in this study it was 31.4% (N=33). In US patients, it was 22.4% at an age of 45-54 years and 28.6% (N=30) in this study. At

an age of more than 55 years, in US patients, it was 65.1% while in the same age group in this study it was 30.5% (N=32)¹¹.

These significant differences support our previous study and show that younger age group (less than 55 years) were more at risk of developing breast cancer in Bahrain (69.5%), while in the United States (65%) were above 55 years.

The second most important risk factor is family history. Women with a family history of breast cancer, especially a first-degree relative (mother, sister or daughter), have an increased risk of developing breast cancer. The risk is higher if more than one first-degree relative developed breast cancer and it increases the younger the relative at the time of diagnosis⁵.

The understanding of familial breast cancer has improved by the study of BRCA1 and BRCA2 genes and other genetic mutations. Women born with a BRCA1 or BRCA2 mutation are more likely to develop breast cancer, with a lifetime risk of about 80% by the age of 70 years¹⁰. It is thought that environmental factors interact with genetic factors in bringing about these breast cancers, but little is known about these interactions. Approximately 5% to 10% of breast cancer cases are thought to be caused by genetic mutations¹⁰. On the other hand, women with a significant family history of breast cancer remain at increased risk for developing the disease, despite having negative BRCA1 and BRCA2 gene mutations, the risk is about 30-40%¹². However, genetic testing is required to identify the patients with genetic mutations.

The family history of malignancy in our previous study was (35%); family history of breast cancer in this study was (20.9%). Both studies support the findings in the international literature. Therefore, family history of breast cancer is considered significant risk factor for developing breast cancer. However, genetic testing is required to identify the patients with genetic mutations.

BRCA1, BRCA2 and TP53 are associated with an increased risk of breast cancer. These mutations are associated with early-onset breast cancer in patients with positive family history of malignancy¹³⁻¹⁵. This study revealed that 30% of patients who are younger than 35 years old have positive family history of malignancy regardless of the degree of relationship and the type of malignancy. We need more studies to initiate a better protocol regarding such patients.

Although previous history of breast cancer is one of the major risk factors, we found it positive in only two patients (1.9%); therefore, no conclusion can be arrived at.

In a study, it was shown that a woman who has had breast cancer, her risk of developing a second primary breast cancer is 2-6 times the risk seen in the general population. Therefore, the past personal history of malignancy is considered a risk factor for developing breast cancer¹⁶.

Estrogens are thought to be associated with the risk of breast cancer through their influence on cell proliferation and DNA damage, as well as promotion of cancer growth. Early menarche results in prolonged exposure to endogenous estrogens and progesterone;

therefore, increases the relative risk of developing breast cancer¹⁷. This study revealed that the average age of menarche was 12.7 years; it also revealed that 19% of patients had early menarche (before the age of 12 years). The age of menarche at 12-13 years old was 47.3% (N=43) and at 14 and above was 30.8% (N=28). Azzena A et al found that the age of menarche was 41.1% under 12 years and 14.1% after 14 years¹¹.

Late menopause is another factor leading to prolonged exposure to the reproductive hormones; hence, is considered a risk factor for developing breast cancer¹⁸. The average age that women go through menopause is 51 years¹⁹. In this study, the average age of menopause is 48.63 years and the patients who had late menopause (after the age of 55 years) were only 2.8%. These data indicate poor correlation between late menopause and developing breast cancer in this group of patients.

The effect of parity on reducing the risk of breast cancer has long been recognized. In the 18th century, Bernado Ramazzini (1633-1714) reported the high rate of breast cancer in nuns compared with married women and speculated that this might be associated with their lack of children. In a meta-analysis, nulliparity was associated with 30% increase in risk compared with parous women²⁰. The results of our study showed that 19% of our patients were nullipara. This percentage of nullipara patients is enough to consider it a risk factor in our patients.

Women with first full term pregnancy after the age of 30 have about two to three fold increased risk of breast cancer compared to women having a full term pregnancy before the age of 20 years²¹. Our data showed that most of our patients were married and had children at an early age. Eighty-one percent of our patients had had children and 75.2% of them had their first child at an early age (less than 30 years).

Lactation is protective against breast cancer and the longer a woman breastfeeds, the greater the protection and the lesser is the risk by 4.3% for each year a woman breastfeeds^{11,18}. However, this study revealed that 74.3% of patients had breastfed their children; this was also found in our previous study; therefore, lactation is not an important risk factor in those patients under study.

In a study, it was found that the use of oral contraceptive pills slightly increases the risk of breast cancer in current and recent users, but there is no significant increased risk after stopping its use (ten or more years). These estimates are based on a collaborative analysis of 54 studies in 25 countries and data of 50,000 women with breast cancer^{22,23}. Cancer diagnosed in woman who had used OCP tends to be less clinically advanced than those detected in never-user. In this study, oral contraceptive pills were used in 20% of our patients. This may support that OCP had some role in developing breast cancer in our patients.

Many studies have shown that the use of hormonal replacement therapy was found to increase the risk of breast cancer and reduce the sensitivity of mammography^{24,26}. The risk of breast cancer for current or recent users of HRT increases by 2% per year of use. In a study, it was shown that risk increases with duration of use. For women who had used it for at least five years (average 11 years) the risk increases to 35%²⁷. The effect is substantially greater for Estrogen-progestagen combinations than for Estrogen only. In

our study, the history of using hormonal replacement therapy was positive in only 1.9% of patient. This result means that HRT cannot be considered a substantial risk factor in Bahraini patient.

CONCLUSION

Risk factors of breast cancer in Bahrain and the gulf region are still under investigated. Our patients develop breast cancer at a younger age. Almost 70% of our patients were below or equal to 55 years at presentation where's in USA 65% of patients are 55 years old or more.

Family history was found significantly high in our patients, which means that familial breast cancer is common in Bahrain and genetic testing may help in prevention. Past personal history of breast or ovarian cancer was very low in this group of patients.

All other moderate risk factors such early menarche, late menopause, nulliparity, no lactation, late age at first delivery, and past history of breast cancer were not the most significant factors for developing breast cancer in our patients.

OCPs were used by 21 (20%) patients in our study group, this is considered high. Only small number of our breast cancer patients were using HRT.

More research is needed to understand the risk factors in our part of the world.

REFERENCES

1. SEER Stat Facts Sheets. Cancer of the Breast. National Cancer Institute, SEER Cancer Statistics Review 1975-2005. <http://seer.cancer.gov/statfacts/html/breast.html>. Accessed on 26.11.2008.
2. Hiranek N. Breast Cancer Recurrence: Follow Up after Treatment for Primary Breast Cancer. *Postgrad Med J* 2004; 80(941):172-6.
3. McIntosh A, Shaw C, Evans G, A. Clinical Guidelines and Evidence Review for the Classification and Care of Women at Risk of Familial Breast Cancer, London: National Collaborating Centre for Primary Care/University of Sheffield, National Institute for Clinical Excellence 2004; 109-38. www.nice.org.uk. Accessed on 11.1.2009.
4. Janowsky EC. Review: Breast Cancer is Associated with a Family History of the Disease in First Degree Relatives. *Evidence-Based Medicine ACP J Club* 2002; 136(3): 115.
5. American Cancer Society, Inc. Detailed Guide: Breast Cancer. What Are the Key Statistics for Breast Cancer? http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_breast_cancer_5.asp?sitearea= Accessed on 26.11.2008.
6. Venkitaraman AR. Cancer Susceptibility and the Functions of BRCA1 and BRCA2. *Cell* 2002; 108(2): 171-82.

7. Easton DF, Ford D, Bishop DT. Breast and Ovarian Cancer Incidence in BRCA1-Mutation Carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet* 1995; 56(1): 265-71.
8. Al Saad SK, A Jalal A. Breast Cancer Risk Factors and Stage at Presentation. *Bahrain Medical Bulletin* 2006; 28(3): 111-5.
9. Pharoah PD, Day NE, Duffy S. Family History and the Risk of Breast Cancer: A Systematic Review and Meta-Analysis. *Int J Cancer* 1997; 7: 800-9.
10. Salem CL. BRCA1/BRCA2 Mutations: Treatment and Counseling for Breast Cancer. American Society for Therapeutic Radiology and Oncology 42nd Annual Meeting CME; October 22 - 26, 2000, Boston, Massachusetts. <http://www.medscape.com/viewarticle/420294>. Accessed on 26.11.2008.
11. Azzena A, Zen T, Ferrara A, et al. Risk Factors for Breast Cancer. Case-control Study Results. *Eur J Gynaecol Oncol* 1994; 15(5): 386-92.
12. Metcalfe KA, Finch A, Poll A, Horsman D, et al. Breast Cancer Risks in Women with A Family History of Breast or Ovarian Cancer Who have Tested Negative for a BRCA1 or BRCA2 Mutation. *Br J Cancer* 2009; 27; 100(2): 421-5.
13. Lalloo F, Varley J, Moran A, et al. BRCA1, BRCA2 and TP53 Mutations in Very Early-onset Breast Cancer with Associated Risks to Relatives. *European Journal of Cancer* 2006; 42(8): 1143-50.
14. Lynch HT, Watson P, Conway T, et al. Family History as a Risk Factor for Early Onset Breast Cancer. *Breast Cancer Res Treat.* 1988; 11(3): 263-7.
15. Malone K E, Daling J R, Thompson J D. BRCA1 Mutations and Breast Cancer in the General Population. *The Journal on the American Medical Association* 1998; 279(12): 922-9.
16. Chen Y, Thompson W, Semenciw R, et al. Epidemiology of Contralateral Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 1999; 8(10): 855-61.
17. Kadlubar FF, Berkowitz GS, DeLongchamp RR, et al. The CYP3A4*1B Variant Is Related to the Onset of Puberty, A Known Risk Factor for the Development of Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 2003; 12(4): 327-31.
18. Kelsey JL, Gammon MD, John EM. Reproductive Factors and Breast Cancer. *Epidemiologic Reviews* 1993; 15(1): 36-47.
19. Lisabeth LD, Harlow SD, Gillespie B, et al. Staging Reproductive Aging: A Comparison of Proposed Bleeding Criteria for the Menopausal Transition. *Menopause* 2004; 11(2): 186-97.
20. Ewertz M, Duffy SW, Adami HO, et al. Age at First Birth, Parity and Risk of Breast Cancer: a Meta-analysis of 8 Studies from the Nordic Countries. *Int J Cancer* 1990; 15; 46(4): 597-603.
21. Ramon JM, Escriva JM, Casas I, et al. Age at First Full-term Pregnancy, Lactation and Parity and Risk of Breast Cancer: A Case-control Study in Spain. *Eur J Epidemiol* 1996; 12(5): 449-53.
22. Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a Reduced Risk of Premenopausal Breast Cancer. *N Engl J Med* 1994; 13; 330(2): 81-7.
23. Kumle M, Weiderpass E, Braaten T, et al. Use of Oral Contraceptives and Breast Cancer Risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2002; 11(11): 1375-81.

24. Collaborative Group on Hormonal Factors in Breast Cancer. Breast Cancer and Hormonal Contraceptives *Lancet* 1996; 347; 9017: 1713-27.
25. Banks E. Hormone Replacement Therapy and the Sensitivity and Specificity of Breast Cancer Screening: A Review. *J Med Screen* 2001; 8(1): 29-34.
26. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women: the Women's Health Initiative Randomized Trial. *JAMA* 2003; 289(24): 3243-53.
27. Collaborative Group on Hormonal Factors in Breast Cancer. Breast Cancer and Hormone Replacement Therapy. *Lancet* 1997; 350; 9084: 1047-59.