Effect of Reproductive, Menstrual and Familial Factors on The risk of Breast Cancer pre and post Menopause

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Abstract

Background: Breast cancer is the most common cancer among women in developed and developing countries. Reproductive factors are associated with higher risk for breast cancer. **Aim of the study:** To clarify the effect of reproductive, menstrual and familial factors on the risk of breast cancer, pre and post menopause. **Subjects and Methods:** A case-control study design was used in this study and convenient sample for the women selection, the sample comprised 300 women that divided into two main groups, 150 for each group, Study group and control groups. Completing questionnaire from all women. **Results:** The study revealed statistically significant associations between breast cancer and age, family history, late age at menopause (p<0.001), early age at menarche, (p<0.009), longer cycle duration (p<0.001), contraceptive pills (p<0.017), also the result revealed that there was no statistically significant between these factors and breast cancer regarding menopausal status. **Conclusion**: the findings of the present study support that there is a statistically significant relation between some of reproductive, menstrual, familial factors, and breast cancer. **Recommendation:** Health education programs regarding breast cancer, risk factors and early detection. Nurses should provide practical training in breast self-examination, especially for those women who are at higher risk of breast cancer.

Key words: Cancer, Breast Cancer & Reproductive Risk Factors.

Introduction

Breast cancer is a kind of cancer that develops from breast cells. It usually starts in the inner lining of milk ducts or the lobules that supply them with milk. A breast cancer that started in the lobules is known as lobular carcinoma, while one that developed from the ducts is called ductal carcinoma. **(Wiechmann et al., 2008)**

It is the most common invasive cancer in females worldwide. It accounts for 16 % of all female cancers and 22.9% of invasive cancers in women. 18.2% of all cancer deaths worldwide, including both males and females, are from breast cancer. **(Howlader et al., 2012)**

While breast cancer is a global issue, in Egypt, the figure for people suffering from breast cancer is alarming. It is the commonest cancer among Egyptian women and represents 35.1% of all female cancers .It is estimated that one in nine Egyptian families will be affected by breast cancer**. (Aboserea et al., 2011)**

Breast cancer rates are much higher in developed nations compared to developing ones. There are several reasons for this, with possibly life expectancy being one of the key factors and it is more common in elderly women; women in the richest countries live much longer than those in the poorest nations. The different lifestyles and eating habits of females in rich and poor countries are also contributory factor. **(James 2012)**

Breast cancer risk is around doubled in women with one first- degree relative with breast cancer, compared with women with no first- degree relatives. Environmental and life style factors explain around three- quarters of breast cancer risk, with hereditary factors explaining only around quarter. The reasons for breast cancer clustering in families remain largely unclear**. (Afonso, 2009**)

The role of reproductive and menstrual factors as a risk of breast cancer has long been recognized**.**

(Trivers et al., 2007) As regards age at menarche, some studies have found a stronger inverse relationship in women with premenopausal breast cancer than in those diagnosed after menopause. Other studies have indicated that early menarche is a weak risk factor for all age groups. **(Walker et al., 2011)**

Several lines of evidence suggest that late age at menopause is an important risk factor for breast cancer. In one study , the increased risk associated with late age at natural menopause was not apparent until 65 years of age, thus suggesting a l0-20 year delay of its effect, but the time- risk relationship for age at menopause is still open. By large, prolonged exposure to sex hormones, as indicated by a high number of reproductive years from menarche to menopause,

has been suggested to increase breast cancer risk. **(Flesch et al., 2008)**

Early age at first birth has conferred, in most studies, persistent protection. However, first birth after age 30, appears to be associated with a breast cancer risk higher than that in nulliparous women . An explanation for these findings is that an early full-term pregnancy reduces the likelihood of cancer initiation, but at a later age it may promote the growth of existing cancer cells**. (Britt et al., 2007)**

Nulliparity has consistently emerged as a risk factor for breast cancer Some studies , which considered age at cancer diagnosis, have found that the elevated risk is confined to nulliparous older women. Parous women seem to be at increased risk during the l0-15 years subsequent to a pregnancy as compared with nulliparous women**.(Albrektsen et al., 2006)**

The influence of spontaneous or induced abortions on the risk of breast cancer remains unclear . Some studies have shown some moderate positive associations, while others have suggested no clear relationship. **(Michels et al., 2007)**

The Aim of the study

The aim of the study was to clarify the effect of reproductive, menstrual and familial factors on the risk of breast cancer, pre and post menopause

Research question

What is the effect of reproductive, menstrual and familial factors on the risk of breast cancer, pre and post menopause?

Subject and methods

Research design

A case-control study design was used in this study.

Setting

The study was conducted at South Egypt Cancer Institute, Assiut University at Outpatient Clinics and female surgical ward for study group which its capacity in total (2642) cases annually , (449) cases from them were breast cancer and Eleman Specialized Hospital for control group

Sample

This study used convenient sample which comprised 300 women that divided into two main groups according to women's diagnosis, 150 for each group, study and control group. Study group included 150 women who had been diagnosed with breast cancer at South Egypt Cancer Institute, Assiut University and control group which included 150 women who suffer from other gynecological disorders and attending at Eleman Specialized Hospital.

Sample size

Women were allocated to this study according to sample size equation. The sample was calculated using Epi- Info statistical package, version3.3 with power 80%a value of 2.5 is chosen as the acceptable limit of precision (D) at 95%level of confidence(CI), with expected prevalence 20%, and worst acceptable 16%. Accordingly, sample size was estimated to be 234+10% individuals to guard against non-despondence rate. The computed sample size plus expected dropout rate was 300(150 study group and 150 control group).

Tools of the study

The following tool was used in the current study

A Structured interviewing questionnaire
which included the following data

- **Part (A) Socio-demographic data:** such as name, age, occupation, address, date of admission, educational level, residence, marital status.
- **Part (B) Family history:** history of chronic diseases as diabetes, hypertension, heart diseases and family history of breast cancer as well as consanguinity.
- **Part (C) Menstrual history:** age at menarche, amount and duration of menstruation, length of the cycle, interval and regularity.
- **Part (D) Obstetric history:** gravidity, parity, age at first labor, stillbirths, and live births, breastfeeding, complications related to previous deliveries and history of previous abortions.
- **Part (E) History of using the family planning methods,** its type, duration of use, its side effect if found and causes of termination.
- **Part (F) Medical history:** history of chronic diseases as diabetes, hypertension, heart diseases, etc.
- **Part (G) History of breast cancer** time of onset, recurrence, type, symptoms and signs, treatment modality and risk factors

Procedure

Before implantation of the study, an official permission was obtained from the Dean of South Egypt Cancer Institute, Assiut University, and from the general director Eleman Specialized Hospital as well as an ethical approval from the ethical committee of Faculty of nursing, Assuit University. The investigator explained the nature and the aim of study then verbal informed consent was taken from every woman before inclusion in the study.

The main procedure for data collection was through personal and single face-to face interview with every case. Before conducting the study, an exploratory visit was done in surgical units in order to estimate the rate of admission and suitable time for collecting data according to each unit. Besides, personal

communication was done with nurses and physician to explain the purpose of the study and gain their best possible cooperation.

The data was collected four days a week, time taking for every case was 20 minutes. The full history was taken as it was in the structured questionnaire which included information for Socio-demographic data, menstrual and reproductive history (e.g. age at menarche, menopausal status, age at menopause, type of menopause, parity, abortions, age at first live birth and length of attempt to first pregnancy), medical history , history of contraceptives using , history of menopausal symptoms and predisposing factors of breast cancer. Every question was addressed to the case and the responses were recorded.

Then the investigator gave each case in study group health education about the Predisposing factors of breast cancer which include family history of breast disease, age, obesity, radiation exposure, dietary factors and Hormonal Replacement Therapy (H R T), nutrition, activity, relaxation technique and pain management **.**

Statistical Analysis

The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by **number and percent** (N, %), where continuous variables described by mean and standard deviation (**Mean, SD**). **Chi-square** test was used to compare between categorical variables where compare between continuous variables by unpaired **t-test**. **A two-tailed p < 0.05** was considered statistically significant. All analyses were performed with the **IBM SPSS 20.0** software.

Ethical considerations

- Research proposal would be approved from Ethical Committee in the Faculty of Nursing
- There was no risk for study subject during application of the research.
- The study followed common ethical principles in clinical research
- Oral consent was obtained from patient or guidance that is willing to participate in the study
- Confidentiality and anonymity was assured.
- Study subjects had the right to refuse to participate and /or to withdraw from the study without any rational any time.
- Study subject privacy were considered during collection of data

Results

Table 1: Sociodemographic characteristics of study and control groups.

Sociodemographic characteristics	Cases (n=150)		Control (n=150)		P. value
	No.	%	No.	%	
Age	48.9+12.1		31.6+7.2		<0.001**
20>30 years	7	4.7	72	48	
30>40 years	23	15.3	61	40.7	<0.001**
40>50 years	46	30.7	11	7.3	
50+ years	74	49.3	6	4	
Marital status					
Single	12	8	4	2.7	
Married	102	68	144	96	<0.001**
Divorced	4	2.7	0	0	
Widow	32	21.3	2	1.3	
level of education					
Illiterate	121	80.7	74	49.3	
Basic education	7	4.7	26	17.3	<0.001**
Secondary	20	13.3	38	25.3	
University	2	1.3	12	8	
Occupational status					
House wife	150	100	147	98	0.082
Employer	0	0	3	2	

Table (2): Obstetric history of study and control groups.

	Cases (n=138)		Control (n=146)		P. value
	No.	%	No.	%	
Gravidity	6.3+3.8		4.3+2.6		<0.001**
1	3	2.2	11	7.5	
2 - 4	26	18.8	76	52.1	<0.001**
5+	109	79	59	40.4	
Parity	5.1+2.3		3.9+1.9		<0.001**
Nulliparous	6	4.3	7	4.8	
Primipara	4	2.9	11	7.5	
2 - 4	50	36.3	87	59.6	<0.001**
5+	78	56.5	41	28.1	
Abortion	2.1+1.5		2.5+2.5		0.234
0	64	46.4	106	72.6	
1	34	24.6	23	15.8	
2 - 4	35	25.4	12	8.2	<0.001**
5+	5	3.6	5	3.3	
Stillbirth	1.8+1.2		1.7+0.6		0.882
0	108	81.8	136	97.9	
1	13	9.8	1	0.7	
2	8	6.1	2	1.4	<0.001**
3+	3	2.3	0	0	
Neonatal death	2.7+1.9		1.5+0.6		0.239
0	115	87.2	135	97.2	
1	5	3.8	2	1.4	
2	6	4.5	2	1.4	0.009**
3+	6	4.5	0	0	

	Cases (n=138)		Control (n=146)		P. value
	No.	%	No.	%	
Age at first pregnancy					
<20	59	42.7	50	36	
20-31	78	56.6	88	63.3	0.511
≥32	1	0.7	1	0.7	
Outcome of first pregnancy					
Live birth	105	76	111	79.9	
Stillborn	10	7.2	1	0.7	
Neonatal death	4	3	11	7.9	0.011**
Induced abortion	19	13.8	16	11.5	

Still birth no=132 Neonatal death no =132*

Table (3): Menstrual history of study and control groups.

Menstrual history	Cases (n=150)		Control (n=150)		P. value
	No.	%	No.	%	
Age at menarche					
≤15	136	90.7	145	96.7	0.033*
>15	14	9.3	5	3.3	
Duration days					
1-3 days	37	24.7	24	16	
4 – 6 days	74	49.3	112	74.7	<0.001**
≥7 days	39	26	14	9.3	
Menstrual cycles					
<26	42	28	19	12.7	
26-30	98	65.3	128	85.3	<0.001**
>30	10	6.7	3	2	
Regularity					
Regular	129	86	130	86.7	0.866
Irregular	21	14	20	13.3	
Amount					
Scanty	10	6.7	13	8.7	
Moderate	62	41.3	107	71.3	<0.001**
Heavy	78	52	30	20	
Menstrual disorders					
No	35	23.3	77	51.3	<0.001**
Yes	115	76.7	73	48.7	

Table (4): Predisposing factors of breast cancer of study and control groups.

	Study =150		Control =150		P. value
	No.	%	No.	%	
predisposing factors of breast cancer which include					
No risk factors	0	0.0	103	68.6	<0.001**
Family history of breast cancer	30	20.0	7	4.7	<0.001**
Age (more than 40 years)	97	64.7	11	7.3	<0.001**
Using oral contraceptive pills (≥5years)	15	10.0	4	2.7	0.017*
HRT	0	0.0	0	0.0	-
Dietary factors(bad habits, as fatty food)	14	9.3	8	5.3	0.268
Early menarche (<10 years)	21	14.0	7	4.7	0.009**
Late menopause(≥55years)	15	10.0	1	0.7	<0.001**
Nulliparous and late pregnancy (≥30years)	17	11.3	9	6.0	0.151

 # More than one available

Table (5): Relation of predisposing factors of breast cancer among menopausal and non-menopausal cases in study group.

	Study group=150				P. value
	Menopause=78		Non menopause=72		
	No.	%	No.	%	
Predisposing factors of breast cancer which include					
Family history of breast cancer	15	19.2	15	20.8	1.000
Age (more than 40 years)	76	97.4	21	29.2	<0.001**
Using oral contraceptive pills	8	10.2	7	9.7	0.997
HRT	0	0.0	0	0.0	-
Dietary factors	2	2.6	12	16.7	<0.001**
Early menarche	11	14.1	10	13.9	0.998
Nulliparous and late pregnancy	10	12.8	10	13.9	0.494

 # More than one available

Table (6): Relation of predisposing factors of breast cancer among menopausal and non-menopausal cases in control group.

	Control group=150				P. value
	Menopause =9		Non menopause=141		
	No.	%	No.	%	
predisposing factors of breast cancer which include					
No risk factors	0	0.0	120	81.6	<0.001**
Family history of breast cancer	2	22.2	5	3.5	0.286
Age (more than 40 years)	9	100	2	1.4	0.011*
Using oral contraceptive pills	0	0.0	4	2.8	0.034*
HRT	0	0.0	0	0.0	-
Dietary factors	3	33.3	5	3.5	0.617
Early menarche	3	33.3	4	2.8	0.997
Nulliparous and late pregnancy	3	33.3	6	4.3	0.344

 # More
than one available

Table (1): as regard the age this table shows that nearly half of cases in study group (49.3%) were in the age group 50+ years, compared to the control group (4%).

Table (2): Regarding the obstetric history, this table points to statistically significant differences between study and control groups in the number of gravidity, parity, stillbirth, abortion and outcome of first pregnancy (p<0.001, p<0.001, p<0.001, p<0.001, p= 0.011)

Table (3): this table shows that more than half of cases in study group (76.7%) had menstrual disorders, compared to the control group (48.7%).

Table (4): this table shows statistically significant differences between study and control groups regarding family history, age, using oral contraceptive pills, early menarche, and late menopause (p<0.001 , p<0.001, p<0.017, p<0.009, p<0.001) respectively.

Table (5): this table shows statistically significant differences among menopausal and non-menopausal cases in study group regarding age and dietary factors (p=<0.001, p <0.001) respectively

Table (6): this table shows statistically significant differences among menopausal and non-menopausal cases in control group regarding age and using oral contraceptive pills (p=<0.001, p <0.001) respectively

Discussion

Breast cancer is the most common cancer among women in developed and developing countries **(Ahmadian et al., 2012).** In 2008, approximately 1.38 million new cases were diagnosed and approximately 458,000deaths were recorded both in developed and developing countries **(Iskandarsyah et al., 2014).**

The rates of breast cancer have increased over the past two decades **(Asnarulkhadi et al., 2012).** The WHO estimates that by the year 2020, the number of cases of cancer will double in developing countries **(Seth et al., 2012)**.

The aim of the present study was to clarify the effect of reproductive, menstrual and familial factors on the risk of breast cancer, pre and post menopause. The analysis of the data of the present study showed that there is a statistically significant relationship between, reproductive, menstrual and familial factors on the risk of breast cancer.

According to the present study findings, several hormone-related factors were identified as having a direct significant association with breast cancer. Thus, it was revealed that women with early age of menarche, longer cycle duration, heavy amount and menstrual disorders were at more risk of breast cancer.

In agreement with this finding, **(Kotsopoulos et al., 2005)** in their study which was conducted in Italy about age at menarche and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers, demonstrated that increasing breast cancer risk has been associated with early age of menarche .This was explained by that mean age of menarche was equal (15years).

In contrast with this finding, **(Bulter et al., 2000)** study which was conducted in California about menstrual risk factors and early-onset breast cancer found that women with a young age at menarche did not experience a significant increase in early-onset breast cancer risk. This was explained by that those women with an early age at menarche also tend to have other characteristics that put them at low risk for early-onset breast cancer such as not establishing regular menstrual cycles.

Concerning obstetric history, the present study showed relation of statistical significance between study and control groups in the number of gravidity, parity, stillbirth, abortion, outcome of first pregnancy and there was no statistical significance regarding null parity and late age of first birth.

These findings agree with study which carried out in North-West of Iran about birth intervals and breast cancer risk **(Kauppila et al., 2009)** who reported an increased risk of breast cancer with repeated pregnancies. This was explained by that short birth interval-associated excess breast cancer risk may be related to stimulatory effects of female steroid hormones produced during two closely connected pregnancies, or defective breast maturation owing to failures in breastfeeding.

In the same line (**Dai et al., 2009**) study about meta-analysis of the risk factors of breast cancer concerning reproductive factors and oral contraceptive use which was conducted in China showed that increase in the number of deliveries was a risk factor for breast cancer. Agreement of these findings was explained by that the mean age of the first pregnancy for both studies is nearly equal (20years).

The present study also investigated that there was significant relationship between abortion and breast cancer where more half women with breast cancer had previous abortion, compared to less than one-third of the control group.

A woman's risk of developing breast cancer may be related to hormone levels in her body. Breast cells normally grow and divide in response to the levels of certain hormones, such as estrogen, progesterone, and prolactin. Levels of these hormones change throughout a woman's life, but can change a great deal during pregnancy. When a woman is pregnant, her body begins to prepare for breastfeeding by altering the levels of these hormones. This could cause changes in the breast tissue **(Stefanidou et al., 2009)**.

In agreement with this present study finding, **(Ozmen et al., 2009)** study about breast cancer risk factors in Turkish women , concluded that a possible link between abortion and breast cancer have been raised because abortion is thought to interrupt the normal cycle of hormones during pregnancy. This interruption is believed by some to increase a woman's risk of developing breast cancer.

On the other hand, a recent report of the American Commission of Obstetrics and Gynecology had a report denying the relationship between breast cancer and induced abortion. The report indicated that the relationship between induced abortion and the subsequent development of breast cancer has been the subject of a substantial amount of epidemiologic study. **(Committee on Gynecologic Practice, 2009)**.

The present study has also investigated the possible risk associated with the use of contraception in the occurrence of breast cancer. Generally, the history of use of contraception did not differ significantly between cases with and without breast cancer. However, the duration of use of oral contraceptive pills was much more among women with breast cancer, and the difference was statistically significant.

These findings agree with a study carried out in London, Oral contraceptives and the risk of death from breast cancer **(Wingo et al., 2007)** stated that the association between estrogen and an increased risk of breast cancer led to a continuing debate about the role birth control pills might play in developing breast cancer. They highlighted that if the ovaries are removed early, for any reason, estrogen levels drop and the risk of breast cancer drops greatly. Therefore, since a woman's own hormones have an impact on the development of breast cancer, it is quite logical that taking hormone pills, particularly estrogen containing pills, might also have an impact on the risk of breast cancer.

The present study has also found that there was a statistically significant difference between cases in study and control group regarding age at menopause. In an agreement with this findings **Bernstein, (2002)** have concluded that risk of breast cancer increases by 2.7% for every late menopause year. Also, a Chinese study showed that there was a significant relationship between breast cancer and age at menopause .It found that menopause after 50 years of age increased risk of breast cancer **(Tam et al., 2010).** This agreement in findings was explained that mean age at diagnosis of breast cancer was equal.

The present study also showed that there was a statistically significant difference between cases in study and control group regarding family history of breast cancer. In the same line **(Antoniou et al., 2006)** study about Parity and breast cancer risk among BRCA1 and BRCA2 mutation carriers which was conducted in Singapore, concluded that the risk of breast cancer increased progressively with numbers of affected relatives.

This finding agree with study which was conducted in New York, about natural history and pretreatment assessment of breast cancer which investigated that women with positive family history of breast cancer are about two to three times more likely to develop the disease than those with negative family history. These women tend to develop breast cancer at much younger age and have higher incidence of bilateral disease. **(Chap et al., 2001**) This agreement in findings was explained that may be due to equality in the sample size.

Age is an important non-modifiable risk factor for many diseases, especially malignant diseases. The present study findings point to a statistically significant difference between breast cancer patients and control regarding their age, where more than half of women with breast cancer were in the age group 40 years or older.

In agreement with this finding, **Singh et al., (2004)** study about the natural history of breast cancer in the elderly which was carried out in Germany, reported that the incidence of breast cancer increased with age. While only one in 225 women aged <40 years develops breast cancer, the rate increases to one in 24 for women aged 40–59 years and to one in 14 for women aged 60-79 years. This agreement in findings was explained that there was equality in the age in both studies for women with breast cancer.

In the same respect, **Benz, (2008)** study which conducted in Singapore about impact of aging on the biology of breast cancer, demonstrated that breast cancer shows a bimodal distribution with respect to age, and specific pathological subtypes are related to different ages at diagnosis.

Also the present study found that there was no significant difference regarding null parity between menopausal and non-menopausal women. In agreement with this study **Russo et al., (2005)** study about the protective role of pregnancy in breast cancer which was carried out in Japan ,found that both pre- and post-menopausal nulliparous women were at increased risk for developing breast cancer. Also **Phipps et al., (2011)** showed that reproductive factors are associated with breast cancer risk regardless of age or menopausal status.

Also the present study found that there was no significant difference regarding using oral contraceptive with menopausal status. In consistent with this study **Newcomer et al., (2003)** study which was conducted in United State about oral contraceptive use and risk of breast cancer by histologic type, found that use of oral contraceptives was elevated for women of all ages.

Regarding dietary factors, the present study found that there was a significant difference among menopausal and non-menopausal cases in study group. In agreement with this study**, Munsell et al., (2014)** study about body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status which was carried out in Japan, concluded that dietary factors were inversely associated with breast cancer among younger women and positively dietary factors were positively associated with risk for older women.this agreement in these findings was explained that number of menopausal and non menopausal women in study and control groups was not equal in these studies.

Conclusion

In conclusion, the findings of the present study support that there is a statistically significant relation between reproductive, menstrual, familial factors, and breast cancer. Women who had family history of breast cancer, younger age at menarche, menstrual irregularities, late age at menopause are at a higher risk of breast cancer.

Recommendations

- In the light of the main study findings, the following recommendations are proposed. Health education programs regarding breast cancer, risk factors, early detection and screening programs should be provided through nurses working in care settings, Nurses should provide practical training about breast self-examination, especially for those women who are at higher risk of breast cancer In order to confirm the relation between reproductive,

menstrual and familial factors and breast cancer, pre and post menopause, follow-up prospective studies are suggested to determine the actual risk.

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