

Reproductive Factors and Risk of Breast Cancer

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Abstract

Background: Breast cancer is the most common type of female cancer among Iraqi women. Some reproductive factors have been shown to be associated with an increase in breast cancer risk. There haven't been any studies investigating the association between pregnancy outcome and breast cancer in Iraq.

Objectives: The aim of this study was to examine the possible associations between some reproductive factors as age of menarche, age at first delivery, parity and pregnancy outcome (i.e normal full term birth, abortion, premature delivery or multiple births) and risk of maternal breast cancer in AL-Anbar Governorate, west of Iraq.

Patients and methods: The study was conducted in the oncology clinic in AL-Ramadi General Hospital during the period from October 2011 to April 2012. The study consisted of 100 breast cancer cases confirmed on histopathology and 200 group- matched healthy controls. Bivariate analyses included odds ratio (OR); and 95% confidence interval (CI) for odds ratio were also performed.

Results: results showed that earlier age at menarche <12 years, older age at first full term birth >30 years, and not having given birth were significantly associated with increased risk of breast cancer. With regards to birth outcome, full term birth was found to be associated with lower risk, the more the number of full term births, the more protection was found.

Premature deliveries < 8 months of gestation was found to be significantly associated with nearly three times risk compared to those with full term deliveries (O.R.=2.98, CI=1.60-5.56, p= 0.002), while premature deliveries > 8 months was not associated with risk, so as the effects of stillbirth. History of more than one abortion was found to slightly increase the breast cancer risk (O.R=1.24, CI= 0.70-2.18, p= 0.57). Having twin or multiple births were found to be protective against breast cancer (O.R=0.32, CI=0.12-0.86, p=0.019).

Conclusion: Risky reproductive factors for breast cancer included early age of menarche, late age at first full term birth, and nulliparity. More than one abortion seemed to slightly increase the risk, while on the other hand premature deliveries < 8 months significantly increased the risk of breast cancer. Pregnancy outcome in a form of full term birth, multiparity and twin births were protective against breast cancer.

Key Words: Breast Cancer, reproductive factors, risk factors

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Introduction:

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20 to 59 years. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer related deaths in women worldwide.⁽¹⁾

The burden of breast cancer is increasing in both developed and developing countries.⁽²⁾

Studies have shown that a woman's risk of developing breast cancer is related to her exposure to hormones that are produced by her ovaries (endogenous estrogen and progesterone). Reproductive factors that increase the duration and/or levels of exposure to ovarian hormones, which stimulate cell growth, have been associated with an increase in breast cancer risk⁽³⁾. These factors include early onset of menstruation, late onset of menopause, later age at first pregnancy, and never having given birth⁽⁴⁾. Pregnancy and breast feeding both reduce a woman's lifetime number of menstrual cycles, and thus her cumulative exposure to endogenous hormones.^(3,5)

Incidence rates are lower among populations that are heavily weighted with women who begin childbearing at young ages and who have multiple full-term pregnancies followed by prolonged lactation.⁽¹⁾

Among the reproductive factors that affect breast cancer is pregnancy outcome whether it is a full term single birth, twin or multiple births, abortions, preterm births, or stillbirth. Some studies show that outcomes other than a full-term birth such as, abortion whether spontaneous or induced, and premature birth may increase breast cancer risk.^(6, 7, 8)

Breast maturation process, and throughout a normal full-term pregnancy, includes the following stages:

At puberty, the ovaries produce cyclic elevations of estrogen and progesterone.

Only Type 1 and 2 lobules are formed, the lobules account for about 10% of the breast tissue.

After puberty, lobules account for 30% of the breast tissue: 75% are Type 1 and 25% are Type 2 lobules with few Type 3.

After conception, human chorionic gonadotropin (hCG) hormone stimulates the ovaries to produce estrogen and progesterone, which cause the breast to start to enlarge by making greater numbers of lobules, and to sustain the pregnancy⁽⁹⁾.

By the end of the 1st trimester, Type 1 lobules mature into Type 2, and the actual numbers of these lobules will increase while the surrounding tissue decreases. The breast now has more places for cancers to start.⁽¹⁰⁾

By mid-2nd trimester, the breast has continued to mature rapidly under the influence of placental hormone. The breast contains now 70% Type 4 cancer resistant lobules and 30% immature cancer susceptible lobules. By the end of the 3rd trimester, 85% of the breast is fully matured to Type 4 lobules and only 15% remain immature cancer susceptible lobules, leaving fewer places for cancer to start. At delivery, the mother's breasts are now predominantly Type 4 lobules. They are fully mature and resistant to carcinogens, resulting in lower long-term risk of breast cancer for the mother^(9, 10).

Thus, if the pregnancy is a normal, healthy one that goes to forty weeks (*full-term*), there will be near complete maturation of the mother's mammary glands into Type 4 lobules.⁽⁶⁾

If the mother ends her normal pregnancy with an *induced abortion*, her breasts will predominantly have Type 1 and 2 lobules, leaving her breast with more sites for cancers to initiate,⁽¹¹⁾ while in a first-trimester *spontaneous abortion*, the mother has no change in breast cancer risk due to inadequate levels of the pregnancy hormones as a result of abnormal development of the embryo⁽¹²⁾.

Premature delivery before 32 weeks may increase the breast cancer risk because it leaves the breast with more places for cancers to start. The effect of premature delivery is thought to be the same as in an induced abortion.⁽⁸⁾

Stillbirth near or at delivery would not change that full-term pregnancy's protective effect on the breast.⁽⁶⁾

No previous study has been conducted to explore reproductive factors risk of breast cancer in Iraq, thus the aim of this study is to find out any association of reproductive factors and pregnancy outcome (full term, preterm, abortion, stillbirth or multiple births) with breast cancer in Al-Anbar, West of Iraq.

Patients and methods:

This is a case control study conducted in Al-Anbar governorate for the aim of exploring the association of reproductive factors with breast cancer. The study was conducted in the oncology clinic in AL-Ramadi General Hospital during the period from October 2011 to April 2012. The cases were defined as those who are definitely diagnosed as breast cancer patients registered in the clinic and living in Al-Anbar Governorate. They were enrolled into the study if they had a confirmed pathological breast cancer diagnosis and

visited AL-Ramady general Hospital (oncology clinic) for either the first time or for follow-up, consultation or receiving chemotherapy treatment.

Control individuals were defined as healthy women recruited from the same hospital. They include those who accompany the cases (relatives) or visiting outpatients for reasons other than breast problems.

The sample size was 300 women; 100 women as cases and 200 women as controls. A structured questionnaire was developed and designed for the purpose of the study by the investigators. Three hundred respondents were interviewed after taking verbal consent.

The information covered by the questionnaire were included age of the women in years, residence of women whether urban or rural, marital status, education level and occupation of women, age at menarche, age at first full term delivery, number of live births, number of stillbirths, and number of previous abortions before the 24th week of pregnancy, and whether it is spontaneous or induced. History of twin births was asked together with history of premature births which is defined as termination of pregnancy between 24 and 36 weeks of gestation with outcomes of live birth or still birth, and it was categorized as preterm birth before 8 months (less than 32 weeks) of gestation and above 8 months (more than 32 weeks).

Statistical analysis: Data was analyzed by using SPSS (Version 18.0), Odds ratio was calculated for every risk factor of concern in this study, confidence interval and P value were calculated too, P values less than 0.05 were considered significant.

Results:

Table I shows the distribution of study subjects according to socio-demographic variables.

Table I: Distribution of study subjects according to socio-demographic variable

Particulars		Cases		Controls	
		No.	%	No.	%
Age	≤40	16	16.0	32	16.0
	41-49	49	49.0	98	49.0
	50-59	24	24.0	48	24.0
	≥60	11	11.0	22	11.0
Education of women	Illiterate	48	48.0	56	28.0
	Read & write	5	5.0	20	10.0
	Primary	31	31.0	28	14.0
	intermed	4	4.0	17	8.5
	Secondary	6	6.0	33	16.5
	University & above	6	6.0	46	23.0
women occupation	House wife	90	90.0	140	70.0
	employees	10	10.0	60	30.0
Income of family (perceived)	Low	26	26.0	27	13.5
	Fairly sufficient	3	3.0	11	5.5
	Sufficient	54	54.0	113	56.5
	More than sufficient	17	17.0	49	24.5
Marital status	Married	78	78.0	147	73.5
	Not married	9	9.0	8	4.0
	Others	13	13.0	45	22.5
residence	Urban	59	59.0	142	71.0
	Rural	41	41.0	85	29.0
Menopausal status	Pre-menopausal	76	76.0	79	60.5
	Post-menopausal	24	24.0	142	39.5

The cases and controls were age-matched, nearly half of them (49%) were between 41 and 49 years, and 24% between 50 to 59 years; 16% of them were less than 40 years, and 11% more than 60 years old. Regarding education of women, most of the cases were either illiterate or just read and write (53%) compared to 38% of controls, while 12% of cases and 39.5% of controls were having secondary and above education respectively.

Most of the cases were housewives (90%) while 70% of controls were housewives and 30% were working. The Table shows that 26% of cases and 13.5% of control's family income was perceived as low, 3% of cases and 5.5% of controls said that their monthly income is fairly sufficient, 54% and 56.5% of cases and controls respectively regard their income as sufficient, while 17% of cases and 24.5% of controls were having more than sufficient income.

With regards to the marital status, 78% of cases and 73.5% of controls were married, 9% of cases and 4% of controls were single while 13% of cases and 22.5% of controls were either divorced or widows at the time of interview.

The residence of the respondents was in urban areas in 59% of cases compared to 71% of controls, while 41% and 29% of cases and controls were from rural areas respectively.

The Table also shows that 76% of cases were in pre-menopausal state and 24% of them were at post-menopause compared to 60.5% and 39.5% of controls respectively.

Forty eight percent of cases in this study were having their age at menarche less than or equal to 12 years, and 51 % of them between 13 to 15 years compared to 23% and 74.5% of controls respectively, while only 1% and 2.5% of them were having menarche at age of 16 years or above. (Table 2)

Table II: Bi-variate analyses for reproductive risk factors of breast cancer:

Risk factors		Cases		Controls		O.R	Confidence Interval		P value
		NO.	%	NO.	%		L	U	
Age at menarche (years)	≤12	48	48.0	46	23.0	3.05	1.82 -	5.09	0.000
	13-15	51	51.0	149	74.5	1.			
	≥16	1	1.0	5	2.5	0.58	0.06	5.12	
Age at first full term birth (years) Cases=81 Control=180	≤20	32	39.5	94	52.2	1.			0.014
	21- 29	34	42.0	73	40.6	1.4	0.77 -	2.42	
	30≥	15	18.5	13	7.2	3.4	1.45 -	7.88	

Parity	Nulliparous	19	19.0	20	10.0	2.1	1.07 -	4.17	0.02
	Parous	81	81.0	180	90.0	1.			
No. of full term live births	absent	19	19.0	20	10.0	1.			0.002
	1 - 3	42	42.0	57	28.5	0.77	0.36 -	1.63	
	4 - 6	20	20.0	55	27.5	0.38	0.17 -	0.86	
	≥ 7	19	19.0	68	34.0	0.29	0.13 -	0.65	
No of stillbirth	0	98	98.0	196	98.0	1			1.0
	≥1	2	2.0	4	2.0	1.0	0.18-	5.55	
History of Premature delivery	0	66	66.0	162	81.0	1.			0.002
	<32 weeks	28	28.0	23	11.5	2.98	1.60-	5.56	
	>32 weeks	6	6.0	15	7.5	0.98	0.36-	2.63	
History of abortion	Never	54	54.0	111	55.5	1.			0.57
	one	17	17.0	41	20.5	0.85	0.44 -	1.63	
	More than one	29	29.0	48	24.0	1.24	0.70 -	2.18	
History of twin Birth	yes	5	5.0	28	14.0	0.32	0.12 -	0.86	0.019
	no	95	95.0	172	86.0	1.			

Women who had menarche at early ages (≤ 12 years) were at increased risk compared with women who had menarche between 13-15 years of age (O.R= 3.05, CI =1.82-5.09, $p=0.000$). Menarche after 15 years of age was associated with reduced risk of breast cancer (O.R= 0.58, CI =0.06-5.12) [Table 2].

Age at first child birth was observed an important risk factor. The risk was more than three times higher for women who had their first child after 30 years compared to women having their first child at or before 20 years of age. (O.R=3.4, CI = 1.45- 7.88, $p=0.014$).

Risk of breast cancer was nearly two times higher in nulliparous than parous women (O.R=2.1, CI = 1.07-4.17, $p=0.02$).

The risk was about 3.4 times more among nulliparous than those having 7 and more children and 2.6 times than those having 4-6 children (O.R of para 0 VS Para 7=3.4, CI=1.71-7.62; O.R for para 0 VS para 4-6=2.6, CI=1.16- 5.87).

No association was observed between having stillbirth and risk of breast cancer (O.R=1).

History of premature delivery < 8 months of gestation was observed to be associated with significantly increased risk. The risk was about three times more among women who had premature delivery < 8 months compared to women who did not have premature deliveries (O.R.= 2.98,

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CI=1.60-5.56, $p=0.002$). While those who had premature deliveries >32 weeks of gestation were not at risk (O.R=0.98).

The risk for breast cancer was not increased for women who had a history of one abortion, while for those who had two and more abortions there was a slight non significant risk (O.R=1.24, CI=0.70-2.18). In this study, it was not possible to determine if there were any induced abortions, all respondents reported their abortions as spontaneous.

Five percent of cases compared with 14% of controls had history of twin birth (one birth or more), twin birth give protection from breast cancer (O.R=0.32, CI=0.12-0.86, $p=0.019$)

Discussion:

Breast cancer incidence rates are increasing worldwide. The continuing increase in breast cancer incidence has created an urgent and quick need to develop strategies for prevention.

The results of this study shows that earlier age at menarche (at or below 12 years of age) was observed as an important risk factor. 48% of our cases had menarche at 12 years of age or earlier, compared to 23% of controls, with increased risk to develop breast cancer by 3 times compared to women at age 13-15 years. This study agrees with Gao YT et al in their case control study who observed higher risk for women who had menarche before 13 years of age.⁽¹³⁾

The effect of age at menarche on breast cancer risk may be mediated simply by the prolonged period of breast epithelium exposure to estrogen produced by regular ovulatory cycles.⁽¹⁴⁾

In addition, a study had demonstrated that women with early menarche have higher estrogen levels compared to women with later menarche.⁽¹⁵⁾

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Women who give birth to their first child at an early age appear to have a reduced risk of breast cancer, and nulliparous women appear to have a higher risk than parous women, at least at older ages.⁽³⁾

In this study the women with breast cancer who had their first full term delivery after 30 years of age were found to be at three times risk than those who had first child at or below 20 years of age (O.R=3.04, P value=0.014), while women who had their first full term delivery at 21 to 29 years had less risk (O.R=1.4). Rao DN et al observed a relative risk of 5.4 times for women delivering first child after 30 years compared to 15 years of first delivery.⁽¹⁶⁾

The ultimate mechanism through which early pregnancy protects the breast from cancer development remains largely unknown. Several hypotheses have been proposed to account for the hormone-driven protective effects of parity. Recent experiments demonstrate the important role of the p53 tumor suppressor gene in the hormone-induced protection.⁽¹⁷⁾

Another study in Western Hemisphere Hispanic and non Hispanic populations have also reported an increased risk with late age at first full term birth.⁽¹⁸⁾

Nulliparous women in this study had twice risk than parous women. The risk decreases as the parity increases (Table 2). The risk was about 3.4 times more among nulliparous than those having 7 and more children and 2.6 times than those having 4-6 children. Other studies also reported similar findings, and concluded that childbearing reduces the risk of breast cancer and the higher the number of full-term pregnancies, the greater the protection; and reported that the risk of breast cancer reduces by 7% with each full-term pregnancy, and overall women who have had children have a 30% lower risk than nulliparous women.^(19, 20)

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Our study also agrees with another study which indicates that women who had given birth to five or more children had half the risk of women who have not given birth.⁽²¹⁾

A woman gains protection from breast cancer by completing a full-term pregnancy as hormones mature 85 percent of the mother's breast tissue into cancer-resistant breast tissue. This is why there is a known protective effect against breast cancer when a woman has a full-term pregnancy. Studies showed that each successive pregnancy causes more of the mother's mammary glands to mature which further reduces her risk by 10 percent with each pregnancy.⁽⁶⁾

Some study suggests that parity may affect not only estrogen levels but also long term secretion of prolactin.⁽²²⁾ Some evidence indicates that the reduced risk associated with an increased number of births may be limited to hormone receptor-positive breast cancer.⁽⁴⁾

Cases with history of one abortion had no risk of developing breast cancer, while those with more than one abortion carried a slight risk of 1.24 times than women with no history of abortion. This finding was supported with the results of Andrieu et al.⁽²³⁾, This result is also consistent with the reports of another study showing that the risk for breast cancer was not increased for women who had a history of abortion, compared to nulliparous women.⁽⁷⁾

Beral V et al studied the relation between breast cancer and abortion through reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries; and concluded that pregnancies that end as a spontaneous or induced abortion do not increase a woman's risk of developing breast cancer, and that the studies of breast cancer with retrospective recording of induced abortion yielded misleading results, possibly because women who had

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developed breast cancer were, on average, more likely than other women to disclose previous induced abortions.⁽²⁴⁾

In our study none of the cases or controls stated that they had history of induced abortion. This is because in Islam induced abortion is prohibited and illegal abortion, if happened, is mostly disclosed. Joel Brind in his Critical Review concluded that there is no relationship between breast cancer and induced abortion, based on the finding of $RR = 0.91$ (95% CI: 0.82-0.99).⁽²⁵⁾

Regarding the association of premature delivery and breast cancer, the results of this study reveals a significant association in women with history of premature delivery at or before 8 months of gestation with almost 3 times risk of developing breast cancer compared to women with no premature births $OR=2.98$, $CI=1.60- 5.56$). This is probably due to the fact that the breast is left with more places for cancers to start. On the other hand, premature births after 8 months of gestation seem to be protective. This is explained as pregnancy hormone levels are usually normal so the breast changes are those of a normal pregnancy.⁽²⁶⁾ Melbye M et al studied the risk of breast cancer in relation to the length of a pregnancy and concluded that a preterm delivery of 32 weeks gestation and above did not significantly increase a woman's risk of contracting breast cancer. Only for the very small group of women with preterm deliveries of less than 32 weeks gestation there was an increased risk.⁽⁸⁾ Another study have found that women who give birth at less than 32 weeks have a twofold to fourfold increased risk of breast cancer.⁽²⁷⁾ On the other hand, another case-control study focusing on live births, with seven women with a delivery of less than 30 weeks, did not find an increased risk among women with preterm deliveries.⁽²⁸⁾

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Stillbirth has not been found in this study to be associated with increased risk of breast cancer, which is in consistent with other studies which have been also based on a very limited number of cases and lacked much information on stillbirth and gestational length of the pregnancy. ^{(29, 30).}

Stillbirth or the death of an infant near or at delivery would not change the full-term pregnancy's protective effect and the maturity of the breast.

Twin births were significantly associated with lower breast cancer risk in our study, a result which is in accordance with another study which revealed a 15% risk reduction for women with a twin birth, compared to women giving birth to a singleton. ⁽³¹⁾

Multiple births have several features that might influence the subsequent risk of breast cancer in the mother. A twin pregnancy associated with higher levels of several placental hormones than a singleton pregnancy as a result of a higher total placental mass which will lead to much maturation of breast tissue. ⁽³²⁾

However, our results do not agree with Kim et al (2012) in which 17 relevant publications were analyzed, some suggest that twin births may be associated with lower breast cancer risk but others do not; therefore, they concluded that the results were inconclusive. However, results of a meta-analysis suggest that twin pregnancy does not significantly decrease the maternal risk of breast cancer. ⁽³³⁾

The study concluded that breast cancer is mostly prevalent in premenopausal women. Risky reproductive factors for breast cancer included early age of menarche, late age at first full term birth, nulliparity, more than two abortions, and history of premature birth before the eighth month of pregnancy. While earlier age at first full term birth, higher parity, and having twin births were protective against breast cancer.

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We recommend primary care physicians to increase their awareness and knowledge regarding breast cancer risk factors, and encouraging them to be more responsible in caring for high risk pregnant women to attain full term pregnancies.

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