



Reproductive Factors and Risk of Breast Cancer: A Jordanian Case Control Study

Mohammad Al Qadire^{1*}

¹Department of Adult Healthcare Nursing, Faculty of Nursing, Al Al-Bayt University, P.O.Box 130040, Mafrq 25113, Jordan.

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: This study aims to identify reproductive factors associated with risk of breast cancer among Jordanian women.

Study Design: A case-control study design was used.

Place and Duration of Study: Data was collected between February and October 2016 from three large hospitals where cancer patients are treated in Jordan.

Methodology: The sample comprised two groups: cases (418 women with breast cancer) and controls (405 women without any type of cancer). In the former, only breast cancer patients who met the following criteria were included: 18 years and older, with a confirmed breast cancer diagnosis as evident from the histopathology report, newly diagnosed, knowing their cancer diagnosis and agreeing to take part in the study. The control group was of women who had no cancer and lived in the same geographical area as the case group. After ethical approval, information about participants' demographic characteristics, parturition, breast feeding and its duration, the use of oral contraceptives and duration of use, the use of HRT, being menopausal or not, age at marriage and at first birth, age at menarche, and the number of children were collected.

Results: The mean age of women in the case group was 49.2 years (SD 10.3), and in the control group 45.9 (SD 10.9). The majority of women were married in the groups (case: 90.1%; control:

*Corresponding author: E-mail: mohammadqadire@aabu.edu.jo, mohammadqadire@gmail.com;

93.5%). Increased age of marriage (OR 1.102, 95% CI 1.04-1.168), increased age at first birth (OR 1.062, 95% CI 1.013-1.113), the use of HRT (OR 0.396, 95% CI 0.184-0.853) and being menopausal (OR 0.622, 95% CI 0.432-0.896) were found to increase the risk of developing breast cancer among Jordanian women.

Conclusion: The findings of the study demonstrate that several reproductive factors increase the likelihood of developing breast cancer among Jordanian women. Some discrepancies between the results of the current study and previous studies were highlighted, which might be the results of differences in culture, behaviour and habits.

Keywords: Breast neoplasms; women; risk factors; reproductive; case-control; adult; Jordan.

1. INTRODUCTION

Breast cancer is one of the most common cancers in Jordan. In 2012 there were 7,456 newly diagnosed cases of cancer, a 7% increment over 2011 [1]. Of these cases, 1,008 were breast cancer [1]. The number of discovered cases of breast cancer is continuously increasing in the country [2], and 14% of deaths in Jordan are cancer related [3].

A considerable number of epidemiological studies have reported that mammary cells can be subjected to numerous carcinogenic substances. These include endogenous (from the ovaries) and exogenous (e.g. oral contraceptives (OC) and hormonal replacement therapy (HRT)) factors, steroid hormones (i.e. oestrogen and progesterone) and hyperinsulinemia (e.g. diabetic and obese patients) [4-7]. Recent systemic reviews examining the risk factors for breast cancer concluded that oral OC, HRT and diabetes increase the risk of developing breast cancer, while breast feeding may reduce the risk [6-8]. Reproductive risk factors associated with breast cancer are numerous and include a family history of breast cancer, early menarche ≤ 12 years of age, late first delivery, null-parturition, lack of breast-feeding, and age of menopause at or after 50 years; all significantly predicted a higher chance of developing breast cancer among women [9-13]. Similar studies, although important, are limited in developing countries. For instance, in Jordan this study is considered to be one the first in this field. Thus, the main aim of this study is to identify reproductive factors associated with risk of breast cancer among Jordanian women.

2. MATERIALS AND METHODS

A case-control study design was used to identify the risk factors of breast cancer in Jordanian women. It was a large multicentre case study that aimed to identify risk factors related to

lifestyle, dietary intake, and reproductive factors. However, in this paper only the results of reproductive risk factors are presented. The sample comprised two groups: cases (418 women with breast cancer) and controls (405 women without any type of cancer). In the former, only breast cancer patients who met the following criteria were included: 18 years and older, with a confirmed breast cancer diagnosis as evident from the histopathology report, newly diagnosed, knowing their cancer diagnosis and agreeing to take part in the study. The control group was of women who had no cancer and lived in the same geographical area as the case group.

The researcher developed a data sheet that included questions designed to elicit information about participants' demographic characteristics such as age, marital status, education, income and previous history of cancer among first-degree relatives. It asked about parturition, breast feeding and its duration, the use of oral contraceptives and duration of use, the use of HRT, being menopausal or not, age at marriage and at first birth, age at menarche, and the number of children.

Ethical approval to conduct the study was sought from the principal author's university and the study setting authorities. Data was collected between February and October 2016 from three large hospitals where cancer patients are treated: a specialist cancer centre where most cancer patients are treated, a large government referral hospital, and a university hospital located in the north of the country.

Research assistants visited each hospital every two weeks to locate all admitted breast cancer patients. The study purpose, procedure and requirements were explained to the patients. If they agreed to participate, they were asked to complete the questionnaire in a semi-structured interview with the research assistant. For each

woman in the case group, a control subject was recruited from the same geographical area.

Statistical analysis was performed using SPSS version 21. Descriptive statistics such as frequency, percentage, mean and standard deviation were used to describe participants' characteristics in both case and control groups. The distribution of dichotomous variables among the two groups was tested using Pearson's chi-square test, and the independent t-test to identify differences in the mean of interval variables across the groups. Odd ratios (OR) and correlated 95% confidence intervals (CI) were also calculated. Finally, logistic binary regression was conducted to confirm the predictors associated with breast cancer.

3. RESULTS AND DISCUSSION

3.1 Results

A total of 418 cases and 405 controls completed the study questionnaire. The mean age of women in the case group was 49.2 years (SD 10.3), and in the control group 45.9 (SD 10.9). The majority of women were married in the groups (case: 90.1%; control: 93.5%). Low family monthly income was reported by women in the case (79.5%) and control (82.3%) groups. Full details of participants' demographic and reproductive characteristics are shown in Tables 1 and 2.

The distribution of dichotomous variables among case and control groups was tested using the chi-squared test (see Table 1). Factors associated with increased risk of breast cancer were as follows: having a first-degree relative with breast cancer (OR 1.48, 95% CI 1.01-2.18), the use of HRT (OR 3.29, 95% CI 1.60-6.71), and being menopausal (OR 2.31, 95% 1.75-3.07). However, the remaining dichotomous variables were not significantly associated with increased risk of breast cancer, $P > .05$ (see Table 1).

Table 2 shows the results of independent t-tests for the difference in mean of interval variable among women in the two groups. An increase in the risk of having breast cancer was associated with women of increased age (mean age: case 49.2, SD 10.3; control 45.9, SD 10.9, $P < .001$). However, women married at a younger age (mean age at marriage: case 22.7, SD 5.6; control 20.2, SD 4.9, $P < .001$) and gave birth at a younger age (mean age at first birth: case 23.5,

SD 6.3; control 20.8, SD 5.0, $P < .001$) were found to have a significantly lower risk of breast cancer. Finally, the mean of total numbers of children was significantly higher in the control group than in the case group (mean number of children: case 4.4, SD 2.0; control 5.1, SD 2.4, $P < .001$).

The significant factors (dichotomous and interval) were further investigated using multivariable binary logistic regression; these factors were having a first-degree relative with breast cancer, the use of HRT, being menopausal, older, number of children, age at marriage and at first birth (see Table 3). Of these factors, increased age of marriage (OR 1.102, 95% CI 1.04-1.168), increased age at first birth (OR 1.062, 95% CI 1.013-1.113), the use of HRT (OR 0.396, 95% CI 0.184-0.853) and being menopausal (OR 0.622, 95% CI 0.432-0.896) were found to increase the risk of developing breast cancer among Jordanian women.

3.2 Discussion

This case study examined the association between reproductive factors of Jordanian women and the risk of breast cancer. It is the first study of its kind in the country, and takes extra importance as breast cancer is the most commonly seen cancer in Jordanian women, with the number of newly diagnosed cases increasing [1,2]. For instance, 566 cases were diagnosed in 2001 [14], rising to 1,008 cases in 2012 [1]. In addition, it is well known that the risk factors of cancer vary from one geographical area to another, and that it is a culturally sensitive disease [15]. Hence, the results of the current study should be seen in the light of Arab Islamic culture, which differs from Western culture in many respects. A wide range of reproductive characteristics of Jordanian women were analysed. The findings confirmed the fact that reproductive factors play an important role in the development of breast cancer [6,7,15,16], although some differences in the role of these factors were noted. For example, some factors that were significant in other places were not significantly associated with breast cancer in Jordanian women.

The findings show significant associations between having a first-degree relative with breast cancer, the use of HRT and being menopausal, and the development of breast cancer. These findings are consistent with previously reported results [6,16,17]. With regard to having a first-

degree relative with breast cancer, our finding supports the hypothesis of heredity's crucial role in the development and increased risk of breast cancer [7,15]. This might be because relatives

have both similar genes and lifestyles [15]. Nevertheless, being menopausal and the use of HRT seems to be inter-correlated, as most of the woman who use HRT are in their

Table 1. Dichotomized characteristics of women in control and case groups

Variable	Controls (n= 418) n (%)	Cases (n=405) n (%)	OR (95% CI)	p-value*
Education level				
High (≥ diploma)	133 (31.8%)	169 (41.7%)	1.62 (1.15 to 2.04)	.004
Low (≤ secondary school))	285 (68.2%)	236 (58.3%)		
Marital status				
Married	391 (93.5%)	365 (90.1%)	0.63 (0.38 to 1.04)	.076
Never married	27 (6.5%)	40 (9.9%)		
Family monthly income				
Low (< 845\$)	344 (82.3%)	322 (79.5%)	1.19 (0.85 to 1.70)	.330
High (≥845\$)	74 (17.7%)	83 (20.5%)		
Having a chronic disease?				
Yes	138 (33%)	146 (36%)	1.14 (0.86 to 1.53)	.379
No	280 (67%)	259 (64%)		
Family history of cancer (first-degree relatives)				
Yes	211 (50.5%)	222 (54.8%)	1.20 (0.91 to 1.56)	.235
No	207 (49.5%)	183 (45.2%)		
Having first-degree relatives with breast cancer				
Yes	81 (39.1%)	107 (48.9%)	1.49 (1.01 to 2.18)	.003**
No (other types)	126 (60.9%)	112 (51.1%)		
Parity				
Nulliparous	50 (12 %)	67 (16.5%)	0.69 (0.46 to 1.02)	.072
Parous	368 (88%)	405 (83.5%)		
Breast feeding				
Yes	399 (81.1%)	307 (75.8%)	0.73 (0.53 to 1.02)	.075
No	79 (18.9 %)	98 (24.2%)		
Use of oral contraceptive				
Yes	162 (38.8%)	160 (39.5%)	1.03 (.78 to 1.37)	.831
No	256 (61.2%)	245 (60.5%)		
Use of hormonal replacement therapy				
Yes	10 (3.6 %)	38 (11%)	3.29 (1.60 to 6.71)	.001**
No	267(96.4%)	309 (89 %)		
Menopause				
Yes	139 (33.3%)	217 (53.6%)	2.31 (1.75 to 3.07)	<.001**
No	279 (66.7%)	188 (46.4%)		

* Chi-squared tests comparing control and case groups

** Significant: $p \leq .005$ (Bonferroni corrected)

Table 2. Interval characteristics of women in control and case groups

Variable	Controls (n= 418)	Cases (n=405)	95% C.I.	p-value
	Mean (SD)	Mean (SD)		
Age (year)	45.9 (10.9)	49.2 (10.3)	-4.69 to -1.79	<.001 **
Marriage age (year)	20.2 (4.9)	22.7 (5.6)	-3.27 to -1.75	<.001 **
Age at first birth (year)	20.8 (5.0)	23.5 (6.3)	-3.48 to -1.80	<.001 **
Age at menarche (year)	13.6 (1.7)	13.4 (1.5)	-2.64 to 0.43	.074
Duration of oral contraceptive use (year)	4.9 (6.2)	4.0 (5.3)	-.44 to 2.17	.192
Duration of breast feeding (months)	13.5 (7.3)	12.8 (7.7)	-0.45 to 1.86	.231
Number of children	5.1 (2.4)	4.4 (2.0)	0.28 to 0.94	<.001 **

Independent t-tests comparing control and case groups

***Significant: $p \leq .007$ (Bonferroni corrected)*

Table 3. Logistic regression model for reproductive risks factors associated with breast cancer

Risk factor	B	S.E.	Odds ratio	95% C. I. for odds ratio		p-value
Marriage age (year)	.097	.030	1.102	1.040	1.168	.001
Age at first birth (year)	.060	.024	1.062	1.013	1.113	.013
Use of HRT	-.926	.392	.396	0.184	0.853	.018
Menopause	-.475	.186	.622	0.432	0.896	.011
Constant	-2.064	.603	.127			.001

menopause. Hormonal changes and their correlation with increased risk of breast cancer are well-established in the literature [6,7,15-17]. However, this correlation needs to be further explored to determine which is the more likely to be the risk, or whether they have a synchronised effect on the risk of breast cancer.

A significant association was found between increased mean age, older age at marriage and at first birth, and increased risk of breast cancer. In addition, a greater number of children decreases the risk of having breast cancer. These results are in line with previously reported findings [7,12,16,18,19]. Increased age and its related events (mean age at marriage and at giving birth) are significant risk factors. Breast cancer cell development and differentiation is mediated by hormonal factors. Hence, it is postulated that the longer period of exposure to reproductive hormones, including the increased use of HRT and longer life expectancy, are the mechanisms behind the development of breast cancer [15]. However, breast feeding, the use of OC, and age at the menarche were found not to be significantly associated with increased risk of breast cancer. At first glance, these results seem to contradict what has been previously reported. In fact, these findings are logical; for example the use of OC for more than five years is likely to

increase the risk of breast cancer [6], but in this study most of the women used it for less than five years. The mean age at menarche for both case and control groups was > 13 years, and it is considered that early menarche occurs at 12 or under. These considerations highlight important cultural differences between Arab Jordanian women and Western women. The former tend to use OC less, and the age of menarche is higher. Thus, replication studies in Jordan and the region are needed, but with a larger sample size to validate the results of the current study.

The logistic regression model shows that only older age at marriage and at first birth (against being married and giving birth at a younger age), the use of HRT (against never using it), and being menopausal (against non-menopausal) predicted a higher risk of breast cancer among Jordanian women. Thus, healthcare providers must pay extra attention to these factors when they assess the risk of breast cancer in early detection clinics. Current risk assessment tools, mostly adopted from Western-based culture studies, need to be modified accordingly. The use of HRT needs to be controlled and used only after a precise risks/benefits analysis. Finally, economic constraints are expected to increase the age at marriage and at giving birth. Within Arab-Islamic culture, getting married is a costly

life event, so the incidence of breast of cancer may increase. Policy makers in the healthcare sector should take this into consideration and take suitable actions to minimise this possibility.

4. LIMITATIONS

There are some limitations in the study. First, most of the women recruited lived in the main urban centres, where reproductive factors and behaviour may differ from those of women living in rural areas. Second, although the sample size was thought to be statistically adequate, a replication study with a larger size is recommended to allow a more representative sample and improve the external validity of the results. Third, we were not able to compare differences in the type of HRT and OC used. Fourth, we did not recruit women from private hospitals and thus they were not represented in the sample. However, despite the limitations, this study is considered as a catalyst for prospective researchers in the field.

5. CONCLUSION

The findings of the study demonstrate that several reproductive factors increase the likelihood of developing breast cancer among Jordanian women. These factors include the use of HRT, being menopausal, and being older at marriage and first birth. Some discrepancies between the results of the current study and previous studies were highlighted, which might be the results of differences in culture, behaviour and habits.

CONSENT

Author declares that 'written informed consent was obtained from the patient for publication of this paper'.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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