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Reproductive factors and breast cancer risk in Palestine: A case control study

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ABSTRACT

Background: Early age at menarche, late age at menopause, and late age at first full-term pregnancy are linked to a modest increase in the risk of developing breast cancer (breast ca). This study aims to investigate the reproductive determinants of breast cancer among women in the West Bank of Palestine.

A structured questionnaire was used to collect data in a case-control study (237 registered cases and 237 controls). A multivariate analysis model was used to adjust for the association between women's reproductive factors and breast ca risk. This study was approved by Al Quds University Ethical Research Committee and the Ministry of Health research unit.

Results: In the multivariate analysis, menarche after 13 years of age, use of oral contraceptives for more than two months, and hormonal contraceptives use significantly doubled the risk for breast ca (Adjusted Odds Ratio (AOR) = 2.03, 95 % CI: 1.21–4.37, $p < 0.011$ and AOR = 2.2, 95 % CI: 1.24–4.01, $p = 0.008$, respectively). Women who used hormone replacement therapy (HRT) were significantly associated with higher odds (5 folds) of having breast ca versus those who did not use them (AOR 5.02, 95 % CI: 1.93–13.06, $p = 0.001$). Similarly, nulliparous women showed 6 times the odds of breast ca compared with women with one or more children ($p = 0.005$). Also, parental consanguinity marriage (AOR 2.59, 95 % CI: 1.53–4.36, $p = 0.001$) and positive family history (AOR 3.88, 95 % CI: 2.19–6.87, $p = 0.001$) of the condition can be strong determinants for breast ca in this study.

Conclusion: This study provides clear evidence that the use of reproductive hormones, whether as a birth control tool or for therapeutic purposes, must be rationalized worldwide and in Palestine in particular.

1. Introduction

Breast cancer (breast ca) is the most common form of cancer mortality among women in the world [1]. Breast cancer is a multi-factorial type of cancer. Being genetically predisposed or having a family history of a first-degree relative with breast ca was shown to increase the cancer incidence [2–4]. Parental marriage to a relative was also shown to increase the risk [5]. Among women aged 40 years or more, breast ca is related to increased risk [6,7]. Modifiable risk factors such as obesity, physical inactivity, sedentary behavior, and poor dietary patterns were also shown to be related to breast cancer risk [8–10].

The effect of reproductive factors strongly supports a hormonal role in its aetiology [11–14]· Early age at menarche, late age at menopause, and late age at first full-term pregnancy are linked to a modest increase in the risk of developing breast cancer [14,15]. However, multiple full-term pregnancies and long-term breastfeeding decrease the risk of breast cancer [16,17].

Reproductive surgeries such as ovariectomy, tubal sterilization, and hysterectomy may also affect the breast cancer risk by altering hormone levels before menopause or by bringing forward the age at menopause [18,19]. Long-term use of hormone replacement therapy (HRT) [20], but not long-term use of oral contraceptives (OC), was also related to an increased risk of breast ca [21]. Moreover, it was noted that the time elapsed since last oral contraceptive use was associated with a higher risk of breast ca than recent use [22].

Breast cancer is the most common and widespread type of cancer in Palestine, and ranks as the third cancer that causes death. It constitutes 17 % of all cancer cases. At the end of 2017, there were 503 new cases documented in the West Bank and 327 new cases recorded in the Gaza Strip. The rate was 33.1 new cases per 100,000 females annually [23]. Few studies have tackled the risk factors of breast ca in Palestine [2,24]. In Gaza, a study among women aged 18–60 years suggested that a

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positive family history of breast ca, high body mass index, and some common diseases (hypertension, diabetes mellitus) maybe epigenetic factors that promote the occurrence of breast ca [2]. The reproductive determinants of breast cancer among women in the southern region of the West Bank will be presented here. The study findings may help to clarify the interaction of these factors in the development of breast cancer among Palestinian women.

2. Study context

The cancer burden in Palestine is expected to increase and will pose a substantial challenge for the healthcare system. The limited financial and infrastructural resources, plus political uncertainty, exacerbate the problem [25]. Cancer care, diagnosis and treatment services are provided in four West Bank hospitals. However, isotope scans like PET-CT are not available and all such cases are referred to Israeli hospitals. The shortage of specialized physicians and of drugs, chemotherapy, and radiation therapy present a challenge in providing proper care for cancer patients [26]. This study was conducted at the major governmental hospital: BeitJala hospital in the southern West Bank. BeitJala hospital has an oncology department and daycare clinic that offers daycare medical services for cancer patients in the central and southern areas of the West Bank. Therefore, this study aimed to explore the various reproductive risk factors for breast cancer in the West Bank of Palestine.

3. Material and methods

3.1. Study design

This case-control study was conducted at Beit Jala governmental hospital in the West Bank of Palestine over the period 2016–2017.

3.2. Study cases and control selection

Based on hospital chart number, a calculated sample of 237 women (estimated odds ratio of 3 assuming 80 % study power (1-β), 5 % level of significance (α) and 0.2 as a correlation coefficient for exposure(s) between cases and their controls) were selected at random as study cases from those attending the daycare oncology department or the chemotherapy unit of BeitJala hospital. These women had a pathologically confirmed breast carcinoma and were aged 40 years or more at the time of interview. To serve as a comparable and representative control group, 237 women of the same age distribution and geographic area were randomly recruited from the screening program for breast ca. The subjects in the control group were confirmed as free from breast ca and had never been suspected of having any previous neoplastic disease or any other cancer. Their medical records were checked to include a normal (BIRADS 1) mammography. Those referred by a physician for a suspected history of breast problems were excluded. Only a very low proportion (2 %) of selected women (study cases and controls) refused to participate in this study.

This study was approved by Al Quds University Ethical Review Committee. Written approval was obtained from the Ministry of Health to access the patients' records from the oncology department and cancer registry. All women provided written informed consent.

3.3. Data collection

The medical records of cancer patients were used to retrieve information related to the breast ca: date of diagnosis, stage at diagnosis, type of cancer, and therapy strategy.

Trained female interviewers administered an in-person structured questionnaire during the patient visit to the oncology department. Controls were contacted by a nurse from the mammography department and were invited to participate. If a control refused to come to the clinic, the interview was conducted via a phone call.

The study risk factor questionnaire was built on the British cancer Cohort Study questionnaire (2014) [27]. The questionnaire was translated into the Arabic language, back translated and piloted before using it in the field. It included questions on demographic and lifestyle factors; parental consanguinity marriage; contraceptive history; use of hormone therapy; menstrual history; pregnancy and breastfeeding history; medical history, including cancer and mammogram history; and family history of malignancy. Women were also asked whether they had undergone surgery to remove one or both ovaries partially or fully. Women were also asked whether they had undergone a hysterectomy or tubal sterilization, and the approximate month and year of the procedure(s).

3.4. Statistical analysis

SPSS version 23 (IBM Corp., Chicago, IL, USA) was used for the data analysis. Bivariate and multivariate unconditional logistic regressions were used to assess the association of breast ca with independent variables. Crude and adjusted odds ratio (AOR) and 95 % confidence intervals (CIs) were calculated to determine the precision of the estimates. The level of significance used was 5 %. The p-value < 0.05 indicated significance.

4. Results

In total, 237 cases and 237 age-matched controls were included. The mean age of those in the study was 54.6 (SD = 10.9) years and 54 (SD = 9.9) years for the control group ($p > 0.05$).

Most of the study cases were diagnosed at stage 2 and 3 of cancer (35 % and 30 % respectively). Most of the study cases (83 %) discovered that they had cancer after they noticed a mass and only 17 % were diagnosed by screening. More than half of the study cases had ductal carcinoma (n = 138, 58 %); 19 women had lobular carcinoma (8 %); 5 women had follicular carcinoma (2.1 %); 4 had mixed type (ductal lobular 1.7 %); and 30 % did not have a documented type in their files. Almost all cases had undergone chemotherapy treatment (98 %). About 83 % of cases had undergone partial mastectomy and half of them had undergone a full mastectomy. Furthermore, 75 % of cases had surgery as the first-line treatment and did not receive neo-adjuvant therapy.

4.1. Socio-demographic factors

Table 1shows the socio-demographic characteristics for cases and controls. Study cases and controls had significantly different distributions for multiple characteristics such as educational level, home type, family size, and parental consanguinity, but not for others (Table 1). Study cases had higher levels of education than those in the control group (41 %) had more than 10 years of education versus 24.5 %). Controls had larger families than study cases (mean 6.35, SD 2.6 versus mean 5.61, SD 2.96 respectively) but lived in smaller residences than the study cases. About 43 % of study cases had married a first-degree relative compared with 21 % in the control group.

4.2. *Reproductive factors*

Table 2 shows the reproductive characteristics for study cases and controls. Study cases reorted to be diagnosed at a median age of 50 years (range 30 to 80 years) and a mean of 51 years, (standard deviation 10.5 years). Study cases and controls had significantly different distributions for multiple characteristics such as age at first menarche, age at first marriage, age at first pregnancy, age of first delivery, and use of oral contraceptives use (OC) and hormone replacement therapy use (HRT). Also, total duration of breastfeeding was significantly different between study cases and controls, but not for duration of OC use and duration of HRT use (Table 1). A woman's age at menarche was significantly higher among the control group compared with study cases mean 13.2 (SD = 1.01) years versus 13.6 (SD = 1.08) years in the study cases, *t*-test

Table 1
Socio-demographic and characteristic of study participants.

Characteristics		Controls N = 237 Frequency (%)	Study cases = 237 Frequency (%)	Chi square P-value
Age groups (years)	39-44	50 (21.1)	50 (21.1)	–
	45-49	40 (16.9)	40 (16.9)	
	50-54	37 (15.6)	37 (15.6)	
	55-59	40 (16.9)	40 (16.9)	
	60-64	19 (8.0)	19 (8.0)	
	65-69	27 (11.4)	27 (11.4)	
	More than 70	24 (10.1)	24 (10.1)	
Educational level (years)	1-6	117 (49.3)	81 (34.2)	0.001
	7-9	62 (26.2)	59 (24.9)	
	10-12	44 (18.6)	49 (20.7)	
	>12	14 (5.9)	48 (20.2)	
Home type	Separate house	147 (62)	198 (83.5)	0.001
	Apartment	90 (38)	39 (16.5)	
Family monthly income**	Less than 1000	55 (23.2)	78 (32.9)	0.012
	1000 to 2000	182 (76.8)	159 (67.1)	
Working status	Yes (now or then)	23 (9.7)	35 (14.8)	0.09
	No	214 (90.3)	202 (85.2)	
Period of work (years)	Less than 15	15 (65.3)	16 (45.7)	0.31
	15-30	7 (30.4)	15 (42.9)	
	More than 30	1 (4.3)	4 (11.4)	
Marital status	Single	10 (4.2)	19 (8.0)	0.20
	Married	189 (79.7)	185 (78.1)	
	Divorced or widowed	38 (16.1)	33 (13.9)	
Parity	No	12 (5.1)	36 (15.2)	0.000
	Yes	225 (94.9)	201 (84.8)	
Family size (persons)	1-5	93 (39.2)	108 (45.6)	0.16
	6 or more	144 (60.8)	129 (54.4)	
Parental consanguinity relation	No Relation	123 (51.9)	100 (42.2)	0.001
	1st degree	52 (21.9)	102 (43.0)	
	2nd degree	62 (26.2)	35 (14.8)	

*p-value was calculated by using Pearson's chi square test.
† Among married/divorced women.
†† Among users only.
** NIS: new Israeli Shekels: 1000 NIS is about 300 dollars.

Table 2
Reproductive characteristic of study participants.

		Controls N = 237	Study cases = 237	P value ***
Family history of breast cancer	Yes	214 (90.3)	164 (69.2)	000
	No	23 (9.7)	73 (30.3)	
Use of HRT*	Yes	8 (3.4)	36 (15.2)	000
	No	229 (96.6)	201 (84.8)	
Ever OC use for ≥ 2 months*	Yes	25 (10.5 %)	47 (19.8 %)	0.005
	No	212 (89.5)	190 (80.2)	
Number of full term pregnancies†	>5 children	177 (74.7)	140 (59.1)	0.001
	1-4 children	49 (20.7)	64 (27)	
Ever breastfeeding†	Yes	217 (95.2)	187 (85.8)	0.001
	No	11 (4.8)	13 (12.4)	
Age at first menarche (years)	Mean (SD)	13.20 (1.01)	13.60 (1.08)	000
	Median (Min-max)	13.00 (10.5–16)	14.00 (10–17)	
Age at first marriage (years)†	Mean (SD)	18.46 (3.20)	20.43 (5.44)	000
	Median (Min-max)	18.00 (13–33)	19.00 (12–44)	
Age at first pregnancy (years)†	Mean (SD)	19.26 (3.44)	21.13 (4.78)	000
	Median (Min-max)	19.00 (14–34)	20.00 (14–42)	
Age at first breastfeeding (years)† †	Mean (SD)	19.85 (3.17)	21.53 (4.66)	000
	Median (Min-max)	20.00 (15–33)	21.00 (6–43)	
Total breastfeeding duration (years) †	Mean (SD)	9.24 (4.09)	6.59 (4.28)	000
	Median (Min-max)	10.00 (0–29)	6.00 (0–20)	
Total duration of oral contraceptives use (years)††	Mean (SD)	3.29 (5.23)	2.47 (1.40)	0.317
	Median (Min-max)	1.50 (1–20)	2.00 (1–6)	
Total duration of HRT use (years)††	Mean (SD)	4.63 (4.98)	4.44 (4.26)	0.92
	Median (Min-max)	1.5 (1–12)	3.00 (0.30–18)	
Age at diagnosis (years)	Mean (SD)	51.4 (10.45)		
	Median (Min-max)	50 (31–80)		

Legend.
*Hormone Replacement Therapy (HRT), OC: Oral Contraceptive.
** Calculations were based on number of non single women.
* Among all participating women.
*** *t*-test (for continuous variables) p-value or Chi-square (categorical variables).
† Age at first pregnancy, age at first delivery, and number of full pregnancy calculations were based on married women with children.
†† Age of first breastfeeding and duration were calculated bases on the number of breastfeeding.

significance <0.001. Controls had significantly higher full term pregnancies (more than 5 children: 74.7 %) than those in the control group (59.1 %). However, more than half of both study cases and controls were postmenopausal women with no significant difference in the age of menopause (mean 49.21 (SD = 3.55) years versus 48.5 (SD = 4.38) years, (*t*-test significance >0.05).

4.3. Socio-demographic factors and their association with breast cancer

The odds ratio between socio-demographic factors and breast ca are summarised in Table 3. The odds of breast ca were higher among women with more than 12 years of education versus those with less education. The odds of breast ca were 3.87 times higher among women living in separate houses compared with those living in apartments (95 % CI: 2.36–6.33, p = 0.00). Women with no children were 2.5 times more likely to get breast ca versus women with children. Interestingly, the odds of breast ca were 2.5 times higher among women married to a first cousin (consanguinity marriage) compared with those whose spouse was not related or were married to a second-degree relative (95 % CI: 1.60–4.08, p = 000).

4.4. Reproductive factors and their association with breast cancer

In the multivaraite regression model, the odds of breast ca were 2.2 folds higher among women with late menarche (≥ 13 years) versus those who got their menarche earlier (< 13 years old) (95 % CI: 1.24–4.01, p = 0.008) (Table 4). The mean age for use of OC in the control group was 29.28 years (SD = 6.02) and 28.91 years (SD = 5.96) in the study cases (*t*-test significance >0.05). Ceasing use of OC was also not significantly different between the two groups 34.38 years (SD = 6.61) in control group and 33.91 years (SD = 7.68) in study, *t*-test significance >0.05). Women who used hormonal contraceptives and hormone replacement therapy (HRT) were significantly associated with higher odds of having breast ca at 2.03 (95 % CI: 1.21–4.37, p < 0.011) and 5.02 (95 % CI: 1.93–13.06, p = 0.001) respectively, compared for those who did not use them (Table 4). Moreover, the odds of breast ca were 2.59 folds higher among women married to a first cousin (consanguinity marriage) compared with those whose spouse was not related or were married to a second-degree relative (95 % CI: 1.53–4.36, p = 000). A similar positive association was seen when cases had a family history of cancer, where the likelihood to have breast ca increased 3 folds (AOR = 3.88; 95 % CI: 2.19–6.87) (Table 4). Moreover, women from low income families were 2 folds more likely to have BC compared to more women from wealthy

Table 3
Socio-demographic factors and their association with breast cancer.

Characteristics		Controls N = 237	Study cases N = 237	Univariate analysis		Multivariate analysis		
		Frequency (%)	Frequency (%)	OR	95 % CI L-U	AOR	95 % CI L-U	P value
Educational level (years)	1-6	117 (49.3)	81 (34.2)	0.20	0.10-0.39	0.14	0.07-0.30	.000
	7-9	62 (26.2)	59 (24.9)	0.28	0.14-0.56	0.27	0.13-0.57	.001
	10-12	44 (18.6)	49 (20.7)	0.33	0.16-0.67	0.32	0.14-0.69	.004
	>12	14 (5.9)	48 (20.2)	1.0	(Ref)	1.0	(Ref)	
Family monthly income (NIS)**	Less than 1000	55 (23.2)	78 (32.9)	1.62	1.08-2.43	1.80	1.13-2.90	0.012
	1000 to 2000	182 (76.8)	159 (67.1)	1.0	(Ref)	1.0	(Ref)	
Home type	Separate house	147 (62)	198 (83.5)	3.1	2.02-4.79	3.87	2.36-6.33	.000
	Apartment	90 (38)	39 (16.5)	1.0	(Ref)	1.0	(Ref)	
Parity	Yes	225 (94.9)	201 (84.8)	0.30	0.15-0.59	0.39	0.19-0.80	.010
	NO	12 (5.1)	36 (15.2)	1.0	(Ref)	1.0	(Ref)	
Parental consanguinity relation	2nd degree	62 (26.2)	35 (14.8)	0.69	0.43-1.13	0.68	0.39-1.16	0.16
	1st degree	52 (21.9)	102 (43.0)	2.41	1.58-3.69	2.56	1.60-4.08	.000
	No Relation	123 (51.9)	100 (42.2)	1.0	(Ref)	1.0	(Ref)	

Multivariate analysis: Logistic regression model using Enter method was used. All variables that were significant in the univariate analysis were included in the multi variate analysis.
Legend: L lower, U upper, COR crude odds ratio, AOR adjusted odds ratio, Ref reference, CI confidence interval.
OR was calculated by using logistic regression, p-value < 0.05. NIS: new Israeli Shekels.

Table 4
Reproductive factors and their association with breast cancer.

characteristic		Controls N = 237	Study cases N = 237	Univariate analysis			Multivariate analysis†		
		Freq (%)	Freq (%)	P-value	OR	95 % CI L-U	AOR	95 % CI L-U	P value
Age at menarche * (years)	≥13	179 (75.5)	205 (86.5)	0.002	2.07	1.29-3.34	2.23	1.24-4.01	0.008
	<13	58 (24.5)	32 (13.5)		1.0	(Ref)	1.0	(Ref)	
Ever OC use for ≥ 2 months*	Yes	25 (10.5)	47 (19.8)	0.005	2.09	1.24-3.52	2.30	1.21-4.37	0.011
	No	212 (89.5)	190 (80.2)		1.0	(Ref)	1.0	(Ref)	
Use of HRT*	Yes	8.0 (3.4)	36 (15.2)	00	5.13	2.33-11.2	5.02	1.93-13.06	0.001
	No	229 (96.6)	201 (84.8)		1.0	(Ref)	1.0	(Ref)	
Educational level (years) *	1-6	117 (49.3)	81 (34.2)		0.20	0.10-0.39	0.16	0.07-0.38	.000
	7-9	62 (26.2)	59 (24.9)		0.28	0.14-0.56	0.26	0.11-0.61	.002
	10-12	44 (18.6)	49 (20.7)		0.33	0.16-0.67	0.32	0.13-0.79	.014
	>12	14 (5.9)	48 (20.2)		1.0	(Ref)	1.0	(Ref)	
Family monthly income (NIS)*	Less than 1000	55 (23.2)	78 (32.9)	0.06	1.55	0.94-2.55	2.17	1.09-4.35	.028
	1000 to 2000	121 (51)	103 (43.5)		0.93	0.59-1.45	0.88	0.49-1.59	.682
	>2000	61 (25.7)	56 (23.6)		1.0	(Ref)	1.0	(Ref)	
Home type*	Separate house	147 (62)	198 (83.5)		3.1	2.02-4.79	3.94	2.25-6.89	000
	Apartment	90 (38)	39 (16.5)		1.0	(Ref)	1.0	(Ref)	
Parental consanguinity relation	2nd degree	62 (26.2)	35 (14.8)		0.69	0.43-1.13	0.51	0.28-0.94	0.03
	1st degree	52 (21.9)	102 (43.0)		2.41	1.58-3.69	2.59	1.53-4.36	0.00
	No Relation	123 (51.9)	100 (42.2)		1.0	(Ref)	1.0	(Ref)	
Family history of BC	Yes	214 (90.3)	164 (69.2)	00	4.14	2.49-6.90	3.88	2.19-6.87	000
	No	23 (9.7)	73 (30.3)		1.0	(Ref)	1.0	(Ref)	
Total breastfeeding (BF) durations (all children) (years) *	No BF	20 (8.4)	50 (21.1)		1.0	(Ref)	1.0	(Ref)	
	≤3	12 (5.1)	28 (11.8)		0.93	0.39-2.19	1.05	0.34	3.20
	4-6	33 (13.9)	58 (24.5)	00	0.70	0.36-1.38	1.10	0.423	2.84
	7-9	59 (24.9)	48 (20.3)		0.33	0.17-0.62	0.78	0.31	1.98
	>9	113 (47.7)	53 (22.4)		0.19	0.10-0.35	0.38	0.16	0.91

Legend Hormone Replacement Therapy (HRT), Oral contraceptives (OC), Chi square p value.
Multivariate analysis includes non-single women. The model includes: Level of education, family monthly income, home type, parity, parental consanguinity relation, age of menarche, age of marriage, full term pregnancy, breastfeeding status, duration of breastfeeding, HRT use, and OC use.
* Among all participating women.
† Only non-single women included in the model.

families (AOR 2.17 (95 % CI: 1.09–4.35, p < 0.028). The odds of breast ca were higher among women with more than 12 years of education versus those with less education. The odds of breast ca were 3.94 folds higher among women living in separate houses compared with those living in apartments (95 % CI: 2.25–6.89, p = 0.00). However, the longer the duration of breastfeeding, the lower the odds for breast ca.

5. Discussion

The reason for international variations in the incidence of breast ca remains unclear. These variations can be seen between both high and low-income countries. Many of the risk factors for breast ca have been investigated but require further examination in individual nations.

In this study, we examined a broad spectrum of risk factors for breast ca, including female reproductive factors. The reproductive risk factors for breast ca identified in Palestinian women are similar to those observed in other studies. This study provides clear evidence that late menarche poses an additional risk for breast ca. Early marriage and having children early in life, both popular in the Palestinian community, were shown to increase the odds of breast ca. The role of oral

contraceptives and hormonal replacement therapy on women's health was also clearly shown and there should be rational use of hormones, whether as a birth control tool or for therapeutic purposes. Having children proved to be protective against breast ca but as most married women in Palestine breastfeed their children, we could not show that breastfeeding is a protective factor for breast cancer among the study group. However, we can still highlight the role of breastfeeding in breast ca protection. More in-depth investigations are needed to identify the relationship between various factors, especially the protective role of having children and breastfeeding practices on breast ca in Palestine. Special attention should be devoted to the particular social and cultural factors related to sexual and reproductive issues among women in Palestine.

Several studies have indicated that women with high socioeconomic status (SES) are at risk for breast ca with an overall estimate of 20 % increased risk [28]. This positive association was clearer among Hispanic and Asian women [29], and not only for breast ca but for other cancers such as colon, ovary, and melanoma cancers [30]. Our study found that breast ca was more common among more educated rather than less educated women, and in women with a lower family income rather than women with a higher family income. In the north of Palestine, a previous study showed that there was a four-fold increase in the risk of breast ca among highly educated women [24]; this was also reported among Egyptian women [31]. In European women, a direct dose-response relationship was seen between educational level and postmenopausal breast ca incidence [32]·

Our results found that women living in an apartment had a significantly lower risk of getting breast ca compared with those living in a separate home; this was assumed to be due to a higher SES. Several studies showed that lower SES increased the risk of breast ca because women were less aware of screening techniques and diagnosis [33]. Our results could be explained by the fact that women with a higher family income can afford health insurance and are more willing to spend money on their health and better medical care access. Greater awareness among educated women about mammography screening tests is very clear in Palestine. It is worth mentioning that screening in Palestine is free of charge for all women over 40 years of age. Another possible explanation is that the more a woman is educated, the later she marries, the later the age of pregnancy, the shorter the period of breastfeeding, and the lower parity is characteristic of women from higher SES. Indeed, socio-economic inequalities could affect the time of diagnosis, survival or mortality due to cancer despite improved knowledge, reduction of risk factors for cancer, early diagnosis, and treatment [34].

Consanguinity is becoming a very strong factor for cancers and other genetic diseases in many countries [35,36]. Our study showed that daughters of unrelated parents had a decreased breast ca risk, whereas the risk increased 2.5-fold for those with first-degree related parents. A similar finding was reported in the United Arab of Emirates (UAE) in which having unrelated parents halved the risk (RR = 0.5, 95 %CI: 0.27-0.93) [36]. A study among Israeli Arabs of Palestinian origin showed an increase in diabetes and duodenal ulcers [35]. Consanguineous practices in populations might affect the gene frequency in these populations, which could have a major effect on the carrier rate of such genes. Therefore, in countries with high consanguinity, the incidence of diseases and syndromes should be monitored with caution.

It is believed that up to 10 % of breast ca cases in Western countries were due to genetic predisposition with a threefold increase in the risk of breast ca among those with a family history of breast ca [37]. In our study, women with a family history of breast cancer had a fourfold increased risk of breast ca. In Qatar, a country with high consanguinity marriage, a study showed that consanguinity was lower in breast cancer patients than in controls, but a family history of breast cancer was significantly more prevalent in breast cancer patients [38]. The risk of breast ca ranged from 1.5 to 3.6 in a pooled analysis depending on the relative in question, with the highest risk reported among women who had a mother or a sister with breast ca [39]. Furthermore, women living in the Gaza Strip and who had a positive family history of breast ca showed an increased risk of breast ca (OR = 2.7, 95 %CI: 1.04–7.20). Similar results were reported among Algerian women, where the odds for breast cancer were four times higher among those with a family history of the disease (95 % CI: 2.22–7.77) [40]. These two factors, i.e. consanguinity and family history of breast cancer, may have a synergistic effect in such studies and the risk might be greater if combined in these women.

Early age at menarche, late age at menopause, and late age at first full-term pregnancy are linked to a modest increase in the risk of developing breast cancer [14–16]· Also, parity and age of marriage are among the most common extrinsic factors that modulate breast cancer risk. It is well documented that parity has a dual effect on breast cancer risk, with an increased risk during 5–10 years after pregnancy, followed by a strong and life-long protective effect [15].

In several studies, older age at menarche was inversely associated with breast ca risk. The high-risk groups were females with menarche before the age of 11 years [4]. Around 117 studies showed that the breast ca risk increased by a factor of 1.050 for every year less at menarche [15], and a delay of two years at menarche led to a 10 % reduction in breast ca worldwide [41]. In our study, older age at menarche was shown to be associated with an increased risk of breast ca. The risk increased three-fold with menarche at the age of 13 or more. In the north of the West Bank, the estimated risk was 6.5 which also showed an increase the risk for breast ca [24]. The protective result of menarche at an older age was explained by the lower cumulative number of ovulatory cycles, which is negatively associated with the risk, younger age at menarche, and older age at menopause, means a female would have more cycles and an increased risk [42,43].

According to the Palestinian Central Bureau of Statistics (2016), the mean age of first marriage was 19.8 years in the southern region of Palestine [44]. Consequently, many women may have their first pregnancy and first delivery at a young age (below 18 years). Women with breast ca in our study had a mean age of marriage of 20.4 years (SD = 5.44). Our multivariate results showed an inverse association between age at first marriage and age of first pregnancy for breast ca. We could not see any difference according to whether a woman had her first child before the age of 18 years or after. In contrast, a study in the north of the West Bank showed that there was a 10 % increase in the risk of breast ca when the first marriage was below 20 years of age [24]. Another study in the Gaza Strip showed that women who had their first pregnancy after the age of 35 years had an 11-fold increase in breast cancer risk [2].

Our results revealed no significant association between full-term pregnancies and the risk of breast ca. However, the number of full-term pregnancies was negatively associated with breast ca risk in almost all studies, even in the Western world. This result was consistent for not only one type but for all subtypes of breast ca in pre- and post-menopausal women. The reduction in the risk in the Arab countries ranged from 18 % to 60 % [45]. In the north of Palestine, a 50 % decrease in risk was reported among women with four full-term pregnancies or more [24].

One of the well-established protective factors against breast ca is breastfeeding. In our results, almost all women who had children had engaged in breastfeeding, but the protective effect in our analysis was not in the breastfeeding itself but in its duration. Previous studies found that breastfeeding itself was protective. A Saudi study reported that never having breastfed doubled the risk (OR = 1.89, 95 %CI: 1.19–2.94) [45]. Furthermore, breastfeeding decreased the risk of having breast ca by almost 60 % in an Israeli study in our region (OR = 0.39, 95 %CI: 0.26-0.59) [46]. Breastfeeding is assumed to protect against breast ca through hormonal mechanisms that include postponing the resumption of ovulatory menstrual cycles after pregnancy, reducing estrogen levels in the breast, and having fully differentiated breast tissue that is less susceptible to hormones [47].

The results of studies about the duration of breastfeeding have been inconsistent. A study that summarized findings from developed

countries showed that for every year a woman breastfed, her risk of developing breast ca was reduced by 4.3 % [48]. Similar results were reported in an American study for different age and ethnic groups [49]. In our study, a very clear inverse dose-response relationship was found with AOR = 0.39 for the group of 9 years or more of breastfeeding versus those who had never breastfed, with a decrease in risk of 25–30 % for an additional three years of breastfeeding. Among Palestinian women in the north, the risk for those who had never breastfed was doubled compared with those who had lactated for four years or more [24]. No association was found between breastfeeding duration and the risk of breast ca in either developed or developing countries [48].

Regarding the use of hormonal contraceptive pills (OCP) and their association with breast ca, our study showed that previous oral OCP use for more than two months significantly doubled the risk of breast ca (AOR = 2.22), but failed to show any link to the duration of using OCP. Similar results were revealed among Jordanian females [50,36]. Regular use of OCPs in Jordanian women was shown to be associated with an increased risk of breast cancer (OR = 2.25, 95 % CI 1.34–2.79; p = 0.002), although the duration of use was not associated with an increased risk of breast cancer ($p > 0.05$) [36]. However, many studies found a slight increase in the risk [51]. Other studies reported that the increased risk was only for the 10 years that followed the last OCP use [32]. Other studies have found a decreased risk among women, but at least 10 years after the last use of OCPs [52]. A study in Iran showed that long term OCP use (>/ = 10 years) (OR = 3.17, 95 % CI: 1.27–7.95, P = 0.01) increased the risk of breast ca [53]. On the contrary, some studies showed that OCP played a protective role against breast ca. A study in the Central African Republic showed a decrease in the risk for breast ca (0.62) [54]. In Palestine, 54.8 % of married women aged 15–49 years reported using contraception and 44.0 % of women of reproductive age used modern contraceptives [55].

Hormone replacement therapy (HRT) was very strongly associated with the risk of breast ca in our results (AOR = 3.97). Similar results were reported among Saudi and Jordanian women, (OR = 2.25, 95 %CI: 1.65–3.08) [45,50]. A population-based study in Korea showed that the risk of breast cancer in HRT users was 1.25 (95 % CI, 1.22–1.29) compared with non-HRT users. As the duration of use increased, so did the adjusted hazard ratio (HR) (adjusted HR for 2 to <5 years was 1.33 and was 1.72 for ≥ 5 years) [8]. In our study, 77 % of women used HRT for less than 5 years (mean 3 years, standard deviation 2.61 years) with no significant difference between the study cases and control group. An increased risk among HRT users was shown in most studies. Martino et al. showed a 30 % increase in risk of breast ca in past users compared with 60 % in current users, revealing a dose-response relationship with duration of use [56]. Nevertheless, it was reported that HRT therapy using estrogen alone had a reduced breast ca risk in young women but increased the risk in older women [57]. In our study, women could not tell us which type of HRT they used and the exact duration of its use.

Some limitations must be taken into consideration to explain the findings of this study. Firstly, the study was carried out on patients living in the south of Palestine. Thus, known risk factors may be different in the general population. Secondly, there could be information (recall) bias from the self-reporting of information of some variables such as the age of menarche, age of menopause, breastfeeding practices, and abortion experiences. Also, women were not able to report which type of OCP and HRT they used and the duration of its use. Thirdly, the use of women who came for screening of breast ca as the control group introduced some selection bias in the study. Nevertheless, the results and limitations of the study contribute to the ongoing research in the field of breast ca among Palestinian women. Also, this study was conducted in an Arab developing country where lifestyle changes can provide other important information about breast ca risk factors.

6. Conclusions

This is the first epidemiological study in Palestine to investigate the risk for breast ca based on women's reproductive factors. Significant differences in breast ca were found between the study cases and control group: age at puberty, use of OCP and HRT, nullparity, early marriage, early pregnancy, and early delivery. All these factors indicated a higher risk of breast ca alongside being from a family with a history of breast cancer and married to a first cousin. In Palestine, most women breast-feed so more in-depth investigations are needed to identify the protective role of having children and breastfeeding practices on breast ca protection. Moreover, the Palestinian community must be aware of the effect of early marriage and parental consanguinity on the risk of breast cancer. These results are very important in clinical practice and women must be aware of the results on their health of the use of OCP and HRT. The use of reproductive hormones whether as a birth control tool or for therapeutic reasons must be rationalized. We encourage more studies to be conducted on breast cancer to tackle the specific types of breast ca in all areas of Palestine and other unknown determinants. Special attention should be given to the particular social and cultural factors related to sexual and reproductive issues among women in Palestine.

Ethics approval and consent to participate

This study was approved by Al Quds University Ethical Research Committee, which is based on the Helsinki declarations. Therefore, all study methods were performed following the Helsinki guidelines and regulations. Al Quds University ethical research regulations adhere to Helsinki regulations

Written approval was obtained from the Ministry of Health to access patient records from the oncology department and cancer registry. All women provided written informed consent.

Consent for publication

NA

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

Nuha El Sharif was responsible for the Conceptualization, Methodology, Visualization, Writing - Original draft preparation. Nuha El Sharif and Imtithal Khatib designed the survey and developed the study tool. Imtithal Khatib was responsible for data collection, data entry, and primary analysis. Nuha El Sharif and Imtithal Khatib participated in the study of advanced analysis and the development of study tables. Nuha El Sharif was responsible for writing the manuscript. All authors read and approved the final manuscript.

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CRediT authorship contribution statement

Nuha El Sharif: Conceptualization, Methodology, validation supervising of data management and analysis. **Nuha El Sharif** was responsible for original draft writing, editing and reviewing. **Imtithal khatib:** Field work, software development, data analysis and data interpretation and participate in MS writing.

Declaration of Competing Interest

The authors declare that they have no competing interests. The authors are alone responsible for the content and writing of the paper.

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