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ORIGINAL PAPER

The association between breastfeeding and breast cancer occurrence among Israeli Jewish women: a case control study

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Abstract
Purpose Breast cancer remains the major malignant disease among Israeli women, with about 4,000 new cases diagnosed annually, and a steadily increasing incidence rates. Early in this century investigators noted that nulliparity and a history of never having breastfed were more common in women with breast cancer than without the disease. Epidemiological evidence on those issues remains controversial. The purpose of this study was to clarify those controversial.
Methods A hospital-based case control study was carried out at Nahariya hospital (North of Israel) to assess the risk of breast cancer in relation to breastfeeding history. A total of 256 recent cases of breast cancer (diagnosed between January 1999 and February 2005) and 536 controls were included. Detailed information regarding breastfeeding, menstruation, reproductive factors and confounders was collected. Adjusted odds ratios and 95% confidence intervals were calculated.
Results Short duration of lifetime breastfeeding, late age at first breastfeeding and experience of insufficient milk were found to increase breast cancer risk. When women who had ever breastfed their infants were compared with females who had not, breastfeeding was found to be protective (OR of 0.39; 95% CI 0.26–0.59).
Conclusions These findings may have significant impact on intervention planning aimed towards breast cancer reduction among Israeli Jewish women.

Keywords Breast cancer · Neoplasm · Pregnancy · Reproduction · Breastfeeding · Israel

This work should be attributed to University of Haifa, Faculty of Social Welfare and Health Studies, School of Public Health, Haifa, Israel and to Western Galilee Hospital, Nahariya, Israel.

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Introduction

Breast cancer is the most frequent cancer in Israeli women, with steadily increasing annual incidence rates of about 80 per 100,000 (Barchana 2002).

Epidemiological studies have indicated that several menstrual and reproductive factors could be associated with breast cancer risk (Raphael et al. 1999; Medina 2004; Zografos et al. 2004). Among these, nulliparity, late age at full-term pregnancy and negative history of breastfeeding were considered risk factors, while long duration of breastfeeding was considered to be protective (Zheng et al. 2000; Yoo et al. 1992; Tao et al. 1988). Studies of western population have provided inconsistent results, mainly regarding the role of breastfeeding (Zheng et al. 2000; Kelsey and John 1994; Chang-Claude et al. 2000) and number of children breastfed (Yoo et al. 1992; Newcomd et al. 1999; Romieu et al. 1996).

Some studies suggest that the inverse association between breastfeeding and breast cancer risk may exist only among premenopausal women (Lee et al. 2003;

Tryggvadottir et al. 2001; Newcomb et al. 1994), particularly those with long breastfeeding duration (Newcomd et al. 1999; Freudenheimet et al. 1997) and early age at first breastfeeding (Newcomb et al. 1994; Freudenheimet et al. 1997; Enger et al. 1998).

Others have found a protective effect of breastfeeding only among postmenopausal women (Zheng et al. 2000; Yoo et al. 1992; Newcomd et al. 1999; Romieu et al. 1996; Freudenheimet et al. 1997; Enger et al. 1998).

Several studies also show that it is the duration of nursing of the first child, not the lifetime breastfeeding duration, that may determine the negative effect of breastfeeding on breast cancer occurrence (Romieu et al. 1996; Zheng et al. 2001).

The current paper is the first to present the results of a study undertaken in order to clarify the above-mentioned relationships.

Materials and methods

This is a case control study of women with breast cancer versus women without the disease, emphasizing breastfeeding characteristics.

Study population

Cases were women who fulfilled all the following inclusion criteria: (1) Breast cancer patients, histologically confirmed, during the period of January 1999 to February 2005. (2) Jewish women aged 30–75 who lived in Western Galilee area (North of Israel) and had received their oncology therapy at Nahariya Medical Center—a general university affiliated hospital serving a population of about 400,000 people.

A total of 309 eligible cases were identified through review of computerized oncology department medical records, of which 256 (82.8%) took part in the study and were included in data analyses. Those excluded were: 41 (13.26%) women who died prior to study conduction, 5 (1.61%) who did not speak Hebrew, 3 (0.97%) who refused to participate, 2 (0.64%) who could not be located, and 2 (0.64%) who were diagnosed at Nahariya hospital but had received their therapy in others hospitals.

Controls were women without breast cancer, who were randomly selected from those referred to the out patient clinics of Nahariya Hospital during January to end of March 2005 (time of data collection). Eligible controls, as eligible cases, originated from the same source population (Western Galilee), and were Jewish women aged 30–75 years old. A total of 592 eligible controls were identified—of these, 21 (3.54%) could not be located, 17 (2.87%) did not speak Hebrew, 16 (2.7%) refused to participate and 2 (0.33%) were too ill to cooperate. Data collection was therefore restricted to 536 (90.5%) of the intended controls.

Data collection

Patients who agreed to participate in the study were interviewed by phone.

A structured questionnaire was designed to obtain information on menstrual and reproductive factors, as well as on disease status, family history of breast and ovary cancer among first-degree relatives, medical history, tobacco use, and demographic factors. All interviews were conducted by a single interviewer, who was blinded to the women's health status (case/control). This was done in order to avoid interviewer bias. At the end of data collection, a repeated telephone survey was conducted on a sample of 50 women (25 cases and 25 controls).

Data analysis

Breastfeeding was analyzed as a dichotomous variable (yes/no) and by summing the total lifetime duration (months). Age at first and last full-term pregnancy was defined as the woman's age at termination of first and last pregnancy. Insufficient milk was defined as either a woman's report of an unsuccessful breastfeeding attempt, or of breastfeeding for less than 1 month and quitting because of milk deficiency. The reported presence of breast and/or ovary cancer in first-degree relatives was considered a positive family history. Ethnicity was defined as a dichotomous variable: Ashkenazi origin (yes/no). Women with regular or unsteady periods, as well as women less than 55 years old who reported a history of hysterectomy (without oophorectomy) were considered premenopausal group. Logistic regression was used to estimate the association between breast cancer risk and various aspects of reproductive factors and breastfeeding history, and to control for potential confounders. Data were stratified by menopausal status in order to examine its role as an interaction term. Odds ratios and 95% CI were calculated using SPSS software. $P < 0.05$ was considered statistically significant.

Results

The distribution of socio-demographic, medical characteristics, reproductive and breastfeeding history among 256 study cases and 536 controls is presented in Tables 1 and 2.

The results of the logistic regression examining the role of breastfeeding as a risk factor for breast cancer, controlling for various characteristics, including reproductive factors are presented in Table 3. Main findings are:

Table 1 Case-control distribution of socio-demographic and medical characteristics

Characteristic	Cases		Controls		*P* value	95% CI
	N	%	*N*	%		
Age (years)					0.01	
30–49	51	19.9	154	28.7		
50–59	91	35.5	148	27.6		
60+	114	44.5	234	43.7		
Marital status						
Married	164	64.1	407	75.9	0.192	
Divorced/separated	35	13.7	49	9.1		
Widowed	50	19.5	70	13.1		
Single	7	2.7	10	1.9		
Other	0	0	0	0		
Country of birth						
Israel	68	26.6	168	31.3	0.097	
Europe/America	138	53.9	245	45.7		
Asia/Africa	50	19.5	123	22.9		
Ashkenazi					0.006	1.12–2.07
No	94	36.7	252	47.0		
Yes	162	63.3	284	53.0		
Education (years)					<0.001	
0–8	33	12.9	102	19.0		
9–12	106	41.4	264	49.3		
13+	117	45.7	170	31.7		
Chronic disease						
No	125	48.8	268	50.0	0.08	
Hypertension	87	34.0	139	25.9		
Diabetes	13	5.1	43	8.0		
Other	31	12.1	86	16.1		
Smoking						0.57–1.10
Never	186	72.7	364	67.9	0.175	
Ever	70	27.3	172	32.1		
Oral contraceptive use						
No	198	77.3	415	77.4	0.225	
Past	58	22.7	115	21.5		
Present	0	0	6	1.1		
Hormone replacement therapy use						
No	213	83.2	460	85.8	0.450	
Past	37	14.5	61	11.4		
Present	6	2.3	15	2.8		
Menopausal status						0.56–1.06
Premenopausal	90	35.2	158	29.5	0.107	
Postmenopausal	166	64.8	378	70.5		
First degree family history of breast and/or ovary cancer						1.92–4.7
No	201	78.5	489	91.2	0.001	
Yes	55	21.5	47	8.8		

1. The proportion of women who had ever breastfed was much lower among breast cancer women (59.8% as compared to 81.2% of controls, $P < 0.001$). This inverse relationship expressed itself with an estimated odds ratio of 0.39. The protective effect was stronger among premenopausal women.

Table 2 Case control distribution of reproductive and breastfeeding history

Characteristic	Cases		Controls		*P* value	95% CI
	N	Mean (SD)	N	Mean (SD)		
Number of births	256	2.53 (1.52)	536	3.12 (1.97)	<0.001	0.31–0.86
Age at first full term pregnancy	232	24.62 (4.23)	516	22.29 (3.82)	<0.001	1.71–2.94
Age at last full term pregnancy	232	31.51 (5.12)	516	30.51 (5.44)	0.01	0.16–1.82
Age at menarche	253	12.53 (1.46)	529	13.37 (1.57)	<0.001	0.60–0.91
Age at menopause	229	48.41 (5.51)	376	47.91 (5.50)	0.286	0.41–1.39
Age at first breastfeeding	152	24.51 (3.88)	435	22.25 (3.93)	<0.001	1.53–2.98
Total lifetime breastfeeding (months)	255	9.90 (14.90)	536	19.01 (26.58)	<0.001	6.23–12.04
Insufficient milk	40	38.8%	15	14.9%	<0.001	1.85–7.16

2. A decreasing occurrence of breast cancer was noted with increasing length of breastfeeding. The trend across categories was statistically significant (*t* test $P < 0.001$) and occurred in both premenopausal and postmenopausal women. For participants who reported a lifetime history of breastfeeding for more than 12 months, the OR was 0.29 compared to women who had never breastfed. This relationship was stronger among premenopausal women. The dose-response relationship between total lifetime duration and breast cancer risk is presented in Fig. 1. It is important to notice that the decrease in breast cancer risk with increasing total lifetime duration of breastfeeding was not linear, and that most of the protective effect was acquired in the first year of nursing. The OR for breast cancer among women who reported total lifetime duration of breastfeeding of 1–12 months, as compared to those who had breastfed for a total period of more than a year was 1.5 (95% CI 1–2.3).
3. Early age (<20 years) at first breastfeeding was protective. The OR for breast cancer occurrence among women who reported starting breastfeeding at age 24–28 years, as compared to those who reported breastfeeding for the first time when less than 20 years old, was 3.9.
4. No association was found between breastfeeding of the first child and breast cancer risk.
5. Insufficient milk (reported by 38.8% of 103 cases and by 14.9% of 101 controls who did not nurse) was associated with a significant increase in breast cancer risk as compared to other reasons given for no or for short (<1 month) breastfeeding (OR 5.53). This effect was much stronger among premenopausal women.

Discussion

The main finding of this hospital-based case control study is a statistically significant inverse association between ever breastfeeding (as well as prolonged breastfeeding) and breast cancer risk. This is in agreement with some important studies investigating this subject (Zografos et al. 2004; Zheng et al. 2000, 2001; Yoo et al. 1992; Tao et al. 1988; Chang-Claude et al. 2000; Newcomd et al. 1999; Romieu et al. 1996; Tryggvadottir et al. 2001; Newcomb et al. 1994; Enger et al. 1998; Lipworth et al. 2000; Tovar-Guzman et al. 2000), but in conflict with others (Stuver et al. 1997; Michels et al. 1996).

Several mechanisms have been proposed to explain the observed protective effect of breastfeeding on breast cancer risk (Zheng et al. 2000; Romieu et al. 1996; Freudenheimet et al. 1997; Tovar-Guzman et al. 2000; Byers et al. 1985): (1) a reduced exposure of breast cells to the cyclic hormones of reproductive life because of ovulatory suppression that occurs with prolonged breastfeeding, (2) direct physical changes in the breast that accompany milk production, (3) a reduction in the concentrations of toxic organochlorines in the breast and (4) an expression of change in growth factor beta during breastfeeding.

As stated earlier, there are inconsistencies in the literature about the protective effect of breastfeeding in premenopausal versus postmenopausal women. We hypothesized, similar to some researchers (Lee et al. 2003; Tryggvadottir et al. 2001; Newcomb et al. 1994) that the protective effect of breastfeeding will be demonstrated in premenopausal women only. The rational behind this is the shorter duration of time since last breastfeeding, characterizing the premenopausal group, accompanied by lower exposure of breast cells to breast fluid estrogen. Contrary to our expectations, we found a protective effect of breastfeeding in both groups. This is consistent with other studies (Zheng et al. 2000, 2001; Newcomd et al. 1999; Romieu et al. 1996; Freudenheimet et al. 1997; Enger et al. 1998). Some of these studies were similar to ours in several respects, such as study methods and number of participants, as well as their age span (Zheng et al. 2000, 2001; Romieu et al. 1996; Freudenheimet et al. 1997), while others restricted the examination of the relationship to postmenopausal women only (Newcomd et al. 1999; Enger et al. 1998).

Table 3 Breast cancer odds ratios and 95% confidence intervals in relation to breastfeeding history by menopausal status

Characteristics	All women				Premenopausal women				Postmenopausal women			
	Cases (%)	Controls (%)	OR	95% CI	Cases (%)	Controls (%)	OR	95% CI	Cases (%)	Controls (%)	OR	95% CI
Ever breastfed												
No	103 (40.2)	101 (18.8)	1		35 (38.9)	31 (19.6)	1		68 (41.0)	70 (18.5)	1	
Yes	153 (59.8)	435 (81.2)	0.4	0.2–0.6	55 (61.1)	127 (80.4)	0.3	0.1–0.6	98 (59.0)	308 (81.5)	0.4	0.2–0.7
Total lifetime breastfeeding (months)			0.98	0.9–0.99			0.97	0.94–0.99			0.98	0.96–0.99
0	105 (41.0)	102 (19.0)	1		36 (40.0)	32 (20.3)	1		69 (41.8)	70 (18.5)	1	
1–12	86 (33.6)	185 (34.5)	0.4	0.2–0.7	36 (40.0)	62 (39.2)	0.3	0.1–0.8	50 (30.3)	123 (32.5)	0.5	0.2–0.8
>12	46 (25.0)	249 (46.5)	0.3	0.1–0.4	18 (20.0)	64 (40.5)	0.2	0.06–0.4	46 (27.9)	185 (48.9)	0.3	0.1–0.6
P for trend				$P < 0.001$				$P < 0.001$				$P < 0.001$
Age at first breastfeeding			1.14	1.07–1.2			1.2	1.06–1.3			1.09	1.01–1.2
<20	24 (15.8)	162 (37.2)	1		4 (7.3)	40 (31.5)	1		20 (20.6)	122 (39.6)	1	
20–23	56 (36.8)	168 (38.6)	1.8	1–3.2	16 (29.1)	50 (39.4)	2.6	0.6–10.8	40 (41.2)	118 (38.3)	1.5	0.7–3.0
24–28	55 (36.2)	82 (18.9)	3.9	2–7.7	25 (45.5)	27 (21.3)	12.2	2.5–59.0	30 (30.9)	5 (17.9)	2.3	1.08–5.2
29+	17 (11.2)	23 (5.3)	3.7	1.4–9.7	10 (18.2)	10 (7.9)	11.6	1.5–87.0	7 (7.2)	13 (4.2)	1.6	0.4–5.8
P for trend				$P < 0.001$				$P < 0.004$				$P < 0.190$
First child breastfed												
No	13 (8.5)	29 (6.7)	1		9 (16.4)	9 (7.1)	1		4 (4.1)	20 (6.5)	1	
Yes	140 (91.5)	406 (93.3)	0.5	0.2–1.07	46 (23.6)	118 (92.9)	0.3	0.1–1.1	94 (95.9)	288 (93.5)	1.06	0.3–3.4
Reason for quitting breastfeeding												
All other reasons	63 (61.2)	86 (85.1)	1	2.4–12.0	76 (84.4)	156 (98.7)	1		138(83.6)	365 (96.6)	1	
Insufficient milk	40 (38.8)	15 (14.9)	5.5		14 (15.6)	2 (1.3)	15.7	2.4–100.0	27 (16.4)	13 (3.4)	4.8	1.6–13.6

Adjusted for socio-demographic factors (age, ethnicity, and education), reproductive factors (age at menarche, number of births, and age at first and last term pregnancy) and first degree family history of breast and/or ovary cancer

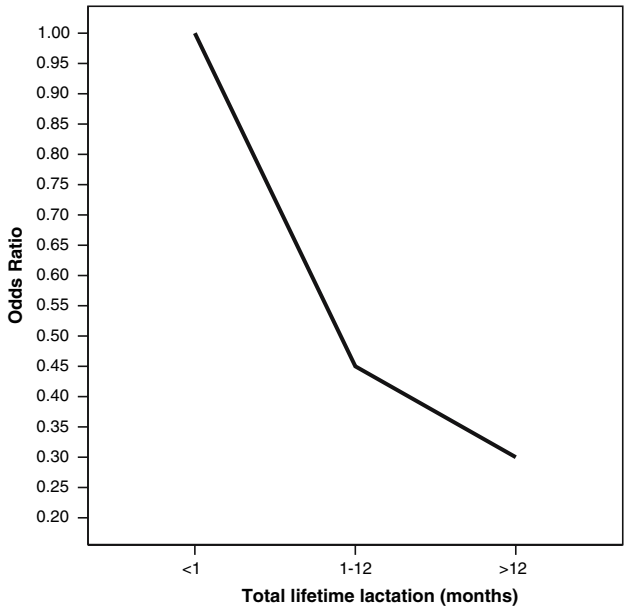

Fig. 1 A dose-response relationship between total lifetime duration of breastfeeding and the risk of breast cancer

It is well known that breast cancer risk increases with increasing age. According to Barchana (2002), referring to the Israeli population, the incidence of breast cancer among Jewish women begins to rise at age 30 and reaches a maximum level at age 70–74. The protective effect of breastfeeding observed in postmenopausal women suggests sustained benefit of breastfeeding into the period of high breast cancer occurrence.

The benefit of breastfeeding was found to be stronger in premenopausal women despite the fact that the duration of breastfeeding was shorter in this group (11 vs. 17 months in premenopausal and postmenopausal women, respectively). This finding is in line with, although not identical to, our assumption of advantage of breastfeeding in premenopausal women. Stronger protective effect in premenopausal women was explained by Lipworth et al. (2000), who claimed that breast fluid estrogen levels were found to be lower in women who were breastfeeding compared with women who did not breastfeed, but it appeared to gradually increase over a period of several years since last breastfeeding, till it reached levels that were found in nulliparous women.

For how long should women breastfeed in order to enjoy a maximum protective effect? Most of the protective effect of breastfeeding was gained during the first year of breastfeeding. Additional benefit existed when nursing for more than a year. We did not show the upper limit of breastfeeding duration among lactating women because of small number of participants who had breastfed for more than a year (64 cases and 249 controls). However, the graph describing the dose-response relationship between total duration of lifetime breastfeeding and breast cancer risk supported the additional benefit of breastfeeding for more than a year.

The finding of an increased risk of breast cancer (3.9-fold) in women who had first lactated at age 24–28 years, as compared to those who had first breastfed earlier (age <20 years), was described also by others (Newcomb et al. 1994; Enger et al. 1998). It is suggested that decreased exposure to ovarian hormones at young ages may be especially beneficial (Kelsey and John 1994). According to one of the hypotheses, breastfeeding at an early age may be more protective because breast stem cells undergo earlier differentiation and resistance to carcinogenesis (Enger et al. 1998).

An unexpected important finding was the role of insufficient milk. About 26% of study population reported never breastfeeding, and 27% of them stated they did not lactate because of insufficient milk. Those women were found to be at 5.5 times increased risk for developing breast cancer compared to women who did not nurse for other reasons. To the best of our knowledge, similar findings were reported in one study only: a case-control study conducted by Byers et al. (1985), who found an increased risk of 2.44 to develop breast cancer for women who experienced insufficient milk. We did not intend to verify what were the reasons underlying the successful or unsuccessful breastfeeding attempts. However, the stronger association observed in our study may be partly a result of some residual confounding, since nursing success is determined by endocrine attributes, as well as by complex relationships of various psychosocial factors. Even if confounding took place, we find it hard to believe that confounders explained the full strength of the association. Our results may suggest that there are women, who are not physiologically able to lactate successfully, and either because of excess estrogen levels or other abnormalities, may be at increased risk for breast cancer.

Unlike findings of other authors (Romieu et al. 1996; Zheng et al. 2001), breastfeeding of the first child was not associated with breast cancer risk. The OR comparing women who have breastfed their first child, with those who did not, was 0.49 (95% CI 0.2–1.0). The borderline inconsistent results observed in our study, compared to the existing literature, might have been explained by the relatively small number of study participants (135 cases and 435 controls).

In interpreting the above results, the first question to be asked is whether the findings are true, or are they a result of an artifact. Every effort was made in study design and conduction to minimize random errors (by obtaining the desired sample size of 256 cases and 536 controls, planned to examine all hypotheses), as well as to prevent flaws that result in bias: *Selection bias*: to avoid selection bias, both cases and controls were selected from women who were

referred to the same medical center, the main hospital serving the source population. A comparison of the demographic characteristics of cases to the 195 breast cancer women, who reside in the Western Galilee, but were diagnosed in other hospitals, revealed no differences between the two groups. In addition, the controls were women selected from a very large group of about 4,000 subjects, who were treated at the hospital on an ambulatory basis (unrelated to their breastfeeding or pregnancies histories). Therefore, no admission rate bias could result. *Information bias*: measures taken to avoid information bias included the use of a single interviewer, blinding of interviewer to the case/control status of participants and blinding of participants to the study hypotheses. Comparison of demographic characteristics of breast cancer women interviewed to those 41 women (13.2% of cases) who were deceased before study commence, revealed no differences. The negligible likelihood of recall bias in a case-control study such as ours is supported by Promislow et al. (2005; Collaborative Group on Hormonal Factors in Breast Cancer 2002). It is important to note that most of participants in this study responded to all questions (only two women had important missing data). To verify reliability of data collected in a retrospective manner, second interviews were carried out on selected sample of 50 women. The Spearman correlation coefficient (r) for duration of lifetime breastfeeding was found to be 0.99. Support to the appropriateness of the retrospective method, as compared to the prospective use of a diary was described by Merlo et al. (2000). *Confounding bias*: one advantage of this study is its ability to control simultaneously, in one population, both breastfeeding and reproductive factors (determinants related to each other). The examination of the association between nursing and breast cancer was carried out controlling for pregnancy history variables, while analysis of the relationship between pregnancies variables and breast cancer risk took place controlling for the breastfeeding attributes.

All the above arguments make us believe the study groups comprise a representative sample of the source population and data collected and analyzed are valid. Are relations found causal? All Hill's criteria were met (Hill 1965): *Temporal relationship*: the mean age of women at last pregnancy was 31.5 years, whereas their mean age at breast cancer diagnosis was 55.4. *Strength of associations*: in most relationships studied the odds ratios were greater than 2.5 (Penny et al. 2005). *Consistency*: the protective effect of breastfeeding was found consistently across a range of studies of different types and/or in different populations (Zheng et al. 2000, 2001; Tao et al. 1988; Newcomd et al. 1999; Gao et al. 2000), as well as in a meta-analysis describing the risk of breast cancer in ever compared to never breastfeeding women (Bernier et al. 2000). This consistency in study results gives some reassurance that it is not an artifact. However, consistency could not be examined among Israeli Jewish women, since this is the first study dealing with this question in the country. *Dose-response relationship*: a dose-response relationship was demonstrated between lifetime breastfeeding duration and the risk for breast cancer. *Biological plausibility*: the several mechanisms that have been proposed to explain the observed association were described earlier in the manuscript.

In summary, an inverse association between breastfeeding and breast cancer risk was found among premenopausal and postmenopausal Israeli Jewish women. These relationships seem reliable and valid, and meet all criteria for causality. Israeli professionals in Ministry of Health (MOH) and others recommend women to breastfeed for 6 months. This recommendation stems from the focus on the benefit of breastfeeding to the nursing infant. Based on the present study we highly suggest to focus also on women's needs, and to promote their health by changing the policy and advising the following: (1) encourage women to first breastfeed at young age <20, (2) encourage women to breastfeed for long duration (cumulative lifetime duration of more than a year), (3) design a special follow-up program and further research for women who experience insufficient milk. Appropriate arrangements should be considered in work places in order to enable women to combine career with family in young age, and to implement the above recommendations. It is important to note that this study did not include the Arab population. In order to generalize those conclusions to Arab women as well further studies are needed. Considering the fact that breastfeeding is one of the potentially modifiable factors in preventing breast cancer, and that understanding the role of breastfeeding may contribute to our knowledge about the etiology of a disease with significant public health consequence, the suggested protective effect from breastfeeding and the proposed carcinogenic mechanisms merit further investigation.

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