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Heterogeneity in risk factors for ductal and lobular breast carcinomas: A case–control study

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Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast are the most common histological subtypes of breast cancer. However, the associations and heterogeneity between histological subtypes and their risk factors are not well established. This study aimed to investigate risk factors for IDC and ILC. This case–control study included 1,009 incident breast cancer cases and 1,009 hospital controls, frequency-matched by age. Data were obtained from the patients' medical files and an interview administered *via* a questionnaire. Multinomial logistic regression was used and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The heterogeneity of the associations was assessed using the Wald test. Family history of breast cancer was associated with IDC (OR 2.64, 95% CI: 1.97–3.55) but not ILC (OR 0.81, 95% CI: 0.42–1.57; *p* for heterogeneity <0.001). Conversely, a history of miscarriage was associated with ILC (OR 1.71, 95% CI: 1.17–2.51) but not IDC (OR 1.18, 95% CI: 0.95–1.46; *p* for heterogeneity = 0.04). Similarly, type 2 diabetes was associated with ILC but not IDC (*p* for heterogeneity = 0.02). Age at first delivery and breastfeeding were significantly associated with IDC but not ILC, though *p* values for heterogeneity did not reach the significance level. Deliberate weight loss and age at menarche were significantly associated with ILC but not IDC (*p* for heterogeneity ≥0.27). Smoking, history of benign breast disease and BMI were associated with both subtypes. The present study supports the hypothesis that IDC and ILC are etiologically distinct tumours.

Introduction

Breast cancer is a common human neoplasm, accounting for about 25% of all malignancies in females. It also accounts for 27% of cancers in developed countries, with an annual incidence of more than 1 million new cases worldwide.[1] Furthermore, the global burden of cancer is increasing. Even though the rate of age-related mortality from breast cancer is decreasing in high-income countries, mortality is increasing in lower income countries.[2] Breast cancer is the most common cancer among Iranian women, and the mean age at diagnosis is significantly lower in Iranian women than their western counterparts.[3,4] Furthermore, the majority of breast cancer cases are premenopausal.[3,5]

Malignancy may occur in any cells of the mammary gland, comprising a wide variety of morphological, immunohistochemical and histopathological subtypes, which may have specific clinical courses and outcomes.[6] Clinical and epidemiologic studies suggest that the histopathological subtypes of breast cancer differ in terms of behaviour, risk factors and response to treatment.[7] Ductal and lobular tumours are the two most frequently diagnosed subtypes of invasive breast carcinomas (75% and 15% of all malignant tumours, respectively), and these two

Key words: ductal breast carcinoma, lobular breast carcinoma, epidemiology, heterogeneity, risk factors

Abbreviations: BC: Breast cancer; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; BMI: body mass index; OCP: oral contraceptive pills; OR: odds ratio; 95% CI: 95% confidence interval; SD: standard deviation; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IGFs: insulin-like growth factors.

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What's new?

Different subtypes of breast cancer may have different risk factors. These authors investigated the diversity of risk factors relevant in "less-developed" countries, where patients tend to be younger than in wealthier countries. They conducted a case-control study comparing risk factors for invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) among 2,000 women in Iran. Many risk factors differed between the two, indicating that IDC and ILC are etiologically different diseases. Factors associated with ILC included type 2 diabetes and history of miscarriage, while IDC risk factors included family history of breast cancer and age at first childbirth.

subtypes have different clinical, molecular and pathologic features.[8,9] However, only few epidemiological studies have examined the heterogeneity of the disease, and the differences in risk factors are not yet fully understood.[10–12]

Given the high incidence and economic burden of breast cancer,[13] it is of great importance that more effective and personalised prevention and treatment strategies are discovered. Epidemiologic studies have suggested that breast cancer risk is associated with an individual's characteristics, mainly behavioural, reproductive and anthropometric factors.[4,14]

Even though less-developed countries accounted for at least one-half of all breast cancer cases and 62% of deaths,[15] the main body of evidence comes from developed countries, with the majority of research on postmenopausal breast cancer and considerably less focus on possible heterogeneity of risk factors between disease subtypes. Moreover, evidence from less-developed countries with different reproductive, environmental and behavioural characteristics, and higher frequency of premenopausal breast cancer is lacking. Thus, the different patterns of environmental and behavioural factors might provide novel information about the aetiology of breast cancer and its subtypes. The present case–control study aimed to examine the associations between reproductive, anthropometric and lifestyle factors, and the risks of ductal breast carcinoma (IDC) and lobular breast carcinoma (ILC). We further examined if the pattern of associations differ by subtype.

Methods

Study population

This case–control study included women who were admitted to the Motahari Breast Clinic located in Namazi Hospital (affiliated with the Shiraz University of Medical Sciences) due to invasive breast cancer. This centre is based in Shiraz (the capital of Fars province), and more than 80% of newly diagnosed breast cancer patients within the Fars province are referred to this hospital for treatment.[4] All women whose disease was histologically confirmed as primary invasive breast cancer (IDC or ILC) during the study period were invited to participate in the study. A total of 1,073 women (response rate 94%) agreed to participate, of whom 64 were excluded due to either missing information on the tumour subtype (n = 29) or incomplete histopathological reports (n = 35). The final study sample included 1,009 cases and 1,009 controls.

Literate patients read and signed informed consent forms, and verbal consent was obtained from illiterate patients. Ethical approval was obtained from the ethical committee of Shiraz University of Medical Sciences (no. 13748).

Case and control selection

In this study, patients included incident histopathologically (ductal: ICD10-O code 8500/3; lobular: ICD10-O code 8520/3) confirmed cases of breast cancer who were admitted to the oncology and radiotherapy wards between April 2014 and March 2017. Controls were selected among female visitors with no history of breast cancer who were visiting patients admitted to the other departments of the same hospital. Women in the control group were considered cancer free if they verbally confirmed no current or past history of cancer (no confirmatory exam or test was required). Control participants were frequency-matched to cases by 5-year age-group. The age distribution of the control group was slightly different from the cases in the youngest and oldest age-groups (<40 years and >60 years, respectively) due to sampling variation and practical issues, but the difference was not statistically significant.

Data collection

Information on reproductive and anthropometric characteristics was obtained during a face-to-face interview conducted by a trained female nurse using an administered questionnaire. Interviews took place in a private and quiet room in the hospital. Patients' pathology reports were obtained from the cancer registry database of the clinic, and the histologic type of breast cancer was extracted. For patients, the interview was conducted within 2–8 weeks of breast cancer diagnosis. The questionnaire and interview procedure were evaluated and revised by five experts in a pilot study including 50 cases and 50 controls. The reliability of the questionnaire was measured using the test–retest method (Cronbach's alpha was 0.83 for cases and 0.72 for controls).

Participants were asked about their education (primary or illiterate, intermediate, high school, academic), occupation (housewife, employed), ethnicity (Fars, Lor, Turk, other), family history of breast cancer (no, second relative, first relative/both first and second relatives), smoking during adolescence and adulthood (yes, no), history of oral contraceptive (OCP) use (ever, never), history of chest X-ray (yes, no), history of benign breast disease (yes, no), physical activity (30 min or more of moderate aerobic exercise at least three times per week on a regular basis)[16,17] (yes, no), body mass index (BMI;

defined as <24.9, 25.0 to 29.9 and ≥30.0 kg/m^2), deliberate weight loss after 18 years of age[18] (yes, no), age at first delivery (<18, 18–23, 24–30, ≥31 years and nulliparous), total number of months of breastfeeding for all children (0–5, 6–17, 18–29, 30–41, ≥42 months), history of miscarriage (yes, no), menarche age (<12, 12–13, ≥14 years), regular menstrual (yes, no), menopausal status (premenopausal, postmenopausal), and diagnosed with type 2 diabetes (yes, no).

Premenopausal was defined as regular menstrual cycles 12 months prior to the interview, and postmenopausal as no menstrual cycles within the past 12 months. Women with no data on menopausal status (n = 9 in the case group, n = 7 in the control group) were categorised as premenopausal if they were younger than 47 years of age and postmenopausal if they were older than 47 years, based on the median age of menopause among Iranian women.[19,20]

Statistical analysis

The chi-square test and T-test were used for univariate analyses, and multinomial logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between each independent variable and risk of IDC and ILC. Based on the adjusted model, the p for heterogeneity was calculated using the Wald test. In the multivariable multinomial logistic regression, models were adjusted for education, occupation, ethnicity, family history of BC, smoking, OCP, chest X-ray history, history of benign breast disease, BMI, physical activity, deliberate weight loss, age at first delivery, breastfeeding, history of miscarriage, menarche age, regular menstrual, menopause status and type 2 diabetes. We tested if the associations between independent variables and each subtype vary according to menopausal status, by adding an interaction term in the models for each subtype. A post-hoc power analysis suggested that our study had statistical power of 80% to detect associations with OR >1.65 for ILC and OR >1.24 for IDC. All p values were two-sided and results were deemed to be statistically significant at $p < 0.05$. All analyses were conducted using Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Results

In total, 1,009 breast cancer cases, 849 IDC and 160 ILC, were included in the analysis. On average, the IDC cases were 3.3 (SD = 10.9) years younger than ILC patients (47.2 and 50.5 respectively, $p < 0.001$). Table 1 describes the distributions of the characteristics of the control participants and IDC and ILC cases.

Simple multinomial logistic analysis revealed that IDC risk was significantly associated with family history of breast cancer, smoking, OCP use, history of benign breast disease, BMI, age at first delivery and breastfeeding duration. On the other hand, ILC risk was associated with smoking, chest x-ray, history of benign breast disease, BMI, history of miscarriage, menarche age and type 2 diabetes (Table 2).

Results from multivariable multinomial logistic regression suggested that having a history of breast cancer among first relatives is associated with a higher risk of IDC only ($OR_{\text{first relatives } vs. \text{ no history}}$ 2.64, 95% CI: 1.97–3.55 for IDC and $OR_{\text{first relatives } vs. \text{ no history}}$ 0.81, 95% CI: 0.42–1.57 for ILC, p for heterogeneity <0.001). Smoking was similarly associated with the risk of both IDC and ILC ($OR_{\text{yes } vs. \text{ no}}$ 2.37, 95% CI: 1.71–3.29 for IDC and $OR_{\text{yes } vs. \text{ no}}$ 2.32, 95% CI: 1.34–4.04 for ILC, p for heterogeneity = 0.66). Use of OCP was associated with a significant increase in the risk of IDC but not ILC ($OR_{\text{ever } vs. \text{ never}}$ 1.63, 95% CI: 1.32–2.00 for IDC and $OR_{\text{ever } vs. \text{ never}}$ 1.46, 95% CI: 0.99–2.12 for ILC, p for heterogeneity = 0.28). First delivery at age ≥31 years was associated with an increased risk of both IDC and ILC ($OR_{\geq 31 \text{ } vs. \text{ } <18 \text{ years}}$ 2.92, 95% CI: 2.03–4.20 for IDC and $OR_{\geq 31 \text{ } vs. \text{ } <18}$ 2.44, 95% CI: 1.22–4.90, for ILC, p for heterogeneity = 0.28). Conversely, a longer duration of breastfeeding was only associated with a lower risk of IDC ($OR_{\geq 42 \text{ } vs. \text{ } <6 \text{ months}}$ 0.59, 95% CI: 0.42–0.83 for IDC and $OR_{\geq 42 \text{ } vs. \text{ } <6 \text{ months}}$ 0.70, 95% CI: 0.36–1.35 for ILC, p for heterogeneity = 0.80), while an older age at menarche was associated with a lower risk of ILC ($OR_{>14 \text{ } vs. \text{ } <12 \text{ year of age}}$ 0.88, 95% CI: 0.65–1.19 for IDC and $OR_{>14 \text{ } vs. \text{ } <12 \text{year of age}}$ 0.60, 95% CI: 0.36–0.98, for ILC, p for heterogeneity = 0.27). In addition, a history of miscarriage ($OR_{\text{yes } vs. \text{ no}}$ 1.18, 95% CI: 0.95–1.46 for IDC and $OR_{\text{yes } vs. \text{ no}}$ 1.71, 95% CI: 1.17–2.51, for ILC, p for heterogeneity = 0.04) and type 2 diabetes ($OR_{\text{yes } vs. \text{ no}}$ 1.17, 95% CI: 0.79–1.72 for IDC and $OR_{\text{yes } vs. \text{ no}}$ 2.29, 95% CI: 1.31–4.03 for ILC, p for heterogeneity = 0.02) were significantly associated with the risk of ILC but not IDC. Similarly, a history of benign breast disease was associated with a higher incidence of both subtypes ($OR_{\text{yes } vs. \text{ no}}$ 2.23, 95% CI: 1.60–3.10 for IDC and $OR_{\text{yes } vs. \text{ no}}$ 2.27, 95% CI: 1.30–3.94 for ILC, p for heterogeneity = 0.99). The results suggested that BMI ≥30 kg/m^2 was associated with a higher risk of both IDC and ILC ($OR_{\text{obese } vs. \text{ normal}}$ 1.92, 95% CI: 1.44–2.56 for IDC and $OR_{\text{obese } vs. \text{ normal}}$ 2.44, 95% CI: 1.43–4.16 for ILC, p for heterogeneity = 0.11), while deliberate weight loss was associated with a significantly decreased risk of ILC and IDC ($OR_{\text{yes } vs. \text{ no}}$ 0.75, 95% CI: 0.61–0.92 for IDC and $OR_{\text{yes } vs. \text{ no}}$ 0.68, 95% CI: 0.46–0.99 for ILC, p for heterogeneity = 0.78) (Table 2).

No significant association between menopausal status and IDC and ILC was found. Moreover, no significant interaction between the study variables (those with a significant association with either ILC or IDC) and menopausal status was found (p for interaction ≥0.05 for all).

Discussion

In this case–control study, we found significant heterogeneity among associations between reproductive and anthropometric factors with the risk of IDC and ILC. While there were significant associations between family history of breast cancer, OCP use, breastfeeding and age at first delivery and risk of IDC, a history of miscarriage, type 2 diabetes, deliberate weight loss and menarche age were associated with a higher

Table 1. Distributions of the characteristics of the control participants and invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast among Iranian women, 2014–2017

Factors	Controls (N = 1,009) n (%)	IDC (N = 849) n (%)	ILC (N = 160) n (%)	*p* Value[1]
Age (year)				0.58
‹40	280 (27.8)	212 (25.0)	37 (23.1)	
41–50	336 (33.2)	280 (33.0)	52 (32.5)	
51–60	255 (25.3)	225 (26.5)	42 (26.3)	
›60	138 (13.7)	132 (15.5)	29 (18.1)	
Education				0.78
Primary or illiterate	349 (34.6)	287 (33.8)	61 (38.1)	
Intermediate	206 (20.4)	152 (17.9)	27 (16.9)	
High school	264 (26.2)	252 (29.7)	48 (30.0)	
Academic	190 (18.8)	158 (18.6)	24 (15)	
Occupation				0.17
Housewife	780 (77.3)	655 (77.1)	124 (77.5)	
Employed	229 (22.7)	194 (22.9)	36 (22.5)	
Ethnicity				0.53
Fars	359 (35.6)	293 (34.5)	60 (37.5)	
Lor	267 (26.5)	244 (28.7)	37 (23.1)	
Turk	188 (18.6)	152 (17.9)	34 (21.3)	
Other[2]	195 (19.3)	160 (18.8)	29 (18.1)	
Family history of breast cancer				0.006
No	867 (85.9)	619 (72.9)	134 (83.8)	
Second relative	54 (5.8)	70 (8.3)	14 (8.7)	
First relative[3]	88 (8.7)	160 (18.8)	12 (7.5)	
Smoking				0.92
No	937 (92.9)	724 (85.3)	136 (85.0)	
Yes	72 (7.1)	125 (14.7)	24 (15.0)	
OCP use[4]				0.54
Never	601 (59.6)	455 (53.6)	82 (51.2)	
Ever	408 (40.4)	394 (46.4)	78 (48.8)	
Chest X-ray history				0.45
No	317 (31.4)	242 (28.5)	114 (71.3)	
Yes	692 (68.6)	607 (71.5)	46 (28.7)	
History of benign breast disease				0.48
No	943 (93.5)	731 (86.1)	138 (86.3)	
Yes	66 (6.5)	118 (13.9)	22 (13.7)	
Physical activity[5]				0.63
No	799 (79.2)	683 (80.4)	132 (82.5)	
Yes	210 (20.8)	166 (19.6)	28 (17.5)	
BMI				0.13
‹24.99	359 (33.2)	270 (29.8)	40 (22.5)	
25.00 to 29.99	489 (48.5)	373 (43.9)	82 (51.3)	
≥30.00	161 (16.0)	206 (24.3)	38 (23.7)	
Deliberate weight loss				0.81
No	643 (63.7)	558 (65.7)	105 (65.6)	
Yes	366 (36.3)	291 (34.3)	55 (34.4)	
Age at first delivery (year)				0.26
‹18	355 (35.2)	200 (23.6)	46 (28.8)	

(Continues)

Table 1. Distributions of the characteristics of the control participants and invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast among Iranian women, 2014–2017 (Continued)

Factors	Controls (N = 1,009) n (%)	IDC (N = 849) n (%)	ILC (N = 160) n (%)	*p* Value[1]
18–23	284 (28.1)	254 (29.9)	52 (32.5)	
24–30	158 (15.7)	142 (16.7)	28 (17.4)	
≥31	131 (13.0)	181 (21.3)	22 (13.8)	
Nulliparous	81 (8.0)	72 (8.5)	12 (7.5)	
Breastfeeding (month)				0.66
0–5	184 (18.2)	204 (24.0)	30 (18.7)	
6–17	53 (5.3)	72 (8.5)	14 (8.8)	
18–29	128 (12.7)	114 (13.4)	20 (12.5)	
30–41	116 (11.5)	90 (10.6)	18 (11.2)	
≥42	528 (52.3)	369 (43.5)	78 (48.8)	
History of miscarriage				0.17
No	694 (68.8)	567 (66.8)	94 (58.8)	
Yes	315 (31.2)	282 (33.2)	66 (41.2)	
Menarche age (year)				0.17
<12	138 (13.7)	131 (15.4)	38 (23.7)	
12–13	431 (42.7)	343 (40.4)	64 (40.0)	
≥14	440 (43.6)	375 (44.2)	58 (36.3)	
Regular menstruation				0.001
No	139 (13.78)	102 (12.01)	20 (12.5)	
Yes	867 (85.92)	745 (87.76)	140 (87.5)	
Missing	3 (0.30)	2 (0.23)	0 (0)	
Menopausal status[6]				0.001
Pre-menopausal	647 (64.1)	518 (61.0)	94 (58.8)	
Post-menopausal	362 (35.9)	331 (39.0)	66 (41.2)	
Type 2 diabetes				0.24
No	942 (93.4)	787 (92.7)	137 (85.6)	
Yes	67 (6.6)	62 (7.3)	23 (14.4)	

[1]Chi-squired test comparing IDC and ILC
[2]Including Arab, Balouch and Kourd ethnics
[3]First or both first and second relatives
[4]OCP = oral contraceptive pills
[5]30 min or more of moderate aerobic activity at least 3 or more times/week on a regular basis
[6]Only natural menopause.

risk of ILC. Moreover, the associations between history of chest X-ray, family history of breast cancer, history of miscarriage and type 2 diabetes differed between the two histological subtypes of breast cancer. Smoking, BMI of ≥30 kg/m^2 and history of benign breast disease were associated with increased risks of both IDC and ILC.

The significant association between history of breast cancer in first relatives and risk of IDC suggests that genetic factors might play important role in the aetiology of this type of breast cancer.[21] Family clustered types of cancer are known as hereditary, which are passed to the next generation through muted genes. Compared to non-inherited cases, hereditary breast cancers develop earlier in life.[21,22] In line with the literature, in our study, IDC cases were significantly younger (more than 3 years on average) than ILC patients.

We observed a positive association between type 2 diabetes and the risk of ILC, but not IDC. The findings of a previous meta-analysis supported a positive association between type 2 diabetes and breast cancer.[23] However, it has been suggested that women with diabetes are less likely to use postmenopausal hormones, and hormone therapy may confound the association between breast cancer and type 2 diabetes.[24] Hormone therapy has never been common in Iran and only a small number of participants in our study (<3%) reported hormone therapy. As a result, the observed association between diabetes and ILC risk is unlikely to be confounded by hormone therapy. To the best of our knowledge, no previous study has examined the association between type 2 diabetes and different subtypes of breast cancer. The observed association between diabetes and breast cancer risk can be attributed to

Table 2. Unadjusted and adjusted odds ratios of the association between the study variables and subtypes of breast cancer among Iranian women, 2014–2017

Variables	Invasive ductal carcinoma		Invasive lobular carcinoma		
	Unadjusted[1]	Adjusted[2]	Unadjusted[1]	Adjusted[2]	
	OR (95%CI) ductal *vs.* control	OR (95%CI) ductal *vs.* control	OR (95%CI) lobular *vs.* control	OR (95%CI) lobular *vs.* control	*p* for *heterogeneity*[3]
Education					
Primary or illiterate	Reference	Reference	Reference	Reference	
Intermediate	0.89 (0.69–1.16)	0.84 (0.63–1.12)	0.74 (0.46–1.21)	0.77 (0.45–1.30)	0.35
High school	1.16 (0.91–1.46)	1.03 (0.79–1.34))	1.04 (0.68–1.56)	1.09 (0.68–1.74)	0.38
Academic	1.01 (0.77–1.31)	0.74 (0.53–1.04)	0.72 (0.43–1.19)	0.68 (0.36–1.27)	0.14
Occupation					0.37
Housewife	Reference	Reference	Reference	Reference	
Employed	1.00 (0.81–1.25)	0.93 (0.72–1.19)	0.98 (0.66–1.47)	0.90 (0.57–1.43)	0.21
Family history of breast cancer					
No	Reference	Reference	Reference	Reference	
Second relative	1.81 (1.25–2.62)	1.46 (0.98–2.16)	1.67 (0.56–1.84)	1.44 (0.90–3.10)	0.80
First relative[4]	2.54 (1.92–3.36)	2.64 (1.97–3.55)	0.88 (0.46–1.65)	0.81 (0.42–1.57)	**<0.001**
Smoking					0.66
No	Reference	Reference	Reference	Reference	
Yes	2.24 (1.65–3.05)	2.37 (1.71–3.29)	2.29 (1.39–3.77)	2.32 (1.34–4.04)	
OCP use[5]					0.28
Never	Reference	Reference	Reference	Reference	
Ever	1.27 (1.06–1.53)	1.63 (1.32–2.00)	1.40 (1.01–1.95)	1.46 (0.99–2.12)	
Chest X-ray history					**<0.001**
No	Reference	Reference	Reference	Reference	
Yes	1.14 (0.94–1.40)	1.12 (0.90–1.39)	0.86 (0.59–1.24)	1.17 (1.11–1.25)	
History of benign breast disease					0.99
No	Reference	Reference	Reference	Reference	
Yes	2.30 (1.68–3.16)	2.23 (1.60–3.10)	2.27 (1.36–3.81)	2.27 (1.30–3.94)	
Physical activity[6]					0.72
No	Reference	Reference	Reference	Reference	
Yes	0.92 (0.73–1.16)	0.90 (0.70–1.15)	0.80 (0.52–1.24)	0.98 (0.62–1.56)	
BMI					
<24.99	Reference	Reference	Reference	Reference	
25.00 to 29.99	1.01 (0.81–1.25)	1.05 (0.84–1.32)	1.56 (1.03–2.37)	1.53 (0.98–2.39)	0.60
≥30.00	1.69 (1.30–2.21)	1.92 (1.44–2.56)	2.20 (1.34–3.60)	2.44 (1.43–4.16)	0.11
Deliberate weight loss					0.78
No	Reference	Reference	Reference	Reference	
Yes	0.91 (0.75–1.10)	0.75 (0.61–0.92)	0.92 (0.64–1.30)	0.68 (0.46–0.99)	
Age at first delivery (year)					
<18	Reference	Reference	Reference	Reference	
18–23	1.58 (1.24–2.02)	1.59 (1.22–2.06)	1.41 (0.92–2.16)	1.77 (1.11–2.84)	0.82
24–30	1.59 (1.19–2.12)	1.61 (1.16–2.23)	1.36 (0.82–2.26)	1.92 (1.07–3.45)	0.79
≥31	2.45 (1.84–3.25)	2.92 (2.03–4.20)	1.29 (0.75–2.23)	2.44 (1.22–4.90)	0.28
Nulliparous	1.57 (1.09–2.26)	1.47 (0.94–2.29)	1.14 (0.59–2.25)	1.57 (0.66–3.75)	0.81
Breastfeeding (months)					
0–5	Reference	Reference	Reference	Reference	
6–17	1.22 (0.81–1.84)	1.25 (0.79–1.99)	1.62 (0.80–3.27)	1.31 (0.57–3.00)	0.54
18–29	0.80 (0.58–1.10)	0.82 (0.56–1.19)	0.95 (0.52–1.76)	0.91 (0.44–1.91)	0.85

(Continues)

Table 2. Unadjusted and adjusted odds ratios of the association between the study variables and subtypes of breast cancer among Iranian women, 2014–2017 (Continued)

Variables	Invasive ductal carcinoma		Invasive lobular carcinoma		
	Unadjusted[1]	Adjusted[2]	Unadjusted[1]	Adjusted[2]	
	OR (95%CI) ductal *vs.* control	OR (95%CI) ductal *vs.* control	OR (95%CI) lobular *vs.* control	OR (95%CI) lobular *vs.* control	*p* for *heterogeneity*[3]
30–41	0.69 (0.49–0.98)	0.67 (0.45–1.00)	0.95 (0.50–1.78)	0.89 (0.41–1.93)	0.87
≥42	0.63 (0.49–0.80)	0.59 (0.42–0.83)	0.90 (0.57–1.42)	0.70 (0.36–1.35)	0.80
History of miscarriage					**0.04**
No	Reference	Reference	Reference	Reference	
Yes	1.09 (0.90–1.33)	1.18 (0.95–1.46)	1.56 (1.11–2.20)	1.71 (1.17–2.51)	
Menarche age (year)					
<12	Reference	Reference	Reference	Reference	
12–13	0.83 (0.63–1.10)	0.82 (0.61–1.11)	0.53 (0.34–0.88)	0.61 (0.38–0.99)	0.34
≥14	0.89 (0.68–1.18)	0.88 (0.65–1.19)	0.47 (0.30–0.75)	0.60 (0.36–0.98)	0.27
Regular menstruation					0.32
No	Reference	Reference	Reference	Reference	
Yes	1.17 (0.89–1.53)	1.28 (0.95–1.72)	1.12 (0.67–1.85)	0.79 (0.53–1.17)	
Menopause status[7]					0.29
Pre-menopausal	Reference	Reference	Reference	Reference	
Post-menopausal	1.14 (0.9–1.37)	1.15 (0.93–1.43)	1.28 (0.89–1.76)	0.82 (0.56–1.21)	
Type 2 diabetes					**0.02**
No	Reference	Reference	Reference	Reference	
Yes	1.10 (0.77–1.58)	1.17 (0.79–1.72)	2.36 (1.42–3.91)	2.29 (1.31–4.03)	

[1]Multinomial logistic regression.
[2]Multivariable multinomial logistic regression, adjusted for education, occupation, ethnicity, family history of BC, smoking, OCP, chest X-ray history, history of benign breast disease, BMI, physical activity, deliberate weight loss, age at first delivery, breastfeeding, history of miscarriage, menarche age, regular menstrual, menopause status and type 2 diabetes
[3]Using *Wald-test* of the hypothesis that both subtypes of breast cancer share the same odds ratio for each exposure under study
[4]First or both first and second relatives
[5]OCP = oral contraceptive pill
[6]30 min or more of moderate aerobic activity at least 3 or more times/week on a regular basis
[7]Only natural menopause.

changes in the amounts of circulating insulin, insulin-like growth factors (IGFs) and endogenous sex hormones.[23] Type 2 diabetes is usually associated with insulin resistance and over secretion of pancreatic insulin. Insulin has been demonstrated to have a mitogenic effect on breast tissues,[25] and insulin receptors are known to be overexpressed in cancerous cells of the breast.[26] Another possible explanation is that, compared to non-diabetic women, diabetic women have a higher concentration of circulating oestrogen,[23] which is an established risk factor for breast cancer.[27,28]

In our study, breastfeeding duration was associated with a decreased risk of IDC but not ILC. The literature is contradictory with regard to the association between breastfeeding and breast cancer. While some studies suggested that breastfeeding may decrease the risk of breast cancer,[29–31] others reported no association.[32,33] These conflicting results may be explained by the different aetiologies of breast cancer subtypes, as ductal tissues are responsible for milk production and are less prone to mutation.[6] In line with our findings, Ursin *et al.* reported that the total duration of breastfeeding was more strongly associated with the risk of IDC than for ductal-lobular or lobular breast cancers.[11] It has been suggested that carcinogenic agents may excrete from the breast ductal tissues through lactation.[11]

The strong association between smoking and breast cancer risk for both ILC and IDC subtypes in our study is in agreement with the findings of previous studies.[4,16] A meta-analysis on 14 published cohort studies based on 73,388 women suggests that active smoking is associated with an increased risk of all subtypes of breast cancer in women who initiate smoking before the birth of their first child.[34] However, a systematic review found no overall association between active smoking and risk of breast cancer. The authors of this review attributed the conflicting results to the confounding effect of alcohol use.[35] Alcohol use is less likely to confound the results of our study because the prevalence of alcohol consumption is very low (<1%) and infrequent among Iranian women.[36]

We also found a positive association between OCP use and risk of IDC and ILC (the association was not significant for ILC). In a study by Rosenberg *et al.*,[37] a history of OCP use

was found to be associated with both IDC and ILC; however, other studies only reported an association with ILC.[12, 38,39]

In our study, BMI of ≥30 kg/m^2 was associated with higher risks of both ILC and IDC, although the association was stronger for ILC. Obesity is an established risk factor for postmenopausal breast cancer; however, the association with different subtypes of breast cancer remains unclear.[40] In the present study, we did not observe any significant difference in the association between BMI and risk of the two breast cancer subtypes, which is in agreement with previous reports.[8,41] The association between deliberate weight loss and a decreased risk of both types of breast cancer observed in our study is in line with the findings of a recently published meta-analysis of 139 prospective and retrospective studies.[42]

We found an increased risk of both IDC and ILC subtypes in women who were older at their first delivery, which is in agreement with the findings of some previous studies,[43,44] but not all.[12,45,46] Another study suggested that there is no significant difference between the risk of breast cancer subtypes and reproductive factors including the age of first delivery.[32]

Our findings are in accordance with earlier studies that reported a decreased risk of IDC and ILC (though the association was not significant for IDC), in women that were older at menarche. Similarly, a study reported that menarche age is inversely associated with the risk of both IDC and ILC and these authors found a stronger association with ILC.[8] In another prospective study, a significant difference was found in the association between age at menarche with lobular and ductal breast cancer.[29]

In our study, a history of miscarriage was associated with a higher risk of ILC but not IDC (the heterogeneity was marginally significant). The evidence is controversial regarding the effect of miscarriage on breast cancer.[41,47,48] In a meta-analysis conducted in 2015,[49] no sufficient evidence was found for an association between abortion (including both induced and spontaneous abortion) and breast cancer.

Finally, with regard to the results of the present study including the younger age at diagnosis and more prevalent family history of breast cancer among IDC patients, and more prevalent history of chest X-ray, type 2 diabetes and miscarriage among ILC patients, may suggest higher importance of environmental factors in ILC and heredity in IDC.[50,51]

Strengths and limitations

To the best of our knowledge, this is the first case–control study from a less-developed country, with a different culture, lifestyle and environmental exposures than developed countries, which compares the risk factors for ILC and IDC among pre and post-menopausal women. As we only included newly diagnosed cases, the results are not prone to bias related to the survival of patients. As alcohol consumption is illegal in Iran and regular use is uncommon among Iranian women,[37] the association between smoking and breast cancer found in our study is less likely to be confounded by alcohol consumption. Anthropometric factors were measured at the time of interview, thus they were not self-reported.

Information about previous exposure to factors of interest in this study are considered to be among those that are generally well remembered, regardless of the status of the participants. However, histories of exposures are prone to differential recall error between cases and controls, which is a common bias in case–control studies. In particular, history of chest X-ray has a potential risk of recall bias; however, the distribution of our findings for chest X-ray history did not significantly differ between patients and controls, suggesting that the risk of recall bias was minimal. Another limitation was the lack of information on the status of oestrogen (ER) and progesterone (PR) hormone receptor and human epidermal growth factor receptor 2 (HER2). Although, we did not find any interaction effect between menopausal status and other factors associated with BC, a limited sample size prevented us to conduct menopause-subtype stratified analysis. Thus, a larger study on the heterogeneity of associations by subtype and menopausal status is recommended.

Conclusions

The heterogeneity of associations among several reproductive factors, type 2 diabetes and weight loss found in our study suggests that IDC and ILC are aetiologically distinctive tumours, and that changes in reproductive behaviour can have different effects on the incidence and proportion of these subtypes. Moreover, our findings suggest that genetic factors might be more important in the aetiology of IDC, while lifestyle and some environmental factors might play more important roles in the aetiology of ILC. Interestingly, smoking and obesity were associated with both subtypes, suggesting effective community based control programs may decrease the incidence of both subtypes.

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