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Influence of Diabetes Mellitus Type 2 and Prolonged Estrogen Exposure on Risk of Breast Cancer Among Women in Armenia

LILIT KHACHATRYAN
Department of Public Health, American University of Armenia, Yerevan, Armenia
ROBERT SCHARPF
Johns Hopkins School of Public Health, Baltimore, Maryland, USA
SARAH KAGAN
School of Nursing, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Diabetes mellitus type 2 (DM2) and breast cancer (BrCa) are prevalent in Armenia. We investigated DM2, reproductive factors, and BrCa in a case control study of 302 women. Multiple logistic regression analyses revealed DM2 increased adjusted odds of BrCa by 5.53 (95% CI 1.34–22.81). Any birth was protective (adjusted OR = 0.36, 95% CI 0.20–0.66). Each year delay in first pregnancy increased risk (adjusted OR = 1.13, 95% CI 1.01–1.27) as did induced abortions (adjusted OR = 2.86, 95% CI 1.02–8.04). Odds ratios were adjusted for age and body mass index (BMI), which confounded associations between DM2 and BrCa. We suggest our findings imply the need for further investigation in Armenian and in other populations with similar characteristics.

Breast cancer (BrCa) is among the most significant chronic disease concerns among women the world, numbering over one million incident cases worldwide (WHO, 2004a). Each year, more than 400,000 women die from the disease (WHO, n.d.b.). As a public health problem, BrCa incidence is increasing around the world. More importantly, incidence has increased as much as 5% per year in developing regions of the world (Groot, Baltussen, Groot, Anderson, & Hortobagyi, 2006). Limiting the impact of BrCa for women in

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Address correspondence to Dr. Lilit Khachatryan, Department of Public Health, American University of Armenia, 40 Marshal Baghramyan, Yerevan, Armenia. E-mail: lilit.khachatryan@meduni.am

nations, both developed and developing, rests in optimal prevention as well as early detection. The role of factors linked to diabetes mellitus type 2 (DM2) in developing BrCa is well studied; however, more specific epidemiology in regions of the world where DM2 is prevalent may help elucidate the links between these two common, chronic conditions. BrCa and DM2 are very prevalent health conditions in Armenia. We conducted a case-control study to explore associations between and among BrCa, DM2, and estrogen exposure among women in Armenia.

Armenia—a post-Soviet society and developing nation with a total population of about 3.2 million and life expectancy at birth of 59 and 63 years for males and females, respectively, (WHO, n.d.c.)—has specific public health concerns that include BrCa as well as other common conditions such as DM2 and obesity. Little BrCa research, however, is specific to Armenia. In Armenia, the most current statistics show that BrCa incident cases climbed from about 870 in 2002 to 990 in 2006 (Ministry of Health of Armenia, 2008). Breast cancer is the leading cause of cancer morbidity and mortality among Armenian women (WHO, n.d.c.). Morbidity has increased almost two-fold from 31.9 per 100,000 (1995) to 59.6 per 100,000 (2006; Ministry of Health of Armenia, 2006). Mortality accounted for 16.4 deaths per 100,000 in 2004, the eighth leading cause of death in Armenia (National Statistical Service of Armenia & Ministry of Health of Armenia, 2006). In summary, while BrCa is not as pressing a concern in Armenia as it is in North American and some European societies, it presents considerable threat to the health of Armenian women.

The magnitude of BrCa is framed by risk factors for the disease. Recently, scientists exposed several important risk factors for BrCa. The most prominent risk factors for developing BrCa are increasing age, family history, and a variety of endogenous and exogenous sources for prolonged estrogen exposure such as reproductive patterns (McPherson, Steel, & Dixon, 2000). More recently, DM2 has been identified as a risk factor as well (Papa, Costantino, & Belfiore, 1997; Yam, Fink, Mashiah, & Ben-Hur, 1996). While some literature suggests there are other important risk factors (e.g., radiation, race, alcohol consumption, medication) for BrCa, these may not be relevant to the Armenian context. Armenian researchers in their recent studies demonstrate that the average scope time for diagnostic and intervention radiological procedures are within acceptable standards (Bakalyan, Demirchyan, & Thompson, 2004), and staff protection is generally acceptable while patient protection slightly exceeds European standards (Tsapaki et al., 2009). Further, there are no notable sources of environmental radiation in Armenia as there are elsewhere in the region. Race, too, is unlikely to be a risk factor in Armenia. It is ethnically homogeneous. The population is 97.9% Armenians who are Caucasians (Demographics of Armenia, n.d.). Health behaviors relevant to breast cancer risk are also unremarkable in risk profile imparted. Alcohol consumption in Armenia is low among both females and males. Per capita recorded alcohol consumption among adults older than 15 years is 1.5 liters

per year (WHO, 2004c). Finally, only 4.0% of women aged 15–49 have ever used oral contraceptives or hormone replacement therapy (National Statistical Service of Armenia & Ministry of Health of Armenia, 2006). Thus, we elected not to further explore these factors in the present study.

Recently scientists and researchers suggest an association between DM2 and BrCa (Augustin et al., 2001; Bruning et al., 1992; Mink & Essig, 2002; Xue & Michels, 2007). While the mechanism for this relationship has yet to be established, a likely cause is hyperinsulinemia, which is common in DM2. As insulin receptors are overexpressed in BrCa (Goodwin et al., 2008), then, hyperinsulinemia may hypothetically stimulate growth of BrCa cells (Goodwin et al., 2002). Investigation of the relationship of DM2 to development of BrCa is especially important in Armenia. In 2005 1.4% of the Armenian population was found to have DM2 (WHO Regional Office of Europe, n.d.a.). In Armenia, morbidity of and mortality from DM2 has increased from 1309.6 and 35.83 per 100,000 population, respectively, in 2001 to 1607.3 and 36.29 per 100,000 population in 2006 (WHO, 2004b).

Type 2 diabetes substantially elevates risk of cardiovascular diseases (CVD) especially in women (Hu et al., 2002), increasing almost 5-fold CVD risk in patients after diagnosis (Bonora et al., 2003). Indeed, Stevens and colleagues (2001) suggest a predictive relationship between DM2 and CVD. The intertwined relationship of DM and CVD results in a mortality rate for CVD of approximately 420 per 100,000 population (Ministry of Health of Armenia, 2006) and make it the leading cause of death for women worldwide (WHO, n.d.d.). Hence the present investigation of DM2 as a risk factor for BrCa is further contextualized by the morbidity and mortality data for DM2, BrCa, and CVD. Improved understanding of the associations between and among DM2 and other diseases is essential to public efforts to control it and its consequences.

Prolonged exposure to estrogen is among the most important established risk factors for BrCa (McPherson et al., 2000). Here again, the precise mechanism is not yet known but may involve prolonged exposure to estrogen, which stimulates mammary cell mitogenic activity and proliferation resulting in risk of BrCa (Key, Verkasalo, & Banks, 2001). Early menarche (before age 12), late age at menopause (above age 54), and late first full-term pregnancy (above age 30) are among the best studied reproductive characteristics hypothesized as resulting in increased risk (Hsieh, Trichopoulos, Katsouyanni, & Yuasa, 1990; Lambe et al., 1996; Pathak, Speizer, Willett, Rosner, & Lipnick, 2006). Nulliparity and limited breastfeeding (generally less than 9 months) also appear to increase risk (Sikind, Schofield, Rice, & Bain, 1989). Evidence on parity and risk of BrCa, however, are contradictory. Along with endogenous estrogens, exogenous estrogens—consumed either as oral contraceptives or hormone replacement therapy—appear to moderately increase risk of BrCa (Colditz et al., 1995; Key et al., 2001). Conversely, childbearing and breastfeeding practices reduce

the number of menstrual cycles and thus may limit lifetime estrogen exposure, reducing risk (Brinton et al., 1995; Key et al., 2001; Layde et al., 1989).

Obesity may represent a more complex risk of BrCa. Adipose tissue produces estrogens and is the primary endogenous source after menopause (McPherson et al., 2000). In postmenopausal women, obesity has been positively associated with risk of BrCa; however, increased body weight is inversely related to BrCa risk in premenopausal women (Morimoto et al., 2004; Stephenson & Rose, 2003). At the same time, obesity is also linked with DM2 (Rose, Komninou, & Stephenson, 2004). Thus, the issue of obesity as a risk factor for both insulin resistance and BrCa development warrants further investigation.

We could not locate any reports of investigation into estrogen exposure and DM2 and risk of BrCa in an Armenian sample (personal communication, Executive Director of Armenian-American Wellness Center K. Hakopyan, December, 14, 2008). The incidence of BrCa and DM2 in Armenia are both increasing (WHO, n.d.c.). A variety of factors prolong exposure to estrogen, including currently low parity (1.7 births per woman in 2005); an elective abortion rate of 1.8 abortions per woman in 2005; and declining rates of exclusive breastfeeding (from 45% to 33% among children of age less than 4 months from 2000 to 2005; National Statistical Service of Armenia & Ministry of Health of Armenia, 2006; Ministry of Health of Armenia, 2006). As more commonly acknowledged risk factors for prolonged estrogen exposure have increased in Armenia, so too has obesity. The prevalence of women with BMI equal to and more than 25 kg/m^2 of age over 30 accounts for 65.7% (WHO, n.d.e.). We conducted the present study to explore associations between and among BrCa, DM2, and estrogen exposure among Armenian women given that BrCa is a common malignancy among Armenian women and that DM2 is prevalent among Armenians.

We investigated the following research questions:

1. Is there a positive association between DM2 and development of BrCa in women of age between 35 and 70 in Yerevan?
2. Is there an association between prolonged exposure to estrogen defined by early age at menarche, late age at menopause, late age at first full-term pregnancy, nulliparity, obesity, breastfeeding practices, induced abortions, and intake of exogenous hormones and development of BrCa in women of age between 35 and 70 in Yerevan?
3. Is there an interaction between family history of BrCa with DM2 and prolonged exposure to estrogen and development of BrCa in women of age between 35 and 70 in Yerevan?

METHODS

Study Design and Population

We used a case-control study design and targeted women aged 35 to 70 years who reside in Yerevan, the capital of the Republic of Armenia. To be eligible, both cases and controls were women aged 35 to 70 on enrollment, who speak Armenian and have documented residency in Yerevan in domiciles with operating telephones. Those agreeing to participate by telephone were enrolled for either case or control given the following criteria. Those eligible as cases were registered at the National Oncology Center (NOC) and Armenian-American Wellness Center (AAWC) between January 2002 and December 2008 with confirmed diagnosis of BrCa. Controls should have no history of breast diseases, no previous breast surgery except for cosmetic procedures, and were identified through random digit dialing. Women were excluded if they had a busy or disconnected telephone line; were out of the country and had an incorrect telephone number (for cases); and had an office telephone dialed (for controls).

Study Variables

The dependent variable was BrCa. Control variables follow: DM2, age, age at menarche, age at first pregnancy, age at menopause, number of pregnancies, number of induced abortions, number of live births, BMI (weight/height^2), family history of BrCa, breastfeeding duration, intake and duration of contraceptives, and hormone replacement therapy.

Study Instrument

We designed a structured questionnaire for telephone use in the study by adapting questions from instruments used in previous studies in Armenia and the United States (Arakelyan, 2007; CDC, n.d.; Champion, 1984; Dündar et al., 2006). Thirty-three items were either forced choice questions or factual reports addressing following domains: a) demographic and anthropometric data; b) medical history on DM2; c) reproductive history including childbearing and breastfeeding; d) use of exogenous estrogens; e) family history of BrCa; and f) smoking habits. We pretested the instrument in five women before proceeding with interviews. Following this pretest, a question about induced abortions was split into two questions to query induced abortions and spontaneous abortion or miscarriage. The other 32 questions remained unchanged.

Sample Size

Sample size was calculated based on proportions (proportion of people exposed to DM2 equal to 0.60 in cases and 0.43 in controls) and OR of 2.0 (Augustin et al., 2001; Goodwin et al., 2002; Mink & Essig, 2002), level of significance (type I error $\alpha = 0.05$, two-sided), power 80% and response rate 80%. The calculated sample projected equal numbers of participants in both case and control groups. Thus, sample size was calculated as 147 in cases and 147 in controls. After adjusting for a response rate of 80%, a typical response rate for telephone surveys conducted in Armenia (Center for Health Services Research & Development, 2007), the prospective sample size was increased to 184 in cases and 184 in controls to account for those declining to participate.

Data Collection

Data were collected by telephone interview in early 2009. We obtained a list of 230 women with a BrCa diagnosis and telephone numbers from AAWC and NOC by permission of the respective center directors.

Data Management and Analysis

Completed questionnaires were entered into and initially analyzed by SPSS 10.0. Data then were converted for use with STATA 10.0 to complete advanced statistical analyses. We used means and standard deviations (if normally distributed) and medians and ranges (if skewed) for continuous variables, while we performed frequency analyses for categorical variables. We used *t* test, chi-square, and Fisher's exact tests and conducted simple and multiple logistic analyses. Possible interactions between family history and all major independent variables of interest were checked and tested. We utilized multiple logistic regression analysis with forward and backward elimination of those variables that showed statistically significant differences in simple logistic regressions as well as including variables with marginally significant level (e.g., less than 0.100). Each model was tested against the nested model using log-likelihood ratio test, and the most parsimonious model with the lowest Akaike information criterion (AIC) was considered as the best fitting model.

Protection of Participants

The project, along with all study materials in English and Armenian, was approved by the Institutional Review Board (IRB). Verbal consent was obtained from all participants before the questionnaire was administered. We ensured

complete anonymity and confidentiality of study participants by assigning identification numbers to participants.

FINDINGS

We collected complete questionnaires from 150 cases and 152 controls for response rates of 81.5% and 82.6%, respectively. Refusal rates were 3.8% (7 participants) among cases and 17.4% (32 participants) among controls. Twenty-seven prospective participants in cases had died before being contacted for the study, accounting for death rate of 14.7%. No incomplete questionnaires were collected (Table 1).

Statistically significant differences ($p < .05$) between cases and controls were observed in a variety of variables. We observed statistically significant differences ($p < .001$) in the mean age of cases and controls, diabetic status in cases and controls, also in the mean age at first pregnancy, absence of menopause status, as well as the reported family history of BrCa in cases and controls, respectively. Cases were different from controls in education level ($p = .021$). More interestingly, cases differed from controls in respect of the following: (a) the mean overall BMI as well within BMI categories ($p < .05$); and (b) the mean age at menarche ($p = .002$). Parity was 1.99 ± 0.9 vs. 2.22 ± 1.02 in cases and controls with a p value equal to .041. Notably, there were almost three times more cases that ever underwent hormone replacement therapy compared with controls ($p = .009$). Interestingly, controls smoked on average almost twice the number of cigarettes smoked by cases ($p = .036$).

Simple logistic regression analyses run for all covariates with corresponding odds ratios, 95% confidence intervals, and p values are detailed in Table 2. There is a statistically significant association between development of BrCa and age. Specifically, the odds of BrCa among women between the ages of 45 and 54 and those of ages 55–70 is 2.5-fold and 4.6-fold, respectively, higher ($p = .010$ and $p < .001$) than the odds for younger women of ages 35–44.

A statistically significant association between development of BrCa and BMI exists with 7% higher odds for each unit increase in BMI. Obese women are at 2.4 higher odds versus women with normal BMI ($p = .010$). Having DM2 increases the odds of developing BrCa by a factor of 5.1 ($p = .001$). Similarly, menarche onset delayed by each one year decreases the odds of BrCa development by 22% ($p = .003$). Onset of menarche after 11 reduces the odds of developing BrCa by 67% ($p = .040$). There is a statistically significant increase of 13% ($p < .001$) in the odds of BrCa associated with each year increase in age at first pregnancy. Compared with women whose first pregnancy was before age 20 years, we estimated a 2.21-fold increase (95% CI 1.32–3.69, $p = .003$) in the odds of BrCa among women whose first

TABLE 1 Descriptive Characteristics of the Study Participants[1]

Covariates	Cases (n = 150) (%)	Controls (n = 152) (%)	p value
Age (years, mean ± *SD*)	55.79 ± 7.89	51.11 ± 9.94	.000*
Education			
Less than 10 years	4 (2.7)	8 (5.3)	.021*
10 years	39 (26.0)	60 (39.5)	
College	35 (23.3)	35 (23.0)	
University	72 (48.0)	48 (31.6)	
Postgraduate	0	1 (0.7)	
Marital status			
Single	11 (7.3)	5 (3.3)	.262
Married	120 (80.0)	129 (84.9)	
Divorced	10 (6.7)	6 (3.9)	
Widowed	9 (6.0)	12 (7.9)	
BMI (kg/m^2, mean ± *SD*)	29.03 ± 4.28	27.67 ± 4.57	.014*
BMI categories			
Normal (19.0–24.9)	25 (18.4)	34 (27.6)	.020*
Overweight (25.0–29.9)	54 (39.7)	57 (46.3)	
Obese (≥30.0)	57 (41.9)	32 (26.0)	
DM2			
Absence	128 (85.3)	147 (96.7)	.001*
Presence	22 (14.7)	5 (3.3)	
Age at menarche (years, mean ± *SD*)	13.47 ± 1.53	14.01 ± 1.47	.002*
Pregnancy			
Never	12 (8.0)	9 (5.9)	.478
Ever	138 (92.0)	143 (94.1)	
# of pregnancies (median, range)	5, 0–35	5, 0–34	.278
Age at 1st pregnancy (years, mean ± *SD*)	23.71 ± 4.38	21.77 ± 3.78	.000*
Live births			
No	17 (11.3)	12 (7.9)	.311
Yes	133 (88.7)	140 (92.1)	
# of living children (mean ± *SD*)	1.99 ± 0.93	2.22 ± 1.02	.041*
Abortion			
Never	34 (22.7)	49 (32.2)	.063**
Ever	116 (77.3)	103 (67.8)	
# of induced abortions (median, range)	2, 0–30	2, 0–30	.529
# of miscarriages (median, range)	0, 0–6	0, 0–4	.797
Breastfeeding			
Never	10 (7.5)	6 (4.3)	.264
Ever	123 (92.5)	133 (95.7)	
Duration of breastfeeding (m, median, range)	12, 1–36	12, 1–72	.262
Menopause			
No	18 (12.0)	64 (42.4)	.000*
Yes	127 (84.7)	83 (55.0)	
Don't know	5 (3.3)	4 (2.6)	

TABLE 1 Descriptive

Covariates
Age at menopause (y, mean ± *SD*)
OC use
Never
Ever
Duration of OC use (median, range)
HRT
Never
Ever
Duration of HRT (m, range)
Family history of BrC
No
Yes
Smoking status
Never
Past
Current
of cigarettes smoke ± *SD*)

[1]Data are presented as f
y = years; *SD* = standa
contraceptive; HRT
*Statistically significant;

pregnancy was b
(95% CI 1.47–16.
first pregnancy w
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p = .014). The re
is not statistically
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Postmenopausal
pendent risk fact
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history was 3.5 ti
tory of BrCa (p <
.010). Compared

TABLE 1 Descriptive Characteristics of the Study Participants[1] *(Continued)*

Covariates	Cases (n = 150) (%)	Controls (n = 152) (%)	p value
Age at menopause (years, mean ± *SD*)	48.75 ± 5.20	48.53 ± 5.30	.765
OC use			
Never	140 (93.3)	141 (92.8)	.846
Ever	10 (6.7)	11 (7.2)	
Duration of OC use (m, median, range)	5, 1–72	3, 1–60	.087**
HRT			
Never	119 (79.3)	137 (90.1)	.009*
Ever	31 (20.7)	15 (9.9)	
Duration of HRT (m, median, range)	8, 2–72	6, 1–36	.059**
Family history of BrCa			
No	108 (72.0)	137 (90.1)	.000*
Yes	41 (27.3)	15 (9.9)	
Smoking status			
Never	122 (81.3)	123 (80.9)	.324
Past	12 (8.0)	7 (4.6)	
Current	16 (10.7)	22 (14.5)	
# of cigarettes smoked (mean ± *SD*)	7.77 ± 6.68	13.44 ± 11.76	.036*

[1]Data are presented as frequencies and percentages unless specified.

y = years; *SD* = standard deviation; # = number; BMI = body mass index; m = months; OC = oral contraceptive; HRT = hormone replacement therapy.

*Statistically significant; **marginally statistically significant.

Controls (n = 152) (%)	p value
51.11 ± 9.94	.000*
8 (5.3)	.021*
60 (39.5)	
35 (23.0)	
48 (31.6)	
1 (0.7)	
5 (3.3)	.262
129 (84.9)	
6 (3.9)	
12 (7.9)	
27.67 ± 4.57	.014*
34 (27.6)	.020*
57 (46.3)	
32 (26.0)	
147 (96.7)	.001*
5 (3.3)	
14.01 ± 1.47	.002*
9 (5.9)	.478
143 (94.1)	
5, 0–34	.278
21.77 ± 3.78	.000*
12 (7.9)	.311
140 (92.1)	
2.22 ± 1.02	.041*
49 (32.2)	.063**
103 (67.8)	
2, 0–30	.529
0, 0–4	.797
6 (4.3)	.264
133 (95.7)	
12, 1–72	.262
64 (42.4)	.000*
83 (55.0)	
4 (2.6)	

pregnancy was between the ages of 21 to 30 years and a 4.95-fold increase (95% CI 1.47–16.71, p = .010) in the odds of BrCa among women whose first pregnancy was after age 30. Further, there is a statistically significant relationship between parity and BrCa development (24% reduction in odds, p = .014). The reduction in the odds of BrCa with each live birth, however, is not statistically significant. We found increased odds (1.6 times) of BrCa with induced abortions that approached significance (p = .064). Nonetheless, we estimate a 77% increase in the odds of BrCa (p = .049) among women with between 1 and 3 induced abortions and a 95% increase in the odds of BrCa for women with between 4 and 10 induced abortions (p = .036). Postmenopausal status, estrogen use, and positive family history are independent risk factors for BrCa. Specifically, the odds of BrCa among postmenopausal women was 5.4-fold (p < .001) higher than the odds for premenopausal women. The odds of BrCa among women with a positive family history was 3.5 times the odds of BrCa among women without a family history of BrCa (p < .001). Estrogen use increased the odds of BrCa by 2.4 (p = .010). Compared with women who used oral contraceptives for fewer than 6

TABLE 2 Simple Logistic Regression Results: Odds Ratios of Developing BrCa Associated With Covariates

Covariate	Case	Control	OR (95% CI)	*p* value
Age (years)	150	152	1.06 (1.03–1.09)	.000*
Age categories (years)				
35–44	16	46	1.00	
45–54	43	49	2.52 (1.25–5.09)	.010*
55–70	91	57	4.59 (2.38–8.86)	.000*
Education (years)				
School (less than 10)	4	8	1.0	
School (10)	39	60	1.3 (0.37–4.61)	.685
College	35	35	2.0 (0.55–7.25)	.292
University	72	48	3.0 (0.86–10.52)	.086**
Postgraduate	0	1	—	
Marital status				
Single	11	5	1.00	
Married	120	129	0.42 (0.14–1.25)	.120
Divorced	10	6	0.76 (0.18–3.27)	.710
Widowed	9	12	0.34 (0.09–1.34)	.122
BMI (kg/m^2)	136	123	1.07 (1.01–1.15)	.015*
BMI (kg/m^2)				
Normal (19.0–24.9)	25	34	1.00	
Overweight (25.0–29.9)	54	57	1.29 (0.68–2.44)	.435
Obese (≥30.0)	57	32	2.42 (1.24–4.75)	.010*
DM2				
Absence	128	147	1.00	
Presence	22	5	5.05 (1.86–13.73)	.001*
Age at menarche (years)	144	144	0.78 (0.67–0.92)	.003*
Age at menarche (years)				
≤11	14	5	1.00	
>11	130	139	0.33 (0.12–0.95)	.040*
Pregnancy				
Never	12	9	1.00	
Ever	138	143	0.72 (0.30–1.77)	.479
# of pregnancies				
1–5	55	58	1.00	
6–15	77	71	1.14 (0.70–1.87)	.591
16–35	5	14	0.38 (0.13–1.12)	.078**
Age at first pregnancy (years)	138	142	1.13 (1.06–1.20)	.000*
Age at first pregnancy (years)				
≤20	35	63	1.00	
21–30	92	75	2.21 (1.32–3.69)	.003*
>30	11	4	4.95 (1.47–16.71)	.010*
Live births	133	140	0.76 (0.61–0.94)	.014*
Live births				
No	17	12	1.00	
Yes	133	140	0.67 (0.31–1.46)	.313
# of living children				
0	17	12	1.00	
1	11	13	0.60 (0.20–1.78)	.355
2	83	71	0.83 (0.37–1.84)	.640
3	35	44	0.56 (0.24–1.33)	.189

TABLE 2 Simple Lo
With Covariates (*Co*

Covariate
4
5
Abortion experience
Never
Ever
of induced abortio
0
1–3
4–10
≥11
Miscarriages
Never
Ever
of miscarriages
0
1–3
4–6
Breastfeeding exper
Never
Ever
Breastfeeding durati (months)
≤9
10–24
>24
Menopause
No
Yes
Age at menopause
≤55
>55
OC use
Never
Ever
Duration of OC use (months)
≤6
7–24
≥25
HRT
Never
Ever
Combined duration (months)
≤6
7–24
≥25
Family history of Br
No
Yes

TABLE 2 Simple Logistic Regression Results: Odds Ratios of Developing BrCa Associated With Covariates *(Continued)*

Covariate	Case	Control	OR (95% CI)	*p* value
4	4	10	0.28 (0.07–1.12)	.071**
5	0	2	—	
Abortion experience				
Never	34	49	1.00	
Ever	116	103	1.62 (0.97–2.71)	.064**
# of induced abortions				
0	34	49	1.00	
1–3	65	53	1.77 (1.00–3.12)	.049*
4–10	46	34	1.95 (1.05–3.65)	.036*
≥11	5	15	0.48 (0.16–1.45)	.193
Miscarriages				
Never	115	115	1.00	
Ever	35	37	0.95 (0.56–1.61)	.837
# of miscarriages				
0	115	115	1.00	
1–3	33	35	0.94 (0.55–1.62)	.831
4–6	2	2	1.00 (0.14–7.22)	1.000
Breastfeeding experience				
Never	10	6	1.00	
Ever	123	133	0.55 (0.20–1.57)	.268
Breastfeeding duration (months)				
≤9	54	56	1.00	
10–24	60	60	1.04 (0.62–1.74)	.890
>24	9	16	0.58 (0.24–1.43)	.240
Menopause				
No	18	64	1.00	
Yes	132	87	5.39 (2.99–9.72)	.000*
Age at menopause				
≤55	117	80	1.00	
>55	10	3	2.28 (0.61–8.54)	.222
OC use				
Never	140	141	1.00	
Ever	10	11	0.92 (0.38–2.22)	.846
Duration of OC use (months)				
≤6	3	8	1.00	
7–24	2	1	5.33 (0.34–82.82)	.232
≥25	4	1	10.67 (0.82–138.22)	.070**
HRT				
Never	119	137	1.00	
Ever	31	15	2.38 (1.23–4.62)	.010*
Combined duration of HRT (months)				
≤6	14	9	1.00	
7–24	6	5	0.77 (0.18–3.30)	.726
≥25	9	1	5.79 (0. 62–53.77)	.123
Family history of BrCa				
No	108	137	1.00	
Yes	42	15	3.47 (1.82–6.60)	.000*

(Continued on next page)

of Developing BrCa Associated

OR (95% CI)	*p* value
1.06 (1.03–1.09)	.000*
1.00	
2.52 (1.25–5.09)	.010*
4.59 (2.38–8.86)	.000*
1.0	
1.3 (0.37–4.61)	.685
2.0 (0.55–7.25)	.292
3.0 (0.86–10.52)	.086**
—	
1.00	
0.42 (0.14–1.25)	.120
0.76 (0.18–3.27)	.710
0.34 (0.09–1.34)	.122
1.07 (1.01–1.15)	.015*
1.00	
1.29 (0.68–2.44)	.435
2.42 (1.24–4.75)	.010*
1.00	
5.05 (1.86–13.73)	.001*
0.78 (0.67–0.92)	.003*
1.00	
0.33 (0.12–0.95)	.040*
1.00	
0.72 (0.30–1.77)	.479
1.00	
1.14 (0.70–1.87)	.591
0.38 (0.13–1.12)	.078**
1.13 (1.06–1.20)	.000*
1.00	
2.21 (1.32–3.69)	.003*
4.95 (1.47–16.71)	.010*
0.76 (0.61–0.94)	.014*
1.00	
0.67 (0.31–1.46)	.313
1.00	
0.60 (0.20–1.78)	.355
0.83 (0.37–1.84)	.640
0.56 (0.24–1.33)	.189

TABLE 2 Simple Logistic Regression Results: Odds Ratios of Developing BrCa Associated With Covariates *(Continued)*

Covariate	Case	Control	OR (95% CI)	*p* value
Smoking status				
Never	122	123	1.00	
Ever	28	29	0.91 (0.66–1.27)	.592
# of daily cigarettes smoked				
≤10	22	16	1.00	
11–20	3	6	0.36 (0.08–1.68)	.194
>20	1	5	0.15 (0.02–1.37)	.092*

OR = odds ratio; CI = confidence interval; BMI = body mass index; # = number; OC = oral contraceptives; HRT = hormone replacement therapy.
*Statistically significant; ** Marginally statistically significant.

months, the odds of BrCa among women who used oral contraceptives for more than 25 months were approximately 11-fold higher (p value = .070).

We assessed the independent contribution of each of the candidate risk factors for the odds of BrCa using multivariate logistic regression. While we evaluated many models in the multivariate analyses, we report the key findings from the model in Table 3. After adjusting for BMI, we found that the linear relationship with age and the log odds of BrCa is no longer statistically significant (OR = 0.96, 95% CI 0.90–1.02). There was no evidence that the effect of BMI on BrCa risk differed by age, nor did we find statistically significant interactions between family history and other primary independent variables and BrCa (Table 3).

Diabetes mellitus type 2 (DM2) is an independent risk factor for the development of BrCa adjusted for age, BMI, age at menarche, age at first pregnancy, and age at menopause, as well as for live birth, abortion,

TABLE 3 Multiple Logistic Regression Model With the Lowest ACI

Risk factors	Adjusted OR (95% CI)	Unadjusted OR (95% CI) from simple logistic regression
DM2	5.53 (1.34–22.81)	5.05 (1.86–13.73)
Age	0.96 (0.90–1.02)	1.06 (1.03–1.09)
BMI	1.05 (0.95–1.16)	1.07 (1.01–1.15)
Age at menarche	0.80 (0.61–1.05)	0.33 (0.12–0.95)
Age at 1st pregnancy	1.13 (1.01–1.27)	1.13 (1.06–1.20)
Live birth	0.36 (0.20–0.66)	0.76 (0.61–0.94)
Abortion	2.86 (1.02–8.04)	1.62 (0.97–2.71)
Breastfeeding duration	1.00 (0.96–1.05)	0.94 (0.57–1.55)
Age at menopause	1.06 (0.98–1.14)	2.28 (0.61–8.54)
Hormone replacement therapy	2.88 (0.88–9.38)	2.38 (1.23–4.62)

Model characteristics: Hosmer-Lemeshow chi^2 (8) = 10.85, Prob > chi^2 = 0.2101, number of groups = 10.

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BrCa than other
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breastfeeding duration, and hormone replacement therapy. For instance, women with DM2 are 5.53 times (95% CI 1.34–22.81) more likely to have BrCa than otherwise similar to women without DM2. Each year increment of age at first pregnancy increases the adjusted odds of developing BrCa by factor of 1.13 ($p < .05$). Giving birth to a child reduces the odds of BrCa by 64% (OR = 0.36) after adjusted for other risk factors ($p < .05$). Even one abortion increases the adjusted odds of developing BrCa by a factor of 2.86 ($p < .05$).

DISCUSSION

We investigated the relationship of DM2 and prolonged exposure to estrogens on the risk of BrCa among women of ages 35–70 residing in Yerevan, Armenia, using a case control design and a telephone interview technique. We found that DM2, BMI, aging, age at onset of menarche and at first full-term pregnancy, parity, induced abortions, and hormone replacement therapy are associated with the risk of BrCa. Our findings corroborate the results from similar studies conducted in other societies (Goodwin et al., 2002; Key et al., 2001; McPherson et al., 2000; Morimoto et al., 2004; Stephenson & Rose, 2003). Notably, we found that age at menopause, breastfeeding, and oral contraceptive use were not associated with the risk of BrCa in our sample.

We identified a statistically significant positive association between DM2 and BrCa (unadjusted OR = 5.05, $p = .001$). This finding was consistent with those reported elsewhere (Augustin et al., 2001; Goodwin et al., 2002; Rose et al., 2004). The OR increased to 5.53 after adjustment for other variables emphasized the positive association between DM2 and BrCa. This increase in the adjusted odds of developing BrCa in diabetic women may be due to the sample characteristics, as well as other confounders and risk factors that were not considered or measured in this study. Based on our findings we posit that future research replicating the present project may inform current clinical education for primary care and specialist physicians in Armenia by encouraging better attention to screening for BrCa among women with DM2. Further, we believe our work informs others studying different populations of women with DM2 in developed nations where the prevalence of DM2 is rising (WHO, 2004a).

We investigated prolonged exposure to estrogen, an acknowledged risk factor for development of BrCa. Based on our findings, we suggest that early age at menarche and late age at first full-term pregnancy, implying prolonged exposure to estrogen, present risk for BrCa (unadjusted OR = 0.33 [95% CI 0.12–0.95] and OR = 4.95 [95% CI 1.47–16.71], respectively). These findings were similar to those found in other studies that suggested a protective effect of late onset of menarche and of early age at first pregnancy (Ewertz et al., 1990; Key et al., 2001; McPherson et al., 2000). In contrast to published

f Developing BrCa Associated

OR (95% CI)	*p* value
1.00	
0.91 (0.66–1.27)	.592
1.00	
0.36 (0.08–1.68)	.194
0.15 (0.02–1.37)	.092*

= number; OC = oral contracep-

ed oral contraceptives for higher (p value = .070). each of the candidate risk istic regression. While we s, we report the key find- r BMI, we found that the Ca is no longer statistically was no evidence that the d we find statistically sig- ther primary independent

endent risk factor for the at menarche, age at first for live birth, abortion,

t ACI

Unadjusted OR (95% CI) from simple logistic regression
5.05 (1.86–13.73)
1.06 (1.03–1.09)
1.07 (1.01–1.15)
0.33 (0.12–0.95)
1.13 (1.06–1.20)
0.76 (0.61–0.94)
1.62 (0.97–2.71)
0.94 (0.57–1.55)
2.28 (0.61–8.54)
2.38 (1.23–4.62)

b > chi^2 = 0.2101, number of

findings (Lambe et al., 1996; Palmer, Wise, Horton, Adams-Campbell, & Rosenberg, 2003), the protective effect of increasing parity and risk of BrCa was not statistically significant. Giving birth to four or more children, however, had a marginally statistical significant protective effect for BrCa development (OR = 0.28, $p = .071$). This modest finding may be explained by the very small number of participants reporting four or more children. After adjusting for other risk factors, however, the estimated protective effect of parity was statistically significant (adjusted OR = 0.3, 95% CI 0.20–0.66). Additionally, each one year delay in age at first pregnancy is positively associated with development of BrCa (adjusted OR = 1.13, 95% CI 1.01–1.27). While these findings are intriguing, they require further investigation. In the light of diverse childbearing patterns (e.g., parity and age at first pregnancy) among women worldwide, we suggest that our findings may be relevant to others conducting research in BrCa and estrogen exposure.

Breastfeeding or the duration of breastfeeding was not associated with BrCa development. These findings are in contrast to literature that suggests that these factors limit risk (Brinton et al., 1995; Collaborative Group, 2002; Sikind et al., 1989). While breastfeeding longer than 24 months was associated with a reduced odds of BrCa development (OR = .58), this finding was not statistically significant ($p = .240$).

Exogenous hormones appear to increase the risk of BrCa over time. Use of replacement hormones increased the odds of BrCa about 2.4 times (unadjusted OR = 2.38, $p = .010$), while combined duration of hormone replacement therapy longer than 25 months shows 5.9 times greater odds when compared with use of less than 6 months. This increase in OR, however, was not statistically significant ($p = .123$). Similarly, overall lifetime duration of oral contraceptive use showed a marginally significant relation (OR = 10.7) in the same comparison. These findings are consistent with those published elsewhere (Colditz et al., 1995; Key et al., 2001). Very few participants, however, reported use of exogenous hormones for contraception or replacement compared with women from the United States or Europe, where use of these drugs is more common.

Age and obesity, measured as BMI, were significantly associated with increased risk of BrCa, findings consistent with the literature (McPherson et al., 2000; Morimoto et al., 2004; Stephenson et al., 2003). As expected, simple logistic regression showed that aging, one of the major nonmodifiable risk factors for BrCa development, elevates odds of disease development (unadjusted OR = 2.5 and OR = 4.6 in age groups of 45–54 and 55–70, $p <$ .010). In respect to the primary variables of interest—DM2—aging turned to be a confounder, however, and it lost its significance in the multivariate logistic regression model (adjusted OR = 0.96, 95% CI 0.90–1.02). More flexible models for the relationship of age and the odds of BrCa provided qualitatively similar findings, suggesting that much of the linear relationship with age and BrCa may be partially explained by BMI.

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Obesity was positively associated with BrCa (unadjusted OR = 1.07, $p =$ .015), corroborating previous findings (Morimoto et al., 2004; Stephenson & Rose, 2003). Moreover, obese women (BMI category greater than 30kg/m^2) have a 2.4-fold increased odds of developing BrCa compared with women with BMI in the interval 19.0–24.9 kg/m^2 (95% CI 1.24–4.75). After adjusting for other risk factors, BMI was not statistically significant (OR = 1.05, 95% CI 0.95–1.16).

As expected, being menopausal conferred about 5.4 times greater unadjusted odds ($p < .001$) of developing BrCa. About 85% of women in the sample of cases reported being menopausal, and the difference between cases and controls was significant ($p < .001$). We did not find a statistically significant relationship between late age at menopause and development of BrCa in contrast to published studies, indicating that late age at menopause is positively associated with development of BrCa (Hsieh et al., 1990; Key et al., 2001).

The odds of BrCa was statistically significantly greater in women who experienced 1 to 10 lifetime abortions (unadjusted OR = 1.95, $p = .036$) compared with women who reported no abortions. Other researchers report some controversy over a possibly protective effect between induced abortions and risk of BrCa development (Beral, Bull, Doll, Peto, & Reeves, 2004; Brind, Chinchilli, Severs, & Summy-Long, 1996). Most evidence, however, points to no effect (Melbye et al., 1997). Interestingly, when adjusted for other covariates, induced abortions showed even higher odds of developing BrCa (adjusted OR = 2.86, $p = .046$). This finding is not robust. Although induced abortions may interrupt estrogen production, thus leading to less exposure, they also may create other reproductive system alterations. Reporting bias may further jeopardize this particular finding given the sensitive nature of induced abortions. Further, we did not find any association between miscarriages and risk of BrCa development. This finding, however, may be explained by the few women in the sample reporting miscarriage. Future investigation is necessary to establish the actual relationship between abortion and BrCa in the Armenian population.

Study Limitations

This case-control study was limited in several ways. The psychometric properties of the questionnaire were not assessed and hence constrain interpretation of the findings. Recall bias, as with all case-control studies, is an important concern. Reporting bias also limits the study given the sensitive issues concerning cancer, smoking, induced abortion, and body weight addressed in the questionnaire. Latency bias could affect the results obtained from controls as BrCa has a long latency period, so a number of controls could have had the problem in its earlier stages, while their reported data were

considered in the light of control data. Other possible confounding variables that were not considered or adjusted for in the current study may have altered observed associations. Finally, as this is a retrospective, population-based survey and not a biological study, the findings have limited direct clinical relevance.

Recommendations

Based on the findings of the current case-control study, we recommend the following: a) a cohort study to find out the incidence rate of BrCa among the study cohort of diabetic women; b) clinical education and training of endocrinologists and mammologists to enhance their clinical collaboration to meet the needs of women with DM2 and address their risk of BrCa and health screening needs; c) reinforcing among clinicians heightened awareness of the need for annual BrCa screening among women at risk, while acknowledging that DM2 likely confers risk; d) similarly reinforcing promotion of weight reduction and maintenance; e) further research replicating the present study with similar samples within and outside Yerevan; f) prospective epidemiological and clinical studies to further explore the influence of weight control, exercise, childbearing, breastfeeding, and contraceptive practices on BrCa risk in the Armenian population; and g) similar cross, national studies in the South Caucasian region.

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