Breast cancer risk factors in south of Islamic Republic of Iran: a case–control study

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عوامل اختطار سرطان الثدي في جنوب جمهورية إيران الإسلامية: دراسة حالات وشواهد

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الخلاصة: أُجريَت دراسة حالات وشواهدها في المدة من نيسان/أبريل 2000 إلى آذار/مارس 2002، لتقصِّي عوامل اختطار سرطان الثدي في مدينة بندر عباس، بجنوب جمهورية إيران الإسلامية. واستُخدم تحليل التحوُّف اللوجستي للمقارنة بين 168 سيدة، تأكَّدت إصابتهن بسرطان الثدي الأوَّلي مع 504 من الشواهد المماثلات في العمر. وشملت عوامل الاختطار الرئيسية: سوابق إصابة إحدى القريبات من الدرجة الأولى بسرطان الثدي، وصغر السن عند بدء الإحاضة، وعدم سبق الزواج، وزيادة السن في أول حمل تام المدة على 30 عاماً، وزيادة مرات الحمل لِتَمَام على خمس مرات. وبيَّن التحليل المتعدِّد المتغيِّرات أن سابقة عدم الإرضاع من الثدي تمثِّل أحد العوامل التي يُعْتَدُّ بها إحصائياً. ولم تُلاحَظ فروق بين الحالات والشواهد في ما يتعلَّق بعدد الولادات، وسوابق الإجهاض، واستخدام موانع الحمل الفموية، والحالة بالنسبة للإياس، والعمر عند الإياس، وسوابق استخدام المعالجة التعويضية بالهرمونات، وسوابق الإصابة بأمراض الثدي الحميدة، وسوابق التدخين.

ABSTRACT A case–control study was carried out from April 2000 to March 2002 to investigate risk factors for breast cancer in Bandar Abbas, south Islamic Republic of Iran. Using logistic regression analysis, 168 women with pathologically confirmed primary breast cancer were compared with 504 age-matched controls. Significant risk factors were: family history of breast cancer in a first-degree relative, younger age at menarche, never married, first full-term pregnancy age 30+ years and > 5 full-term pregnancies. In multivariate analysis, negative history of breastfeeding was also significant. Cases and controls did not differ with regard to parity, history of abortion, oral contraceptive use, menopausal status, age at menopause, ever-use of hormone replacement therapy, history of benign breast disease or history of cigarette smoking.

Les facteurs de risque de cancer du sein dans le sud de la République islamique d'Iran : une étude cas-témoins

RÉSUMÉ Une étude cas-témoins a été menée entre avril 2000 et mars 2002 à Bandar Abbas, dans le sud de la République islamique d'Iran, afin d'évaluer les facteurs de risque de cancer du sein. Cette étude a comparé, sur la base de la régression logistique, 168 patientes présentant un cancer du sein primitif confirmé par l'anatomopathologie avec 504 femmes témoins appariées en âge. L'analyse a identifié les facteurs de risque significatifs suivants : histoire familiale de cancer du sein au premier degré de parenté, apparition plus précoce des premières règles, absence de mariage, primiparité à terme au-delà de 30 ans et plus de 5 grossesses menées à terme. L'analyse multivariée a également montré l'importance d'une histoire négative d'allaitement au sein. Les cas et les témoins se sont avérés comparables en termes de parité, d'histoire d'avortement, d'utilisation de contraceptifs oraux, de statut ménopausique, d'âge à la ménopause, de naïveté de tout traitement hormonal substitutif, d'antécédents de pathologie mammaire bénigne et de tabagisme.

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Introduction

Similar to other human cancers, breast cancer arises from a multifactorial process. Recent attention has focused on genetic predisposition to breast cancer [*1,2*] and on its association with factors relating to modern affluence, including diet and alcohol consumption [*3–5*]. Furthermore, the effect of reproductive factors strongly supports a hormonal role in its etiology in some industrialized countries [*6,7*]. Earlier age at menarche [*8–10*] and later age at first full-term pregnancy [*9–12*] are associated with a significant increase in the risk of the disease, whereas the few studies that have been conducted in northern and central parts of the Islamic Republic of Iran have not confirmed a significant effect of these factors [*13–15*].

While numerous studies have been conducted in industrialized countries to assess the epidemiology of breast cancer, there have been few studies in Eastern Mediterranean Region populations. Such studies are of interest because their different risk profiles may help to explain the different occurrence of the disease in different populations. Although breast cancer is the most common form of cancer in Iranian women [*16*], few epidemiological studies have been conducted on its risk factors, especially in the south of the country. The age-adjusted incidence of the disease is estimated to be 22.4 per 100 000 [*16*]. Epidemiological studies have revealed a lower age of Iranian patients compared with their counterparts in industrialized countries [*14,17*] and a moderately rapid increase in the incidence of the disease in recent years [*16*]. The question therefore arises as to whether or not breast cancer in the south of the Islamic Republic of Iran is influenced by some of the risk factors previously established in studies of high or moderate incidence areas.

This case–control study was undertaken to investigate this subject and the inconsistency between the results of the studies in northern and central parts of the Islamic Republic of Iran and populations elsewhere.

Methods

A case–control study was conducted from April 2000 to March 2002 in Bandar Abbas city, Hormozgan, Islamic Republic of Iran. Hormozgan province is the southernmost province of the country located along the Straits of Hormoz.

The eligible cases were all incident (i.e. diagnosed within 2 years before the interview) breast cancer patients living in the city during the study period. We approached 173 women with primary breast cancer who were eligible for our study but only 168 agreed to participate, giving a participation rate for cases of 97.1%.

Women were entered into the study if they had a confirmed pathological primary breast cancer diagnosis from the pathology department of Bandar Abbas Shahid Mohammadi Hospital, the leading university-based hospital in the region. For each case, 3 age-matched (to within 3 years) women were recruited from patients without any history of breast problems or neoplastic diseases who attended the outpatient ophthalmology or dermatology clinic in the same hospital. Women with a history of hysterectomy or artificial menopause were excluded from the study.

After taking informed consent from the women, a structured questionnaire was administered was completed at the time of recruitment including the following: demographic characteristics, family history of breast cancer in a first-degree relative, age at menarche, marital status, parity, age at first full-term pregnancy, number of chil-

dren or full pregnancies, history of previous breastfeeding (defined as having breastfed for > 2 months), history of induced or spontaneous abortion, history of ever-use of oral contraceptives, menopausal status, age at menopause, history of ever-use of hormone replacement therapy (HRT), past history of benign breast disease and history of cigarette smoking. All interviews were carried out by 2 interviewers who had been thoroughly familiarized with the study protocol.

This study did not use 'blinding' procedures with respect to the case status of subjects and it is possible that women who were diagnosed with breast cancer were more likely to provide more detailed complete information about past exposure history than controls. However, the investigators and the interviewers were fully informed about the possibility of recall/interviewer bias and their potential impact on our study. A number of efforts were made to minimize such bias, including standardization of wording in the interview and repeat interviews for some participants.

Odds ratios from univariate logistic regression were used to estimate the relative risk of breast cancer associated with the various factors, and their predictive effects. Based on the univariate analysis, the odds ratios (OR) were adjusted for potential confounding variables and 95% confidence intervals (CI) were calculated. A forward multivariate logistic regression model was used for significant associated risk factors and $P < 0.05$ was considered statistically significant.

Results

Of 173 women with breast cancer who were newly diagnosed, 168 patients were entered in the study as cases and 504 women were selected as controls. As controls were age-matched with cases, there was no significant difference between the mean age of the 2 groups: 48.6 [standard deviation (SD) 13.7] years for cases versus 48.4 (SD 13.6) years for controls (Table 1).

The results of univariate binary logistic regression analysis are shown in Table 2. There were no significant differences between cases and controls with regard to parity, history of breastfeeding, history of induced or spontaneous abortion, oral contraceptive use, menopausal status, age at menopause, history of HRT use, history of previous benign breast disease or having ever smoked cigarettes.

However, breast cancer history in a first-degree relative was a significant risk factor (OR 9.07, 95% CI: 4.06–12.26). Women with younger age at menarche (< 13 years old) were found to be at higher risk for breast cancer than women with older age of menarche (OR 4.00, 95% CI: 1.82–9.84). Never married women demonstrated a higher risk of breast cancer than the others (OR 2.69, 95% CI: 1.38–7.12). Breast cancer risk was significantly greater in women where first full-term pregnancy was at age 30+ years in comparison with the others with first full-term pregnancy at lower age

Table 1 **Distribution of breast cancer patients and controls according to age**

Age (years)	Cases (*n* = 168)		Controls (*n* = 504)	
	No.	%	No.	%
< 35	24	14.2	67	13.3
36–45	54	32.1	162	32.1
46–55	33	19.6	124	24.7
> 55	57	33.9	151	29.9
Mean (SD)	48.6 (13.7)		48.4 (13.6)	
Range	27–92		25–95	

SD = standard deviation.
n = *total number of respondents.*

Table 2 **Distribution of breast cancer cases and controls according to selected risk factors and associated odds ratios derived from univariate logistic regression analysis**

Parameter	Cases (*n* = 168)		Controls (*n* = 504)		OR (95% CI)	*P*-value
	No.	%	No.	%		
Family history of breast cancer						
No	154	91.7	499	99.1	1.00[a]	
Yes	14	8.3	5	0.9	9.07 (4.06–12.26)	*P* < 0.01
Age at menarche (years)						
< 13	49	29.2	47	9.3	4.00 (1.82–9.84)	*P* < 0.01
≥ 13	119	70.8	457	90.7	1.00[a]	
Marital status						
Married	128	76.2	425	84.3	1.00[a]	
Divorced/widowed	28	16.7	65	12.9	1.43 (0.88–3.76)	
Never married	12	7.1	14	2.8	2.69 (1.38–7.12)	*P* < 0.05
Parity						
Parous	154	91.7	490	97.2	1.00[a]	
Nulliparous	14	8.3	14	2.8	3.18 (0.77–12.26)	NS
Age at first full-term pregnancy (years)						
≤ 30	144	85.7	481	95.4	1.00[a]	
> 30	7	4.2	3	0.6	7.79 (4.25–9.12)	*P* < 0.01
(Nulligravida)	17	10.1	20	4.0		
No. of full-term pregnancies						
0	17	10.1	20	4		
1–2	26	15.5	98	19.4		
3–5	57	33.9	278	55.2		
> 5	68	40.5	108	21.4		
History of breastfeeding						
No	13	7.7	27	5.4	1.00[a]	
Yes	155	92.3	477	94.6	0.68 (0.12–0.97)	NS
History of induced or spontaneous abortion						
No	128	76.1	387	76.8	1.00[a]	
Yes	44	23.9	117	23.2	1.14 (0.48–2.26)	NS
History of oral contraceptive use						
No	137	81.5	403	79.9	1.00[a]	
Yes	31	18.5	101	20.1	0.91 (0.39–1.99)	NS
Menopausal status						
Premenopause	81	48.2	236	46.8	1.00[a]	
Postmenopause	87	51.8	268	53.2	0.95 (0.43–2.28)	NS
Age at menopause (years)						
< 45	8	4.8	29	5.7		
45–50	57	33.9	207	41.1		
> 50	22	13.1	32	6.4		

Table 2 **Distribution of breast cancer cases and controls according to selected risk factors and associated odds ratios derived from univariate logistic regression analysis** *(concluded)*

Parameter	Cases (*n* = 168)		Controls (*n* = 504)		OR (95% CI)	*P*-value
	No.	%	No.	%		
History of HRT use						
No	77	42.3	239	41.5	1.00[a]	
Yes	10	6.0	29	5.4	1.09 (0.53–1.82)	NS
History of previous benign breast diseases						
No	161	95.8	492	97.7	1.00[a]	
Yes	7	4.2	12	2.4	1.78 (0.83–3.12)	NS
History of cigarette smoking						
No	101	60.1	315	62.5	1.00[a]	
Yes	67	39.9	189	37.5	1.13 (0.58–2.16)	NS

[a] *Reference category.*
NS = not significant, CI = confidence interval; OR = odds ratio; HRT = hormone replacement therapy.
n = *total number of respondents.*

(OR 7.79, 95% CI: 4.25–9.12) (Table 2). Furthermore, it was shown that > 5 full-term pregnancies would be expected to correlate with an increase in the risk of breast cancer ($\chi^2 = 111.12$, $P < 0.05$).

In forward multivariate logistic regression analysis, in addition to those factors which were significantly associated with breast cancer, parity and breastfeeding were included in the model because of their relatively high but not statistically significant OR. The final model revealed that in addition to those factors which were significant in univariate logistic regression analysis, negative history of breastfeeding was a significant factor in increasing risk of breast cancer (OR 1.55, 95% CI: 1.08–2.90), but nulliparity remained not significant.

Discussion

The purpose of the present study was to characterize breast cancer epidemiology, especially in determining the generally accepted or suspected risk factors in the Islamic Republic of Iran.

As in industrialized countries, we found that a family history of breast cancer was an important factor contributing to breast cancer in the south of the Islamic Republic of Iran. This observed familial association is likely to imply a genetic predisposition. Therefore, it is of interest to determine whether known breast cancer susceptibility genes, such as *BRCA1* [*18*] and *BRCA2* [*19*], responsible for a proportion of breast cancers in other countries [*8,9,20*], also play a role in breast cancer in Islamic Republic of Iran.

The relation between women's risk of breast cancer and reproductive history has been the subject of many investigations [*5–17,21–31*]. Despite the large number of studies, the findings for reproductive risk factors have been inconsistent. Our findings suggest an inverse relationship between age at menarche and breast cancer risk, which is consistent with findings in some studies

[*8–10*], although it was not a significant risk factor for breast cancer in some other populations [*5,11,13–15,17*]. The basis of this difference in different populations is not clear and warrants further study.

The findings of our study show that never married women were at higher risk for breast cancer. However, results of multivariate logistic regression analysis revealed that nulliparity was not a statistical significant risk factor for breast cancer. These results are in agreement with the results of another study on the Iranian population [*17*]. In some studies, single and nulliparous married women were found to have a similar increased risk for breast cancer as compared with parous women of the same age [*21*]. Thus one possible explanation for these results is that marital status or nulliparity by itself is not a determining factor for increased or decreased beast cancer risk, and rather the main effect is due to age at first full-term pregnancy or parity number.

Our findings clearly suggest that older age at first full-term pregnancy increased the risk of breast cancer. Although this result is consistent with some studies in different nations and ethnic groups [*9–12*], it is inconsistent with findings from some other studies and particularly from studies in northern and central parts of the Islamic Republic of Iran [*5,8,13–15,17*].

Although on the basis of a suggested influence of full-term pregnancy on breast cells [*22*] an increase in full-term pregnancies would be expected to correlate with a decreased risk of breast cancer in some women [*8,11,23*], evidence suggest that there is a dual effect of parity on breast cancer risk with pregnancy [*11,24,25*]. Our findings showed that more than 5 full-term pregnancies would be expected to correlate with an increase in the risk of breast cancer.

The results of the few studies in northern and central parts of Islamic Republic of Iran do not indicate a significant relationship between history of breastfeeding and breast cancer rate [*13–15*], but according to the results of the present study, the protective effect of breastfeeding was clear on multivariate analysis. This finding is consistent with a large collaborative study [*26*] and some other studies in different populations [*5,8,9,11,23,27–29*] showing breastfeeding to be protective for breast cancer through hormonal or other mechanisms.

Recent reviews reach conflicting conclusions on breast cancer risk after spontaneous or induced abortion [*13,15,30,31*]. In our study, history of abortion, either spontaneous or induced, was not found to be correlated to breast cancer.

Disagreement remains in the literature on the direction and magnitude of effect, if any, of oral contraceptive use on breast cancer risk [*5,8,9,17,28,32–34*]. Despite large studies designed to address such differences, chance, selection factors, changes in formulations, pattern of use and different background risk for breast cancer might account for some of the variation in findings. No association was found between the use of oral contraceptives and breast cancer risk in our study participants.

Our results show that there was no large difference in ever-use of HRT among cases and controls, which was similar to some recent case–control studies [*5,35*]. However, a small increased risk has been observed in larger studies [*36,37*], which might be accounted for by the specific questions about types of HRT and the small sample size of our study; future studies may need to examine the detail of different HRT regimens and duration or age of use.

Smoking history was not associated with breast cancer risk. This result is in

agreement with the results of some other studies [*5,8*].

A number of limitations such as the small sample size and the selection of case and controls may affect the interpretation of our results. Although the results cannot be generalized, the findings suggest that the associations between some known risk factors for breast cancer may differ in the south of the Islamic Republic of Iran as compared with other populations. Intensive studies of breast cancer risk factors in developing countries might reveal other important risk factors in these populations.

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Global age-friendly cities: a guide

Population ageing and urbanization comprise major forces shaping the 21st century. At the same time as cities are growing, their share of residents aged 60 years and over is increasing. Older people are a resource for their families, communities and economies.

The World Health Organization (WHO) regards active ageing as a lifelong process shaped by several factors that favour health, participation and security in older adult life. The purpose of this Guide is to engage cities to become more age-friendly so as to tap the potential that older people represent for humanity.

WHO asked older people, caregivers and service providers living in 33 cities in all WHO regions to describe the advantages and barriers they experience in eight areas of city living. The results led to the development of a set of age-friendly city checklists.

The challenge facing cities and the "active ageing" concept are outlined. Issues and concerns voiced by older people and those who serve older people are highlighted. The principal traits of the "ideal" age-friendly city are listed and the Guide shows how changing one aspect of the city can have positive effects on the lives of older people in other areas.

WHO collaborators are now undertaking initiatives to translate the research into local action, to expand the scope beyond cities, and to spread it to more communities. An age-friendly community movement is growing, for which this Guide is the starting point. It can be downloaded from: http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf