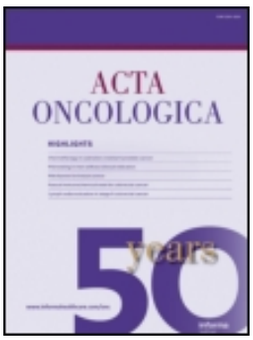

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Risk Factors for Breast Cancer in Turkish Women with Early Pregnancies and Long-lasting Lactation

A Case-control Study

Bekir Kuru, Cihangir Ozaslan, Pınar Ozdemir, Soykan Dinç, Mithat Camlibel and Haluk Alagöl

From the Department of General Surgery, Ankara Oncology Education and Research Hospital (B. Kuru, C. Ozaslan, S. Dinç, M. Camlibel, H. Alagöl) and the Department of Biostatistics, School of Medicine, Hacettepe University (P. Ozdemir), Ankara, Turkey

Correspondence to: Bekir Kuru, Serdar sok. 45/4, 06170 Yenimahalle, Ankara, Turkey. Tel: +90 532 775 56 68. Fax: +90 312 345 49 79. E-mail: bekirkuru@hotmail.com

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A hospital-based case-control study was carried out among 504 women with breast cancer and 610 controls to analyse the risk factors for breast cancer in Turkey. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each risk factor were obtained from logistic regression analysis. Risk factors for breast cancer were found to be long-term lactation (≥ 5 years versus never OR 0.31, 95% CI 0.12–0.79), young age at menarche (< 15 years versus ≥ 15 OR 1.72, 95% CI 1.30–2.28), late age at first full-term pregnancy (≥ 30 versus < 20 OR 2.86, 95% CI 1.32–6.21), oral contraceptive use (ever versus never OR 1.51, 95% CI 1.10–2.08), positive family history (positive versus negative OR 2.81, 95% CI 1.35–5.82), and menstrual irregularity (yes versus no OR 1.61, 95% CI 1.05–2.49). The results of the present study will lead to a better understanding of the risk factors for breast cancer in a developing country.

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It has been estimated that more than a million new female breast cancers were diagnosed world-wide in 2000 (1). The incidence in Turkey is fairly low (5.2 per 100000) and did not change between 1987 and 1995 (2). It is highly probable that, due to under recording, these figures are underestimated. However, according to the cancer registry of our hospital, breast cancer was number four on the list of leading cancers among women in 1980, while in recent years it became the most common cancer.

The incidence of breast cancer varies greatly from one population to another, depending on the prevalent risk factors mostly influenced by lifestyle (3). These factors are well established in many countries (4–39). In developing countries such as Turkey, the lifestyle of populations is changing due to internal migration, education, and Westernization.

Traditionally, women in Turkey get married at a young age, do not use oral contraceptives, enjoy having many children, and breastfeed them for as long as possible. But now that they are becoming more educated and taking part in social life, many women are getting married in their late twenties, using oral contraceptives, having fewer children and breastfeeding them for a shorter time. We are not aware of any earlier investigation on risk factors for breast cancer carried out in our country.

MATERIAL AND METHODS

Using a standard questionnaire the cases and controls were recruited between January 1998 and September 1999. We visited the wards and outpatient clinics of the hospital every day, interviewed all eligible women, measured the weight and height of the subjects, and administered the questionnaire. The review board of Ankara Oncology Education and Research Hospital approved the study proposal, as well as the manner in which informed consent was obtained from the subjects. We followed the principles outlined in the Declaration of Helsinki (40).

Ankara Oncology Education and Research Hospital (AOERH) is a reference hospital to which patients with various oncological diseases, as well as non-oncological orders, are admitted from all regions of Turkey. AOERH is not the only provider of treatment for breast cancer, but about one-fifth of all breast cancer patients in Turkey are treated here.

Cases were all women admitted to the surgical clinics of the AOERH, with a histologically proven breast cancer,

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and residents in Ankara, the capital city, or in five other geographical regions of Turkey. Controls were women residing in the same geographical regions, and admitted to the wards or outpatient clinics of the same hospital during the same interval. One-half of the controls had no disease (52%), the others had an acute abdominal disease (9%), upper respiratory disease (4%), hypertension (1%), inguinal or umbilical hernia (11%), cholecystitis (2%), duodenal or gastric ulcer (5%), liver cysthydatics (0.5), haemorrhoids (3%), anal fissure (2%), anal fistula (1.5%), conjunctivitis (1.5%), glaucoma (1%), cataract (2.5%), urinary infection (4%), and so on. Women, who had a malignant, endocrine, or gynaecological disease, were not included as controls, and women with breast cancer who had another malignant disease, or an endocrine or gynaecological disease were also excluded. Cases and controls were enrolled prospectively from the same hospital. None of the participants refused the interview. Twelve cases and 26 controls that could not recall their ages at menarche and menopause were excluded from the study, resulting in inclusion of 504 cases (range 19–80 years), and 610 controls (range 18–79 years).

Data were collected through questionnaires and interviews about the following items: age, weight, height, residence, education, age at menarche, menstrual cycle history, parity, age at first full-term pregnancy, history of previous benign breast biopsy, family history, history of oral contraceptive use, total duration of breast-feeding, age at menopause, and menopausal status. Body mass index (BMI) was calculated as weight (kg)/height (m^2), according to Quatelet's formula. Family history was accepted as positive if one first-degree relative—mother, sister or daughter—had had breast cancer. Parity was the number of full-term pregnancies, which were defined as pregnancies longer than 6 months regardless of the outcome. Menstrual irregularity was defined as menstrual-like episodes less than 21 or more than 35 days apart. Women were labelled as postmenopausal if they had not had a natural menstrual period within 12-month or had had a hysterectomy with bilateral oophorectomy. The median age of natural menopause in this study was 48 years. Women under age 48 years who had had a hysterectomy without bilateral oophorectomy were classified as premenopausal.

Data about all risk factors were entered into an SPSS 10.0 for Windows computer program, and odds ratios (OR) and 95% confidence intervals (CI) were obtained from unconditional logistic regression models to evaluate the association between breast cancer and various risk factors (39). No matching was used.

The covariates included in regression analyses were age (in years), BMI (<20, 20–24, 25–29, 30–34 and ≥ 35), residence (six different regions), age at menarche (<15, ≥ 15 years), menstrual irregularity (regular, irregular), nulliparity (nulliparous, parous), parity (1–2, 3–4, and ≥ 5 births), age at first full-term pregnancy (<20, 20–24, 25–29, and ≥ 30 years), breastfeeding (never, <1, 1– <2, 2– <5 and ≥ 5 years), family history (yes, no), oral contraceptive use (never, ever), education (≥ 5, <5 years), previous benign breast biopsy (yes, no), menopausal status (premenopausal, postmenopausal), and age at menopause (<40, 40–49, 50–54, ≥ 55 years). The distributions of weight and height were normal, and the variances were equal. We used the t-test to compare the weight and height of the cases and controls. Since the age distribution was not normal, the Mann–Whitney U-test was used to compare age.

RESULTS

Patients with breast cancer were taller than the controls. The mean weights were similar. The mean ages of the cases and controls were 49.4 and 46.4 years, respectively (Table 1).

Adjusted ORs and CIs are shown in Table 2. BMI was inversely, and weakly, associated with the risk of breast cancer. The trend was not significant. The risk increased significantly if menarche occurred at younger than 15 years of age compared with 15 or older (OR 1.72). High parity (5 or more births) was associated with a decreased breast cancer risk, compared with 1–2 births, but the linear trend between parity and risk was not significant (p for trend = 0.25). Nulliparity was not found to be a risk factor.

Compared with an age at first pregnancy of under 20 years, age at 30 or more increased the risk (OR 2.86, 95% CI 1.32–6.21) (Table 2).

Long-term lactation was associated with a significantly decreased risk. Compared with never breastfed, women who were parous and had breastfed for less than 1 year, 1– <2 years, 2– <5 years, and 5 or more years had ORs of 0.60, 0.47, 0.39 and 0.31, respectively. The linear trend was significant ($p = 0.035$).

Family history was found to be a risk factor with an OR of 2.81 (95% CI 1.35–5.82). Menopausal status was not found to be a risk factor (OR 1.16, 95% CI 0.78–1.73).

Use of oral contraceptives increased the risk, with an OR of 1.51 ($p = 0.01$). Compared with the controls, cases that had an irregular menstrual cycle had an increased risk; the OR being 1.61. Education, previous benign breast biopsy, and age at menopause were not found to be risk factors.

DISCUSSION

We interviewed the subjects face to face, to preclude the possible limitations caused by communication problems. The subjects found age at menopause and age at menarche to be the most difficult questions to answer. Our study revealed that early menarche was found to be a risk factor, but age at menopause was not. The proportion of women

Table 1

Features of the cases and controls

	Cases	Controls	t	p
Number	504	610		
Age (years), mean (SD)	49.4 (11.3)	46.4 (12.2)		0.000
<30	13 (2.6%)	49 (8%)		
30–34	28 (5.6%)	61 (10%)		
35–39	70 (13.9%)	91 (14.9%)		
40–44	77 (15.3%)	84 (13.7%)		
45–49	80 (15.8%)	81 (13.3%)		
50–54	72 (14.3%)	77 (12.6%)		
55–59	60 (12%)	65 (10.7%)		
60–64	45 (8.9%)	49 (8%)		
65–80	59 (11.7%)	53 (8.7%)		
Residence				
Ankara	122 (24.2%)	164 (27%)		
Black Sea	130 (25.7%)	141 (23.1%)		
East and Southeast	77 (15.2%)	97 (15.9%)		
Mediterranean	74 (14.6%)	82 (13.4%)		
Middle Anatolian	73 (14.4%)	90 (14.6%)		
Aegean and Marmara	28 (5.5%)	36 (5.9%)		
Weight, mean (SD)	69.9 (12.9)	69.5 (11.9)	0.79	0.61
Height, mean (SD)	157.6 (5.8)	155.5 (6.9)	4.1	0.000

excluded because of not knowing their exact ages at menarche and menopause (2.4% of eligible cases and 4.2% of eligible controls) was low and did not influence the results. Moreover, if the approximate menarche and menopause ages stated by these women had been included in the analysis, the results would not have changed. Recall bias, however, is always a possibility in retrospective studies such as this. We tried to prevent the probable limitations by careful and detailed conversation.

A potential limitation relates to the appropriateness of hospital controls instead of community controls. Our controls had a wide variety of diagnoses, unrelated to breast cancer (39). Furthermore, some of the controls visited this hospital for routine examination only, not for treatment, and the controls came from same areas as the cases.

BMI was not a risk factor as also found in some other studies (4, 5). Many previous studies have reported either a positive (6, 7) or an inverse (8) relationship between BMI and breast cancer risk.

Our study showed a decreased risk with high parity and an increased risk with nulliparity; both were insignificant. This does not support the common idea of high parity decreasing the risk and nulliparity increasing the risk (6, 9–20). A protective effect of high parity has not been found in some studies (21–23). A strong correlation was found between lactation and parity, and if lactation had been removed from the logistic regression, parity would have been found to be significantly protective, and nulliparity to be an increased risk factor. Therefore, our results do not accord with those of MacMahon et al. who found that high parity does not reduce the risk when age at first birth is taken into account (22). In a meta-analysis of eight studies, with the exception of one study (Meirik et al.), all studies showed a decreasing risk with increasing parity, but none of the studies included breastfeeding as a potential confounding variable; in three studies the relative risk was significant (18). In most of the studies nulliparity increases the risk (9, 14, 15, 17, 19–21, 24). In some reports nulliparity was not found to be a risk factor (18, 25). In our Turkish material, nulliparous women were not at increased risk of breast cancer compared to parous women (16).

Risk factors of breast cancer were now analysed in a population with exceptionally high fertility, and long duration of lactation. The women were frequently multiparous and showed low average age at first full-term pregnancy. Forty percent of the cases and 50% of the controls bore a child before the age of 20, compared with 31% and 44% in a South African study (26), and similar frequencies in many other studies (12, 16, 18, 20, 23, 27). Our population also had a higher frequency of high parity: 34% of the controls and 26% of the cases had more than four children compared with 15% and 12% in another study (27), and similar figures elsewhere (16, 18, 23, 26).

Since the report by MacMahon et al., age at first full-term pregnancy has been considered more important to the risk of developing breast cancer than parity. In an international study, MacMahon et al. showed that the breast cancer risk increased as the age at first birth increased (22). It has been stated by some authors that age at first full-term pregnancy is not an independent risk factor (20, 21). In our series it was a strong risk factor, which supports many previous studies (6, 9–12, 14–17, 19, 22, 24, 28).

Table 2

Distribution of 504 cases and 610 controls according to risk factors, and adjusted odds ratios (OR)[1] and 95% confidence intervals (CI)[1]

Factor	Cases	Controls	OR[1]	95% CI[1]	P or p for trend
Age at menarche					
<15	383	397	1.72	1.30–2.28	0.00
≥15	121	213	1[2]		
Menstrual irregularity					
Yes	54	49	1.61	1.05–2.49	0.03
No	450	561	1[2]		
Parity					
1–2	141	151	1[2]		0.25
3–4	173	222	1.15	0.78–1.68	
≥5	130	207	0.86	0.52–1.40	
Parous	444	580	1[2]		
Nulliparous	60	30	1.18	0.41–3.35	0.75
Age at first pregnancy					
<20	202	305	1[2]		0.06
20–24	144	213	0.95	0.70–1.27	
25–29	62	51	1.40	0.86–2.26	
≥30	36	11	2.86	1.32–6.21	
Breast feeding					
Never[3]	18	8	1[2]		0.035
<1 year	82	64	0.60	0.24–1.56	
1–<2 years	49	56	0.47	0.18–1.24	
2–<5 years	132	183	0.39	0.16–0.98	
≥5 years	163	269	0.31	0.12–0.79	
Body mass index					
<20	13	16	1[2]		0.45
20–24	142	133	0.92	0.40–2.08	
25–29	191	241	0.75	0.34–1.68	
30–34	109	158	0.66	0.29–1.50	
≥35	49	62	0.79	0.33–1.90	
Menopause					
Yes	254	242	1.16	0.41–3.35	0.45
No	250	368	1[2]		
Age at menopause[4]					
<40	25	24	1[2]		0.98
40–49	127	123	1.12	0.56–2.22	
50–54	79	71	1.05	0.50–2.21	
≥55	23	24	1.00	0.39–2.54	
Education					
<5 years	213	291	1[2]		
≥5 years	291	319	1.04	0.78–1.37	0.79
Previous benign biopsy					
Yes	23	27	1.03	0.56–1.90	0.91
No	481	583	1[2]		
Oral contraceptive use					
Never	385	507	1[2]		0.01
Ever	119	103	1.51	1.10–2.08	
Family history					
Yes	30	12	2.81	1.35–5.82	0.005
No	474	598	1[2]		

[1] Adjusted through logistic regression for age, residence, age at menarche, menstrual irregularity, parity, nulliparity, age at first pregnancy, breastfeeding, oral contraceptive use, family history, body mass index, education, previous benign breast biopsy, menopausal status and age at menopause.
[2] Reference category.
[3] Nulliparous excluded.
[4] Among postmenopausal women.

Our study confirmed that early menarche age was associated with an increased risk. In many previous studies (6, 15, 16, 21, 25, 27) the age at menarche was not found to be a risk factor, but in some other studies it was (9, 11, 19, 28).

Forty-four percent of our controls lactated for 5 or more years. These figures are probably among the highest ever reported including the study (13) from Brazil in which 19% of the cases and 28% of the controls lactated for more than 5 years, and a study from Atlanta (20), in which 24% of the controls lactated for 3 years or more. Because women in Turkey have more children and lactate for a longer period than women in most places elsewhere, examination of the relation between high parity and prolonged duration of lactation should be successful here. In many studies it has been suggested that long-term lactation does not reduce the risk of breast cancer (10, 13, 14, 20, 23, 26–35). On the other hand, there are reports of an independent protective effect of long-term lactation (15, 17, 21).

A Mexican study reported that long-term lactation decreases the risk compared with parous women who never lactated (15). In that study, the ORs were 0.52, 0.33 and 0.31, respectively, for women who had lactated 1–2 years, 3–5 years, and ≥ 5 years; the trend was significant. In our study, the risk gradually decreased as the duration of breastfeeding increased; the ORs were 0.39, and 0.31 for those who lactated 2– < 5, and ≥ 5 years, respectively. The trend was significant ($p = 0.035$).

Our findings also agree with reports that a positive family history of breast cancer is associated with an increased breast cancer risk (6, 9, 12, 15, 21, 24). In two studies, family history was not found to be a risk factor (25, 27).

Many epidemiological studies have been performed to evaluate the potential effects of oral contraceptive use and subsequent risk of breast cancer. When all studies were considered together, oral contraceptive use did not show a statistically significant increase in risk (19, 36, 37). In our study oral contraceptive use was a risk factor, and increased the risk (25, 38).

Menstrual irregularity was an independent risk factor, and increased the risk. Our results do not support most of the previous studies (13, 16, 21, 25). However, it has been reported that menstrual irregularity decreased the risk (6).

Our study confirmed that age at menopause was not a risk factor, in accordance with some other studies (6, 21, 23, 27), while many other studies reported that late menopause was a risk factor (9, 12, 13, 16, 19, 24).

The level of education of our subjects was higher than that of the controls, but education was not a significant risk factor. It has been reported that the years of education increase the risk of breast cancer (12, 24).

These overall findings suggest that first full-term pregnancy after the age of 29 years, menstrual irregularity, oral contraceptive use, age at menarche younger than 15 years, and positive family history increase breast cancer risk independently, and long-term lactation is protective against breast cancer.

The low incidence of breast cancer in Turkey is partially attributable to the special characteristics of the Turkish women, such as early pregnancy age, and long-term breastfeeding. The lifestyle of Turkish women is changing, and ready-made baby foods are increasingly being used. On the other hand, the Ministry of Health and the Turkish Medical Association strongly recommend breastfeeding. The idea that breastfeeding has a protective effect on conception is a common misconception among Turkish women. Fortunately, this belief causes the women to lactate for as long as possible. Controlling some parameters, such as pregnancy age and menarche age, is out of the women's own control. However, women are more able to control breastfeeding, which is good for both the mother and the baby, and therefore must be encouraged.

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