RESEARCH COMMUNICATION

Breast Cancer Risk Factors in Turkey: a Hospital-based Case–control Study

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Abstract

Background: Regional disparities in breast cancer (BC) outcomes have been reported in Turkey. Methods: In a hospital-based case-control study in Sivas, Turkey, 172 patients with histologically confirmed BC were compared with 383 controls, recruited from visitors in various departments of the same hospital, who had not been previously diagnosed with BC. Information was collected from both groups using a questionnaire and logistic regression analysis was applied to assess associations between each risk factor and BC risk with adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Results: In multivariable models, family history of BC (OR= 4.67, 95% CI: 2.23-9.76), history of smoking (OR= 1.75, 95% CI: 1.08-2.84), and higher education level (OR= 2.88, 95% CI: 1.64-5.07) were the strongest predictors of BC in the study population. A separate analysis studying only postmenopausal women using hormone replacement therapy (HRT) (comparing duration of use, >36 months versus ≤36 months, P<0.05) found that use of HRT was also a risk factor for BC. Duration of HRT use (P<0.05) was significantly associated with the elevated risk. On the other hand, certain factors such as first full-term pregnancy before age 30 ($\chi 2$=5.755 P<0.05) and higher parity ($\chi 2$=20.731, P<0.05) were found to be protective factors for BC. Conclusion: The findings of the present study indicate that family history of BC, history of smoking, education, and HRT are factors significantly associated with increased BC risk among Turkish women within the area of Central Anatolia, Turkey.

Keywords: Breast cancer - risk factors - case-control study

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Introduction

Breast cancer (BC) is reported to be the most common type of cancer in women worldwide, with an estimated 1.4 million cases in 2008 (Cuzick, 2010). Despite early BC detection by screening with mammography and improvements in modern treatment regimens, BC is currently the second leading cause of cancer death among women throughout the world. Research guiding individual disease management through the natural course of BC is important for increasing survival after BC diagnosis (Hellmann et al., 2010). Epidemiologic studies have shown that the incidence of BC has increased in developing countries, however, there is limited data about BC risk factors in these countries (Lotfi et al., 2008; Hadjisawas, 2010; Özmen, 2011).

Numerous risk factors have been associated with the development of BC, including familial/genetic (Czene et al., 2009), environmental, reproductive and hormonal (Parsa and Parsa, 2009) and nutritional (meat and fat consumption) (Ceber et al., 2005) influences. However, 75% of women who are diagnosed with BC have no risk factors (Amir et al., 2010), therefore, it is not possible to identify specific risk factors in the majority of cases (Lacey et al., 2009). The greatest increases of BC are in the developing world, where rates have traditionally been low (Cuzick, 2010). It has been postulated that the adoption of cancer-associated lifestyle choices including smoking, physical inactivity and "westernized" diets may contribute to these rising rates of BC (Jemal, 2011). Additionally, the lifespan of women in the developing world is increasing and thus many more women are reaching an age where BC rates are high (Cuzick, 2010). It is possible that the rates of BC in developing countries may approach rates seen in western country (developed country estimated new cases: 692.200; developing country estimated new cases: 691.300; woldwide: 1.383.500). About half the BC cases and 60% of the deaths are estimated to occur in economically developing countries (Jemal, 2011).

BC incidence has increased rapidly in Turkey recently. According to the Ministry of Health in Turkey, between 2003 and 2005 statistics showed a 1.54% increase in the incidence of BC (Ministry of Health of Turkey, 2005). Since the beginning of the 20th century, Turkey has been in a sociodemographic, cultural and economic transformation due to the increase in women's educational level. This transformation has also brought about many lifestyle changes, such as an increase in the habit of

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smoking, an increase in the age of marriage and first pregnancy, a decrease in the duration of breastfeeding and fertility and changes in dietary habits (Ceber et al., 2005). Many of these behaviors may have contributed to the increase of BC.

Sivas is a region of Turkey located in Central Anatolia that has a population of about 603,000. The lifestyle in Sivas is considered traditional, with women getting married at an early age, having children at a young age, having multiple births and breastfeeding. In Turkey, the number of studies focused on BC to determine the incidence and risk factors of BC is very small and restricted to a limited number of subjects. Therefore the main aim of this study was to assess the strength of associations between recognized risk factors and BC among Turkish women residing in the urban area of Central Anatolia. The results of this study can contribute to a better understanding of the specific risk factors for BC in a developing country.

Materials and Methods

Design and sample

The present hospital-based case-control study collected information on women aged 35-60 years who resided in the urban areas of Central Anatolia. Age was matched for both the case and control groups (with an interval of ± 2 years).

This study was completed in the Department of Oncology at the Research Hospital at Cumhuriyet University located in Sivas, Turkey. According to clinic records in the Department of Oncology, in 2010 there were 203 individuals who had a histologically confirmed diagnosis of primary BC. Using the telephone numbers included in the clinic files, investigators contacted the women to see if they wanted to participate in the study. Information about the aim and method was provided over the phone and the women were invited to the oncology clinic for data collection. A total of 172 women agreed to participate in this study as the case group.

For the control group, women with similar sociodemographic characteristics as the case group were selected from female visitors at the same hospital A total of 383 women were identified as candidates for the control group. To qualify as a control, the women could not have any previous diagnosis of BC and have no other illness. In order to match the controls the case group, the women also had to be 35 years or older. Three hundred and eighty-three women consented to participate in the study as controls. All women who were invited to participate in the study were explained that that their participation in the study was strictly voluntary, that they could withdraw at any stage and that their confidentiality would be maintained. Inclusion criteria included age, being 35 years or older, and willingness to participate. Researchers contacted the subjects, both the cases and the control group, at the hospital and administered questionnaires for data collection.

Instrument

The information for this study was collected using a self-administered questionnaire survey. A structured quantitative questionnaire was developed by the researchers of this study that was adopted from a survey used in previous studies (Lotfi et al., 2008; Beji and Reis, 2007; Özmen et al., 2009).

The questionnaire consisted of 20 questions collecting information about the following: general characteristics of the women (age, education, marital status, body mass index (BMI), chronic diseases, smoking and alcohol use), menstrual and reproductive history [parity, age at first birth, breastfeeding, age at menarche, age at menopause, oral contraceptive (OC) use and hormone replacement therapy (HRT) use] and family history of BC (first-degree relatives).

Categorization

The following cut-off points were used to define each category. In the case of age at first delivery, we chose a cut-off point of 30 years old. For parity, the cut-off point was 2. BMI was calculated as weight (kg)/height (m2) and BMI calculations were divided into two categories (normal weight and obese). BMI of ≤29 kg/m2 was defined as normal, while >29 kg/m2 was defined as obese. In the case of age at menarche, we chose a cut-off point of 12 years based on many observations that the onset of menarche occurred most frequently at 12 years old. Educational level was divided into two categories depending on the number of school years attended, <11 years was considered low level, and ≥11 years was high. Smoking habits were classified into two categories. Smokers were defined as those individuals who were currently smoking or had given up smoking within one year before the diagnosis. Non-smokers were subjects who had never previously smoked. A similar definition was used to categorize drinking habits. Drinkers were individuals who classified themselves as occasional drinkers and had alcohol at least one year before the diagnosis of BC. Non-drinkers were subjects who had never previously had alcohol. For menopause and physical exercise, women were categorized into groups of 'Yes' or 'No'. To collect information on family history, women were defined as having a history of BC and placed in the group 'Yes' if they had a mother or sister previously diagnosed with BC. For analyzing the association between body weight and BC risk, weight one year prior to the diagnosis was used since many cancer patients lose weight as the disease progresses.

Data Collection

Interviews with both case and control groups were conducted face-to-face by researchers at the hospital Before the interview, the investigators introduced themselves, explained the aim of the study and obtained informed consent from all subjects. Demographic and risk factor data was collected from both cases and controls using a customized questionnaire as well as personal interviews.

Statistical Analyses

The data was evaluated with the chi-square test and logistic regression analysis using SPSS 15.0 software,

odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. The chi-square test was used to identify factors to enter into the logistic regression model. A separate analysis among postmenopausal women on the association between hormone replacement therapy use (duration of use >36 months versus ≤36 months) and BC was performed with the Fisher's exact test. In the logistic regression analysis, the enter technique was used to generate the logistic regression model for determination of the independent predictors of BC. The Hosmer and Lemeshow test was used to asses the fitness of the model; a P=0.151 indicated that the model fit quite well. A P-value of <0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Institutional Ethics Board of The University Medical Faculty. This study complied with the principles described in the Declaration of Helsinki.

Results

Description of the sample

Demographic characteristics of cases and controls were similar between the two groups. Among the cases, 13.4% were in the ≤39 age group, 33.1% in the 40-49 age group and 53.5% in the ≥50 age group. The distribution of cases (n=172) and controls (n=383) by age, education, BMI, smoking, alcohol use, physical exercise and family history of BC (first degree relatives) is shown in Table 1.

The analysis showed that education ($\chi2$ = 42.35, df =2, p <0.05), smoking ($\chi2$ = 8.49, df =1, p <0.05), and family history of BC ($\chi2$ = 19.74, df = 1, p <0.05) were associated with BC. A separate examination analyzed the distribution of BMI in cases and controls within the menopause subgroups (yes vs. no). There was no significant difference between cases and controls in the subgroups regarding BMI ($\chi2$ =0.22, df = 1, p >0.05 for the 'no' menopause subgroup; $\chi2$ = 0.656, df = 1, p >0.05 for the 'yes' menopause subgroup). The distribution of cases and controls by menstrual and reproductive factors (age at menarche, menopause, parity, age at first birth, breast feeding, OC use, HRT use and its duration during post menopause) are shown in Table 2.

Among these menstrual and reproductive factors, two of these variables (age at first birth $\chi2$ = 5.76, df = 1, P<0.05, and parity $\chi2$ = 20.73, df = 1, P<0.05) were

Table 1. Distribution of Cases and Controls According to Selected Characteristics of Breast Cancer

Factor	Case n% (n=172)	Control n% (n=383)	Test $\chi2$	P-value
Age (years)				
≤39	23 (13.4)	53 (13.8)	0.042	>0.05
40-49	57 (33.1)	124 (32.4)		
≥50	92 (53.5)	206 (53.8)		
Education				
Non-literate	54 (31.3)	117 (30.5)	42.35	<0.05
Intermediate	67 (39.0)	231 (60.3)		
≥High school	51 (29.7)	35 (9.1)		
Body mass index				
≤29 kg/m^2	77 (44.8)	161 (42.0)	0.361	>0.05
>29 kg/m^2	95 (55.2)	222 (58.0)		
Family history of breast cancer [first-degree relative(s)]				
Yes	24 (14.0)	14 (3.7)	19.74	<0.05
No	148 (86.0)	369 (96.3)		
Physical exercise				
Yes	32 (18.7)	66 (17.2)	0.154	>0.05
No	140 (81.3)	317 (82.8)		
Smoking				
Never	120 (69.8)	310 (80.9)	8.491	<0.05
Ever	52 (30.2)	73 (19.1)		
Alcohol				
Never	167 (97.1)	378 (98.7)	Fisher's	>0.05
Ever	5 (2.9)	5 (1.3)	Exact test	

Table 2. Distribution of Cases and Controls According to Reproductive History and Menstrual Factors

Factor	Case n% (n=172)	Control n% (n=383)	Test $\chi2$	P-value
Age at menarche				
≤12	91 (52.9)	212 (55.4)	0.286	>0.05
>12	81 (47.1)	171 (44.6)		
Menopause				
Yes	94 (54.7)	200 (52.2)	0.282	>0.05
No	78 (45.3)	183 (47.8)		
Parity				
Nullipara	15 (8.7)	18 (4.7)	20.73	<0.05
1	14 (8.1)	18 (4.7)		
2	51 (29.6)	67 (17.5)		
≥3	92 (53.5)	280 (73.1)		
Age at first birth				
<30	147 (93.6)	357 (97.8)	5.755	<0.05
≥30	10 (6.4)	8 (2.2)		
Breast feeding				
Never	17 (10.8)	26 (7.1)	1.993	>0.05
Ever	140 (89.2)	339 (92.9)		
Oral contraceptive use				
Never	131 (76.2)	312 (81.5)	2.069	>0.05
Ever	41 (23.8)	71 (18.5)		
HRT use (postmenopausal period)				
Never	79 (91.3)	181 (95.0)	2.607	>0.05
Ever	15 (8.7)	19 (5.0)		
Duration of HRT (months)				
≤36	8 (53.3)	17 (89.5)	Fisher's	<0.05
>36	7 (46.7)	2 (10.5)	Exact test	

Table 3. The Results of Logistic Regression Analyses of Family History and Modifiable Risk Factors for Breast Cancer

Factor	B	SE	df	Sig.	Exp(B)	95.0% CI for OR Lower	Upper
Family history of breast cancer							
No (Reference category)							
Yes	1.540	0.376	1	<0.05	4.67	2.23	9.76
Smoking							
Never (Reference category)							
Ever	0.559	0.248	1	<0.05	1.75	1.08	2.84
Education (years)							
<11 (Reference category)							
≥11	1.057	0.289	1	<0.05	2.88	1.64	5.07
Age at first birth							
<30 (Reference category)							
≥30	0.392	0,540	1.	>0.05	1.48	0.51	4.26
Parity							
>2	0.339	0.24	1	>0.05	1.40	0.88	2.25
(Reference category)							
≤2							

found to be associated with BC. The five factors that were significantly associated with BC were included in the logistic regression model. Logistic regression analysis (Table 3) resulted in the following adjusted odds ratio of BC: women with a first degree family history of BC (OR=4.67, 95% CI: 2.23-9.76), smoking (OR=1.75, 95% CI: 1.08–2.84), and for education ≥ 11 years, (OR=2.88, 95% CI: 1.64–5.07). The adjusted odds ratio of BC for the women with a parity ≤ 2 was higher than women with a parity of >2, but without statistical significance (OR=1.40, 95%CI: 0.88-2.25). For women ≥30 years of age at their first birth, the adjusted odds ratio of BC was also not found to be significant, though higher than women <30 years of age at first birth (OR=1.48, 95%CI: 0.52-4.51). Although the distribution of postmenopausal women using HRT was not significantly different among cases and controls (Table 2), the percentage of women using HRT for longer than 36 months was significantly higher (P<0.05, Fisher's exact test) in the women with BC (46.7%) compared to the controls (10.5%).

Discussion

The findings of this hospital-based case-control study have identified several factors among women residing in the urban area of Central Anatolia of Turkey that are risk factors for BC. The factors that were found to be significantly associated with BC in this study include having over 11 years of education, a family history of BC (first-degree), a history of smoking and use of HRT for greater than 36 months. On the other hand, several factors were also found to be protective factors for BC; first full-term pregnancy before the age of 30 and parity greater than 2.

Previous studies that were similar to our study have determined the following as risk factors of BC: higher education (Beji and Reis, 2007; Naieni et al., 2007; Fujino et al., 2008; Yilmaz et al., 2011), positive first-degree family history (Naieni et al., 2007; Lotfi et al., 2008), and delay in the age of the first delivery, (>22 age) (Lotfi et al., 2008), (≥35 age) (Özmen et al., 2009) Whereas other studies (Lee et al., 2004; Özmen et al., 2009) found that higher education was a protective variable for BC. In our study, the level of education was an independent risk factor and increased the risk of BC. The relationship between education and BC may be related to lifestyle differences that occur in women with higher education, such as >25 age at first birth, number of births ≤2, smoking or breastfeeding (never breastfed or inadequately breastfed). Positive family history of BC is one of the most well established risk factors and is widely accepted as the strongest risk factor for this disease. A family history of female BC is associated with an increased risk of BC in first-degree female relatives by approximately two-fold, however, the magnitude of risk depends on a number of factors such as age at diagnosis (Brant et al, 2010). The results of our study that showed an increase in the risk of BC associated with positive family history is consistent with the findings of previous studies (Kuru et al., 2002; Brant et al., 2010; Hadjisavvas et al., 2010).

Smoking and drinking has been linked to an elevated risk of BC in several studies. The prevalence of smoking in Turkey is increasing especially among women as a result of increase in the level of women in education and of participation working life. One-sixth of women are smokers and the smoking prevalence among women in Turkey is 24% (Bilir et al., 2010). Our finding that smoking was associated with an increased risk of BC is consistent with the results of Conlon et al. (2010) and Ceber et al. (2005), but disagree with our study the findings of Özmen et al. (2009). Alcohol has also been consistently associated with an increased risk of BC (Lew et al., 2009), however, our study did not identify alcohol as a risk factor. This result may be due to the low number of women who consumed alcohol in the region of Turkey where the study took place.

Previous studies (Russo et al., 2005; Naieni et al., 2007) have identified higher parity as a protective factor for BC, similar to the results of our study. The influence of parity on the risk of developing BC is also related to maternal characteristics such as age, family history, lactation postpartum, and multiparity. Women who gave birth to a child when they were younger than 24 years of age exhibit a decrease in their lifetime risk of developing BC, and additional pregnancies increase the protection (Russo et al., 2005). The mechanism of parity for reducing BC is related to the changes in the hormonal profile of parous women. It is postulated that a mammary gland that is more differentiated is less susceptible to changes within specific epithelial cell subpopulations (Britt et al., 2007). One study (Tamakoshi et al., 2005) has found that women with a parity of four or more had a 69% lower risk of BC than uniparous women. Those women who had their first delivery before the age of 25 also reduced their BC risk compared to those who delayed this event until after age thirty-four.

Investigators (Britt et al., 2007; Parsa and Parsa, 2009) reported that the protective effect of pregnancy on BC may be due to prolactin levels, which are substantially lower in multiparous women than in nuliparus women. Multiparous women also have lower levels of circulating estradiol and a higher level of bioavailable or free estradiol that may contribute to the protective effect. In the present study, parity and age at first live birth was found to be negatively associated with the risk of BC. In our study, however, the majority of women in both the case and control groups were less than 30 years of age at first birth. Many women in our study also breastfed their children. When comparing the cases to the controls, there were fewer cases who had ever breastfed. Based on this finding we can conclude that breastfeeding is protective against BC, however, these results were not found to be statistically significant. In the most recent studies (De Silva et al., 2010; Liu et al., 2011) it was found that prolonged breastfeeding significantly reduced the risk of BC and this protective effect was supported by a dose–response relationship. The result of this study may be due to a women number.

In this study we showed that there was no significant difference between the cases and controls who were using HRT. However, the percentage of women with HRT use longer than 36 months was found to be significantly higher among the postmenopausal cases using HRT than

among the postmenopausal controls using HRT (46.7% versus 10.5%). The Collaborative Group Study (1997), which is a metaanalysis based on 51 epidemiological studies, showed that HRT use after menopause has been associated with an increased risk of BC. The risk of having BC diagnosed is increased in women using HRT, which appeared to increase with the duration of use. The WHI (Women's Health Initiative) Study (2002) confirmed an increase in BC risk of about 26% over 5.2 years with combined estrogen/progestin therapy. A study in Turkey (Beji and Reis, 2007) also found the use of HRT to be associated with BC. However, a recent Japanese survey showed a significant negative correlation between HRT use and BC (Saeki et al., 2008).

Epidemiological, clinical, and experimental data indicate that the risk of developing BC is strongly dependent on the ovary and on endocrine conditions modulated by ovarian function, such as early menarche and late menopause (Russo et al., 2005). Both early age at menarche and delayed first full-term birth are factors that contribute to the susceptible period of time for BC development due to the prolonged exposure of undifferentiated breast tissue to mitogenic estrogen and progesterone (Li et al., 2008). The mechanisms of carcinogenesis in the breast caused by estrogen include the metabolism of estrogen to genotoxic, mutagenic metabolites and the stimulation of tissue growth (Yager et al., 2006). In one study (Oran et al., 2004), menopausal status has been shown to be significantly associated with BC in Turkey. But, the present study found no association between the occurence of menopause, early age at menarche, delayed first full-term birth, use of OC, breastfeeding, physical activity and obesity with the risk of BC. Obesity is a common and modifiable risk factor, investigators from a recent study claim that intervention strategies for obesity can have a substantial impact in reducing BC incidence and mortality (Sinicrope and Dannenberg, 2011). Physical activity is one of the most important strategies for reductions of obesity. According to the results of other studies (Suziki et al, 2008; Peters et al., 2009), it has been suggested that physical activity is protective for BC. Hellmann et al. (2010) found that moderate physical activity for 2–4 hours/week and high physical activity for more than 4 hours/week showed no association with increased survival after BC diagnosis.

The results from this study must be considered in light of certain limitations. First, the study was carried out in a small group of 172 cases over one year. Another limitation of the study is that all of the data was obtained from the women's self-reports. All of the information provided to the investigators may not be reliable, since some of the questions were too difficult for them to remember; i.e. the age of menarche and history of BC in relatives. However, the findings and limitations of the study are quite useful in that they contribute to the progressive research in this field. Also, this study was performed in a developing country where changes in lifestyle may provide important information about the risk factors of BC.

In conclusion, the results of this study show that a family history of BC, smoking, higher education level, and duration of HRT use were associated with BC risk among Turkish women living in Central Anatolia. Women living in this region should increase their awareness about BC and the associated risk factors. More studies are recommended to explore other determinants of BC in Turkey.

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