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RESEARCH ARTICLE

Risk Factor Mapping Associated with Breast Cancer: A National-Based Study

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ABSTRACT

Objective: Many risk factors have been associated with breast cancer (BC) in years. The objective of our study was to predict possible risk factors related to BC and to contribute national and global screening programs.

Materials and Methods: A case–control study was created among women who were examined at the department of Surgery, Oncology Institute, Istanbul University, between January 2009 and December 2015. The patients were divided into two groups as 1006 women with BC diagnosis and and 3439 women witout BC. A database was formed by questioning demographics, clinical characteristics of patients, and the possible factors that could be associated with BC were analyzed.

Results: According to the results of the study, high education level and being postmenopausal were found to be closely related to BC (p<0.0001). In addition, as having history of smoking (Odds Ratio [OR] 2.3; 95% confidence interval [CI]: 1.2–4.7, p=0.02), as having first-degree relative with BC (OR 2.4; 95% CI: 1.1–5.3, p=0.03), as having a member in family with BC under the age of 50 (OR 3.1; 95% CI 1.9–8.1, p=0.005), as being high body mass indexed-patient (OR 1.2; 95% CI: 1.1–1.3, p=0.001), such as not giving birth (OR 2.1; 95% CI: 1.2–4.6, p=0.01), and used postmenopausal hormone replacement therapy (OR 2.88; 95% CI: 0.02–2.4, p=0.049) were identified as important risk factors associated with BC.

Conclusion: This present study has determined national-based significant risk factors associated with BC. We can surely extrapolate that this study is one of the important briefs to support national and also worldwide risk models and screening programs.

Keywords: Breast cancer, risk assessment, risk factors, screening program

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INTRODUCTION

Breast cancer (BC) remains a major public health problem. The incidence is rising in most countries and is projected to rise further over the next 20 years despite current efforts to prevent the disease.[1,2] Given global increases in population growth and the strong evidence that a woman's ability to control her fertility may improve her social, economic, and overall health, it is not considered desirable to increase the birth rate per woman or to encourage pregnancies at a very young age; therefore, globally evidence-based risk factor determinations have become more important to prevent BC.

When we reduce this condition to the national basis, according to our national database, it is not difficult to predict that the incidence of BC increases in older or postmenopausal women such as among worldwide women population. In addition, it is seen that the frequency of BC in the east of our country is at least 2 times less. The probability of conducting a study with a high level of evidence that can analyze the demographic, environmental, and genetic factors that can clearly reveal the causes of more frequent cancer in the West is very low. With the analysis of the results of the national database and the federation of breast associations, and the analysis of the data consisting of observational studies, in which information on frequency such as incidence and prevalence are shared, it can be concluded that the western lifestyle causes an increase in the risk of BC.[3,4]

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Habbits in lifestyle have been associated with BC; alcohol consumption causes blood estrogen levels to rise, resulting in an increased risk of BC. High-grade alcohol consumption of two glasses or more per day is associated with a marked increase in cancer risk. It has been reported that there is an increase in hormone receptor positive breast ca cases, especially with alcohol consumption. This can be explained by the fact that alcohol contributes to the increase in estrogen levels.[5,6] Regular sportive activity is associated with a reduced probability of developing BC, especially in premenopausal women. This is explained by the fact that especially high-tempo exercises cause un-ovulation.[7–10]

It is known that the presence of genetic mutation is an important factor in itself. Here, in defining the genetic risk and mutation, the risk of BC varies depending on whether the mutations in the causative gene have low, medium, or high penetrance. In other words, not all genetic mutations increase the risk of BC equally. Therefore, in determining the genetic risk, it is important what kind of genetic problem is there and in which group the responsible genetic mutation is categorized in terms of penetrance. Genes whose clinical importance is known and should be emphasized are BRCA-1 and BRCA-2 genes causing familial breast-ovarian cancer syndrome, TP-53 gene seen in Li Fraumeni syndrome and PTEN seen less frequently in Cowden syndrome. The relationship between mutations in these genes and BC has been clearly demonstrated and has been defined in international guidelines.[11–13]

In addition to known risk factors, there are models (such as the Claus and Gail methods), in which the risk is evaluated by questioning the family history. MYRIAD II, BOIDICEA, and BRCAPRO can be given as examples of computer-aided programs used for this purpose.[14–16]

The association of BC risk factor with reproductive history is related to the duration of exposure to estrogen. Estrogen level and duration of exposure to estrogen are associated with the function of the ovaries. The main source of estrogen in the postmenopausal period is dehydroepiandestronesulfate, which is produced from the adrenal gland. Surrenally produced, this dehydroepiandestronesulfate is converted to estrogen subtypes in adipose tissues. In this context, conditions associated with prolongation of the duration and amount of estrogen exposure may increase the incidence of BC. On the other hand, the differentiation that occurs in the epithelium that forms the breast duct structure with pregnancy is considered to be protective. Along with this, it is thought that the number of term pregnancies is as important as the number of pregnancies. Not having given birth increases the relative risk by 1.5 times.[17–20]

In the light of all this information, the researchers aimed to create a Turkish woman-spesific clinical and genetic risk mapping by analyzing all potential risk factors and to support national and also global screening programs and models with these results.

MATERIALS and METHODS

Study Protocol

A case–control study was conducted among women who addmitted to Istanbul University, Oncology Institute, Surgical Oncology Outpatient Clinic between January 2009 and December 2015. All patients who addmitted for the examination filled out a standard BC risk assessment form, and clinical examinations were performed and appropriate imaging methods, due to malignancy suspicion, needed core needle biopsies, or axillary fine needle aspiration biopsies were requested to prove or exclude the presence of BC. The patients were divided into two groups as patients diagnosed with BC and patients without BC. Standard question including age, education, social status, body mass index (BMI), smoking and alcohol use history, menstrual and reproductive history (age at first birth, number of births, miscarriage and abortion numbers, and breast-feeding history), and family history of BC evaluated with the form.

In the light of the data obtained, the importance of possible risk factors for BC in Turkish women was investigated.

At the beginning of the study, the approval of Istanbul University, Oncology Institute Academic Coordination Committee was obtained. All interviews were conducted face-to-face with patients and direct questions and clinical evaluation.

BMI was calculated using the weight (kg)/height squared (m^2) method.

Statistical Analysis

The obtained data were recorded with Microsoft Excel program. Factors associated with BC were evaluated together with odds ratios at 95% confidence intervals. Chi-square test was used to compare categorical variables, and Student t-test was used to compare continuous variables. A logistic regression model was created for the multivariate analysis of risk factors associated with BC. Forward regression model was preferred for the evaluation of factors with a frequency of more than 10% and a univariate significance level of <0.05. Statistical analysis was performed with SPSS 22.0 (SPSS Inc, Chicago, Illinois) program and p value less than 0.05 was considered significant.

RESULTS

According to sociodemographic (age, education, BMI, smoking, and alcohol use history (independent of total duration), family history of BC, menstrual, and reproductive characteristics) of BC patients (n=1006) and control cases (n=3439), distribution is shown in Table 1.

The mean age of the groups was in a similar distribution and no difference was found (p=0.75). It was determined that BC patients were overweight and their BMIs were higher in the BC group (p<0.0001). It was observed that the patients in the BC group had a higher education level, smoked more, were more often postmenopausal, and had a higher familial incidence of BC. In patients with a family history of BC, it was determined that the incidence of BC before the age of 50 (p=0.05) and first-degree relatives (p<0.0001) was statistically higher in the group of BC patients.

A close relationship was found between the reproductive history and the incidence of BC (p<0.05). A history of more births, miscarriages and abortions, and cases where the age at first birth is below 35 and breast-feeding history were found to be advantageous to reduce the risk of BC developement. In the BC group, use of hormone replacement therapy among postmenopausal women (p<0.0001) and duration longer than 5 years (p<0.0001) were more common. A similar relationship was not observed in oral contraceptive use (p=0.44). It was noted that the history of ovulation induction was higher in the BC group (p<0.0001).

According to the results of the logistic regression analyzes, high educational status and being postmenopausal were found to be closely associated with the development of BC. In addition, having a history of smoking (odds Ratio [OR] 2.3; 95% confidence interval [CI] 1.2–4.7, p=0.02), having a family history of first-degree BC (OR 2.4; 95% CI 1.1–5.3, p=0.005) and having a family history of BC <50 years of age (OR 3.1; 95% CI 1.9–8.1, p=0.03), history of birth (OR 2.1; 95% CI 1.2–4.6, p=0.01), use of postmenopausal hormone replacement therapy (OR 2.88; 95% CI 0.02–2.4, p=0.049), and high BMI (OR 1.2; 95% CI 1.1–1.3, p=0.001) were found to be significant factors in women with BC (Table 2).

DISCUSSION

With regard to BC risk factors, risk estimation models can be used to determine who will benefit most from screening. Current practice in BC prediction focuses on determining BC risk over time and/or probability of being a BRCA1 or BRCA2 mutation carrier. Many predictive models have been developed to identify individuals at a higher-than-average risk of developing BC. Models evaluate many factors such as family history, hormonal and reproductive history, and other personal and environmental factors.[21]

Frequently used models such as Claus, Gail, and Rosner-Colditz have been used to determine the expected cumulative BC risk over time.[22,23] The Claus model calculates the risk using only the number and degree of relatives affected by BC, and the age of onset of the disease. While direct and useful for those with a family history, this model is not a valid method for calculating risk, lifestyle, environmental, or non-Mendelian genetic risk factors. When only family history is included, it can lead to inaccurate risk estimation, as close relatives are less likely to be affected in younger patients (especially in the 20–29 age group). These models used are models that have been used in Europe and United States for many years and were developed by epidemiological studies conducted there.[24,25]

Considering that BC is multifactorial and the importance of genetic and environmental factors in cancer development, it is of great importance that we create our own epidemiological data and shape our own models according to our own epidemiological data. In this context, it can be thought that this study, which is carried out with the analysis of a large number of parameters, will also constitute an important step for the development of our own models.

The incidence of BC increases with age, doubling approximately every decade until menopause. According to a population-based study, two out of 1000 women aged 50 years old are diagnosed with BC, and approximately 15 of them are diagnosed with BC before the age of 50. The prevalence of BC is approximately 2%.[26] When women participating in the study are categorized according to age and age-related menopausal status, it is seen that BC incidence increases significantly in postmenopausal women over 50 years of age. Although our study was a questionnaire-based study, the menopausal status was questioned and it was found that the postmenopausal status, which can be considered as another indicator of the increase in patient age, is closely related to BC and statistically significant.

In many studies, it has been reported that the incidence of BC increases with the increase in education level and sociocultural level.[27–29] Here, the reasons for the increased risk were thought to be more frequent hormone replacement therapy history, late first birth age, less breast-feeding, obesity, and changes in dietary habits.

Our findings also show that BC is more common in patients with a reproductive history that can be defined as lifestyle

Table 1. Frequency and relationship of possible risk factors in control group and breast cancer group

	Control group (n=3439)		BC group (n=1006)		p
	n	%	n	%	
Age, avarage, SD	51.7 (10.9)		51.8 (12.9)		0.75
BMI, mean±SD	26.5±3.2		27.5±5.3		0.000
Education level					
None	143	4	11	1	0.000
Primary school	1880	55	493	49	
High school	778	23	282	28	
University	638	19	220	22	
Smooking history					
Absence	2771	81	771	77	0.006
Presence	668	19	235	23	
Alcohol history					
Absence	3398	99	993	99	0.8
Presence	41	1	13	1	
Menopausal status					
Premenopausal	837	53	467	46	0.000
Postmenopausal	1602	47	539	54	
Family history of BC					
Negative	3097	90	851	85	0.000
Positive	342	10	155	15	
Age of BC developement in family					
≤50	65	19	40	26	0.05
>50	277	81	115	74	
First-degree relative with BC					
Absence	303	89	114	74	0.000
Presence	39	11	41	26	
Birth history					
Absence	831	24	576	57	0.000
Presence	2608	76	430	43	
History of abortion					
Negative	2831	82	936	93	0.000
Positive	608	18	70	7	
History of miscarriages					
Negative	2071	60	882	88	0.000
Positive	1368	40	124	12	
Age of first birth					
≤35	2472	95	389	90	0.001
>35	136	5	41	10	
History of breastfeeding					
Negative	88	3	66	15	0.000
Positive	2520	97	364	85	

Table 1. Cont.

	Control group (n=3439)		BC group (n=1006)		p
	n	%	n	%	
HRT					
Negative	3181	93	857	85	0.000
Positive	258	7	149	15	
Duration of HRT					
≤5 years	202	78	79	53	0.000
>5 years	56	22	70	47	
Use of OC					
Negative	2279	66	680	68	0.44
Positive	1160	34	326	32	
Duration of OC treatment					
≤5 years	990	85	286	88	0.32
>5 years	170	15	40	12	
Ovulation induction					
Negative	3351	97	908	90	0.000
Positive	88	3	98	10	
Chronic disease					
Absence	3246	94	937	93	0.15
Presence	193	6	69	7	

Data are given in number and percentage, unless otherwise stated. P<0.05; Chi-square test (Pearson Chi-square, continuity correction, Fisher's exact test). Independent t-test to estimate the average of age and the mean of BMI. BC: Breast cancer; SD: Standard deviation; BMI: Body mass index; HRT: Hormone replacement therapy; OC: Oral contraceptive

of western side of country and accompanied by relatively higher education levels. Although this condition seems to be a disadvantage, according to the data of the Federation of Turkish Breast Diseases Associations and the Ministry of Health, although BC is more common in the west of the country, the stage of the cases seen is seen to be earlier. This finding makes this disadvantage to a advantage in treatment.

The results of studies questioning the relationship between smoking and BC are inconsistent. In some studies published in recent years, it has been reported that the risk of BC is increased among women who have smoked for a long time and/or started smoking before their first pregnancy.[30–34] The Canadian National Breast Screening Study is based on BC with long-term smoking (>40 years smoking, OR:1.50 for never-smokers), heavy smoking (>2 pack/day smoking, OR:1.20 versus never-smoker), or cumulative exposure to cigarettes which reported that there is a significant relationship between smoking cessation (>40 pack-year smoking, OR:1.17) according to never-smokers.[35] It can be thought that smoking has antiestrogenic effects. Estrogen is actually a well-understood risk factor for BC. Estrogen is actually a well-understood risk factor for BC. Smoking causes the age of menopause to be earlier and may protect against BC with its antiestrogenic effect. In our study results, a relationship was found between BC and smoking, and smoking attracted attention as a disadvantage in the development of BC. The point that should be underlined is that analyzes related to smoking intensity and duration that were not made in our data. It is known that smoking has many potential harms, increases the frequency of heart and vascular and neurological diseases, and is associated with many cancers (such as lung, esophagus, and larynx cancers).

One of the most important risk factors for BC is a family history of BC.[36] Consistent with previously published studies, a higher rate of BC was detected in patients with a family history of BC. Having a family history in first-degree relatives

Table 2. Evaluation of possible risk factors with logistic regression analysis

	OR	CI (95%)	p
Educational level (None/Primary school vs High school/University)	4.4	2.3–8.5	0.000
History of smooking	2.3	1.2–4.7	0.02
Menopausal status	4.2	2.1–8.4	0.000
History of BC <50 of age in family	3.1	1.9–8.1	0.005
History of first-degree relative with BC	2.4	1.1–5.3	0.03
BMI (<25 vs>25)	1.2	1.1–1.3	0.001
History of birth	2.1	1.2–4.6	0.01
First birth under the age of 35	0.9	0.6–1.9	0.09
History of abortion	0.8	0.3–2.2	0.67
History of miscarriages	0.66	0.34–1.3	0.22
History of breastfeeding	0.31	0.08–1.17	0.08
HRT	2.88	1.01–8.24	0.049
History of ovulation induction	0.24	0.02–2.4	0.23

Odds ratios are presented with their 95% confidence interval and p value. OR: Odds ratio; CI: Confidental interval; BC: Breast cancer; BMI: Body mass index; HRT: Hormone replacement therapy

seems to increase the risk more. Regardless of family history, the presence of genetic mutation was not questioned in our study. It is thought that the frequency of genetic mutations and the frequency of mutation-related BC in BC patients are not more than 5–10%. The presence of mutation causes the patient to enter the very high-risk group and requires the application of risk-reducing treatments. These patients were diagnosed as a result of mutation screening in the light of clinical and pathological information in addition to a high family history. The aim of our study is not the population of patients who are currently diagnosed with genetic analysis as very high risk. It is the determination of the high-risk patient population other than the patients with known and detected genetic mutations.

There are studies that draw attention to the relationship between obesity and BC. It has been shown that the risk of BC increases significantly in women with a BMI of 25 and above.[37–41] It has been reported that especially the risk of BC is associated with weight gain in the postmenopausal period. In our study, it was noted that the BMI values of BC patients were higher and this factor was statistically significant. Our findings indicate that obesity is one of the important factors in the development of BC. Our study is important in terms of shedding light on the consideration of obesity as a modifiable and controllable factor in the determination of national health policies with preventive medical studies.

It has been reported that the age at first birth being 35 and over increases the risk of BC, and our data support this information. Delayed age at first birth may delay proliferation of terminal ducts in the mammary gland, and increased epithelialization sensitive to carcinogenic damage may be responsible in these women. Similarly, it has been shown that breastfeeding and long duration of breastfeeding reduce the incidence of BC.[42–45] Kim et al.[46] reported that the risk of BC in women with an average breastfeeding duration of 11–12 months was 54% lower than those who breastfed for 1–4 months. In a similar study conducted at our breast surgery clinics, it was found that breastfeeding reduces the risk of BC.[24] In our study, it is noteworthy that BC is less common in women who are breast-feeding, similar to the literature and the study published previously. However, although the logistic regression analyzes showed that breast-feeding and having the first birth under 35 years of age were associated with BC risk, the difference was not statistically significant. It was thought that this relationship could be shown more clearly in studies with a higher number of patients. It was found significant in our previously published study that spontaneous abortion reduces the risk of BC. In the EPIC study, the relative risk of BC was found to be higher in those who had never had a spontaneous abortion.[47] On the other hand, it has been reported that induced abortion increases the risk of BCin women under 50 years of age and decreases it in women over 50 years of age.[48] In general, it can be said that the number of pregnancies

decreases the risk of BC. In our study, there was no difference between spontaneous or induced (abortion) abortion. In both cases, a decrease in the incidence of BC is remarkable.

Many epidemiological studies have commented that the use of hormone replacement therapy after menopause is a trigger for BC.[49–52] It can be said that there is a consensus that there is no relationship between oral contraceptive use and history of ovulation induction and increased cancer risk.[53,54] Our study results are consistent with the literature, but it can be said that dose and time-scheduled studies with a larger number of patients should be conducted to test our findings, since they are dose and time independent.

CONCLUSION

According to the national evaluation, between education level, smoking history, postmenopausal status, birth history, postmenopausal hormone replacement therapy, obesity, a first-degree relative under the age of 50 diagnosed BC, and in the developement of BC, significant close relationships were determined. The differences between our study and other studies in the literature may be caused due to the characteristics of Turkish women.

In this context, we think that this and similar studies, in which we can use our own demographic and clinical findings, will guide the determination of national health policies, of course comprimizing global BC risk models. With the national risk analysis models to be created by taking into account our own genetic and environmental factors, the target population to be screened will be calculated more precisely. This topic deserves further researches.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul University Oncology Institute Academic Coordination Committee (No: 2011/94, Date: 28/03/2011).

Informed Consent: Written informed consent was obtained from all patients.

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REFERENCES

1. Eccles SA, Aboagye EO, Ali S, Anderson AS, Armes J, Berditchevski F, et al. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. Breast Cancer Res 2013;15:R92.
2. Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. CA Cancer J Clin 2014;64:186–94. [CrossRef]
3. Tuncer M. Significance of cancer in Turkey, the burden of disease and cancer control policies. In: Tuncer M, editor. Cancer Control in Turkey. Ankara: Health Ministry Publication; 2008. p. 5–9.
4. Özmen V, Özmen T, Doğru V. Breast cancer in Turkey; an analysis of 20.000 patients with breast cancer. Eur J Breast Health 2019;15:141–6. Erratum in: Eur J Breast Health 2019;15:276.
5. Terry MB, Zhang FF, Kabat G, Britton JA, Teitelbaum SL, Neugut AI, et al. Lifetime alcohol intake and breast cancer risk. Ann Epidemiol 2006;16:230–40. [CrossRef]
6. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: A prospective cohort study. J Natl Cancer Inst 2005;97:1601–8. [CrossRef]
7. Mahoney MC, Bevers T, Linos E, Willett WC. Opportunities and strategies for breast cancer prevention through risk reduction. CA Cancer J Clin 2008;58:347–71. [CrossRef]
8. Howard RA, Leitzmann MF, Linet MS, Freedman DM. Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort. Cancer Causes Control 2009;20:323–33. [CrossRef]
9. Tehard B, Friedenreich CM, Oppert JM, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: Results from the E3N cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:57–64. [CrossRef]
10. Bernstein L, Patel AV, Ursin G, Sullivan-Halley J, Press MF, Deapen D, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97:1671–9.
11. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: Collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001;358:1389–99. [CrossRef]
12. Ellisen LW, Haber DA. Hereditary breast cancer. Annu Rev Med 1998;49:425–36. Erratum in: Annu Rev Med 1999;50:582. [CrossRef]
13. NCCN. Clinical practice guidelines in oncology (NCCN Guidelines®). Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 3.2019. Available at: https://www2.tri-kobe.org/nccn/guideline/gynecological/english/genetic_familial.pdf. Accessed Jan 24, 2023.
14. Koçak S, Çelik L, Özbaş S, Dizbay Sak S, Tükün A, Yalçın B. Risk factors in breast cancer, risk assessment and prevention: 2010 İstanbul Consensus meeeting report. J Breast Health [Article in Turkish] 2011;7:47–67.
15. Bluman LG, Rimer BK, Berry DA, Borstelmann N, Iglehart JD, Regan K, et al. Attitudes, knowledge, and risk perceptions of women with breast and/or ovarian cancer considering testing for BRCA1 and BRCA2. J Clin Oncol 1999;17:1040–6. [CrossRef]
16. Berry DA, Iversen ES Jr, Gudbjartsson DF, Hiller EH, Garber JE, Peshkin BN, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol 2002;20:2701–12. [CrossRef]
17. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. Int J Cancer 1990;46:796–800. [CrossRef]

18. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the Nurses' Health Study. Am J Epidemiol 2000;152:950–64. [CrossRef]
19. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047–59. Erratum in: Lancet 1997;350:1484. [CrossRef]
20. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: The Nurses' Health Study. Am J Epidemiol 1994;139:819–35. [CrossRef]
21. Braaten T, Weiderpass E, Kumle M, Adami HO, Lund E. Education and risk of breast cancer in the Norwegian-Swedish women's lifestyle and health cohort study. Int J Cancer 2004;110:579–83. [CrossRef]
22. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. For the Nurses' Health Study Research Group. J Natl Cancer Inst 1996;88:365–71. [CrossRef]
23. Cui Y, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: Update of a prospective cohort study. Breast Cancer Res Treat 2006;100:293–9. [CrossRef]
24. Ozmen V, Ozcinar B, Karanlik H, Cabioglu N, Tukenmez M, Disci R, et al. Breast cancer risk factors in Turkish women--a University Hospital based nested case control study. World J Surg Oncol 2009;7:37. [CrossRef]
25. Velentgas P, Daling JR. Risk factors for breast cancer in younger women. J Natl Cancer Inst Monogr 1994;16:15–24.
26. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ 2000;321:624–8.
27. Helmrich SP, Shapiro S, Rosenberg L, Kaufman DW, Slone D, Bain C, et al. Risk factors for breast cancer. Am J Epidemiol 1983;117:35–45.
28. Negri E, Braga C, La Vecchia C, Levi F, Talamini R, Franceschi S. Lactation and the risk of breast cancer in an Italian population. Int J Cancer 1996;67:161–4. [CrossRef]
29. Tavani A, Braga C, La Vecchia C, Negri E, Russo A, Franceschi S. Attributable risks for breast cancer in Italy: education, family history and reproductive and hormonal factors. Int J Cancer 1997;70:159–63. [CrossRef]
30. Ha M, Mabuchi K, Sigurdson AJ, Freedman DM, Linet MS, Doody MM, et al. Smoking cigarettes before first childbirth and risk of breast cancer. Am J Epidemiol 2007;166:55–61. [CrossRef]
31. Magnusson C, Wedrén S, Rosenberg LU. Cigarette smoking and breast cancer risk: a population-based study in Sweden. Br J Cancer 2007;97:1287–90. [CrossRef]
32. Gram IT, Braaten T, Terry PD, Sasco AJ, Adami HO, Lund E, et al. Breast cancer risk among women who start smoking as teenagers. Cancer Epidemiol Biomarkers Prev 2005;14:61–6. [CrossRef]
33. Terry PD, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: A long latency period? Int J Cancer 2002;100:723–8. [CrossRef]
34. Ceber E, Sogukpinar N, Mermer G, Aydemir G. Nutrition, lifestyle, and breast cancer risk among Turkish women. Nutr Cancer 2005;53:152–9.
35. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162:502–14. [CrossRef]
36. Tsuchiya M, Iwasaki M, Otani T, Nitadori J, Goto K, Nishiwaki Y, et al. Breast cancer in first-degree relatives and risk of lung cancer: Assessment of the existence of gene sex interactions. Jpn J Clin Oncol 2007;37:419–23. [CrossRef]
37. Lipworth L. Epidemiology of breast cancer. Eur J Cancer Prev 1995;4:7–30. [CrossRef]
38. Cold S, Hansen S, Overvad K, Rose C. A woman's build and the risk of breast cancer. Eur J Cancer 1998;34:1163–74. [CrossRef]
39. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. Curr Oncol Rep 2019;21:41. [CrossRef]
40. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: Findings from the British Women's Heart and Health Study. Cancer Causes Control 2004;15:267–75. [CrossRef]
41. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 1983;303:767–70. [CrossRef]
42. Shantakumar S, Terry MB, Teitelbaum SL, Britton JA, Millikan RC, Moorman PG, et al. Reproductive factors and breast cancer risk among older women. Breast Cancer Res Treat 2007;102:365–74. [CrossRef]
43. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187–95. [CrossRef]
44. Lee SY, Kim MT, Kim SW, Song MS, Yoon SJ. Effect of lifetime lactation on breast cancer risk: A Korean women's cohort study. Int J Cancer 2003;105:390–3. [CrossRef]
45. Enger SM, Ross RK, Paganini-Hill A, Bernstein L. Breastfeeding experience and breast cancer risk among postmenopausal women. Cancer Epidemiol Biomarkers Prev 1998;7:365–9.
46. Kim Y, Choi JY, Lee KM, Park SK, Ahn SH, Noh DY, et al. Dose-dependent protective effect of breast-feeding against breast cancer among ever-lactated women in Korea. Eur J Cancer Prev 2007;16:124–9. [CrossRef]
47. Reeves GK, Kan SW, Key T, Tjønneland A, Olsen A, Overvad K, et al. Breast cancer risk in relation to abortion: Results from the EPIC study. Int J Cancer 2006;119:1741–5. [CrossRef]
48. Michels KB, Xue F, Colditz GA, Willett WC. Induced and spontaneous abortion and incidence of breast cancer among young women: A prospective cohort study. Arch Intern Med 2007;167:814–20. [CrossRef]
49. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Cushing-Haugen KL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 2003;289:3254–63.
50. Newcomb PA, Titus-Ernstoff L, Egan KM, Trentham-Dietz A, Baron JA, Storer BE, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:593–600.
51. Fentiman IS. 20. Oral contraceptives, hormone replacement therapy and breast cancer. Int J Clin Pract 2002;56:755–9.
52. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33. [CrossRef]
53. Malone KE, Daling JR, Weiss NS. Oral contraceptives in relation to breast cancer. Epidemiol Rev 1993;15:80–97. [CrossRef]
54. Vessey M, Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968-2004. Br J Cancer 2006;95:385–9. [CrossRef]