
New Evidence On Breast Cancer Risk Factors In Greece – A Cross Sectional Case Control Study

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Abstract

Objective: Epidemiological studies on factors implicated in pathogenesis of breast cancer reveal international variations. The aim of this study was to identify the actual risk factors among Greek women in Macedonia.

Design: A cross-sectional case-control study among women with or without breast cancer was prospectively conducted in outpatient breast department of two surgical clinics of Thessaloniki.

Materials and Method: Fifty three histopathologically confirmed breast cancer cases were included. The control group consisted of 131 women. Data were collected by a face to face interview using a questionnaire consisting of 33 questions. Statistical adjustment was rendered more efficient by matching cases and controls in groups, choosing a control group (n=75) with an age distribution similar to that of the cases (n=53).

Statistical comparisons were performed using logistic regression analysis, to compute the odds ratios (ORs) for the variables of interest.

Results: Differences in distribution of age at first live birth were found between cases (Median age: 25 years, Range: 22 years) and controls (Median age: 22 years, Range: 35 years), $p=0,021$, Odds ratio= 1,086. All of the rest key risk factors were interestingly found to have no significant effect in breast cancer risk.

Conclusion: We did not find any statistical relationship between key risk factors and development of breast cancer, except for age at first live birth. Our miscellaneous results may be due to specific characteristics of our study population. Further studies are required to test the consistency of our findings in larger sample sizes and hopefully in other study populations.

INTRODUCTION

Breast cancer is the most common cancer worldwide for women, with more than 1.676.000 new cases diagnosed in 2012. There is a nearly four-fold variation in the incidence of the disease reported among different countries.¹

Identification of factors responsible for increasing the chance of breast cancer developing is important in daily clinical practice. Numerous epidemiological studies on these risk factors have produced evidence on international variations. These studies are limited among women of less-industrialized countries, including Greece. Therefore, we aimed to assess various factors implicated in the aetiology of breast cancer to identify the actual risk factors among Greek women in Macedonia, so as to develop appropriate clinical

practice guidelines and hopefully prevention strategies.

MATERIALS AND METHODS

Between January 2008 and December 2010, a university hospital cross-sectional case-control study among Greek women with or without breast cancer was conducted. The survey was prospectively carried out among women in outpatient breast department of two surgical clinics of Thessaloniki (Hippokratia and AHEPA, Aristotle University of Thessaloniki) by using a questionnaire. The source population was a group of subjects that visited the outpatient breast department, consisting of 234 women. Fifty three histopathologically confirmed breast cancer cases were included. The control group consisted of 131 women without clinical evidence of breast cancer at the time of the study.

The remaining 50 women could be clearly regarded neither as cases nor as controls. An institutional ethical committee approval was obtained before starting with the study. All interviews were conducted at the hospital. Data were collected by a face to face interview using a questionnaire form after having the informed consents of the participants. The questionnaire consisted of 33 questions related to potential risk factors. These included: a) general characteristics of women: age, body mass index (BMI), weight (and BMI) difference after the age of 18 years old, after menopause and in the last 5 years, smoking, alcohol consumption, b) menstrual and reproductive history: exogenous hormone exposure (use of hormone replacement therapy, oral contraceptive pills), age at menarche and menopause, parity, age at first live birth, breast feeding, c) family history of breast cancer: number of affected first degree relatives (mothers, sisters, daughters), number of affected second degree relatives, and significant characteristics of their disease (age of onset, menopausal status, bilaterality, and presence of associated cancer, specifically ovarian, colon, prostate, pancreatic, gallbladder, bile duct, and stomach cancers, as well as melanoma), d) breast imaging: history of false positive mammography, breast density [using the American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) density categories: almost entirely fat (category 1), scattered fibroglandular densities (category 2), heterogeneously dense (category 3), and extremely dense (category 4)], e) number of previous biopsies and histologic risk factors, specifically, Atypical ductal hyperplasia, Atypical lobular hyperplasia, Lobular carcinoma in situ, Ductal carcinoma in situ, and f) bone density, history of spontaneous fracture and height loss. The data was stored by using Microsoft Access program.

STATISTICAL ANALYSIS

All data were recorded using the Statistical Package for Social Sciences (SPSS) 21 for Windows for statistical analyses. Data were tabulated comparing cases with controls according to the risk factors.

Descriptive statistics were compiled to characterize the study population and to examine case-control differences. Potential risk factors were compared between cases and controls by the Chi-square Test for Independence for categorical variables and utilizing the methodology of the Independent Samples T-Test for continuous variables or Mann-Whitney U Test for continuous variables without normal distribution. Statistical comparisons were performed using Binary logistic regression analysis (BLRA), which

was carried out to compute the odds ratios (ORs) for the variables of interest. P values below 0.05 were considered to be significant.

Statistical adjustment was rendered more efficient by matching cases and controls in groups, choosing a control group (n=75) with an age distribution similar to that of the cases (n=53).

Moreover, several variables were revised as categorical dichotomous variables, specifically: affected first-degree relatives (presence/absence, instead of number of first-degree relatives with history of breast cancer), affected second-degree relatives (presence/absence, instead of number of second-degree relatives with history of breast cancer), menopausal status of affected first-degree relatives (pre/post menopausal, or else negative/positive for menopause), menopausal status of affected second-degree relatives (pre/post menopausal, otherwise negative/positive for menopause), bilateral disease in first-degree relatives with history of breast cancer (negative/positive), bilateral disease in second-degree relatives with history of breast cancer (negative/positive), first-degree relatives with history of breast cancer along with associated cancer (negative/positive), parity (never/ever, instead of number of offspring), breastfeeding (never/ever, instead of weeks of lactation, which was also worked out as a discrete variable), history of previous breast biopsy (never/ever, instead of number of previous biopsies), history of benign breast disease, particularly atypical hyperplasia (presence/absence), history of non infiltrative breast cancer (presence/absence), history of false positive mammography (positive/negative), breast density [most dense breasts (higher percentage of non-fatty tissue/least dense breasts, instead of classic BI-RADS density categories), smoking (current or former active smokers/never smokers, instead of number of cigarettes per day), alcohol consumption (heavy or light drinkers/non-drinkers, instead of units of alcohol per day or per week), exogenous hormone exposure: use of hormone replacement therapy, oral contraceptive pills (never/ever), bone density (normal/abnormal), history of spontaneous fracture (positive/negative), nation (Greek/other).

Continuous variables were measured in units of kg/m² for BMI and discrete variables were also measured in years for age and in weeks for lactation.

RESULTS

Comparison of patients with breast cancer (n = 53) and

control cases (n = 75) according to risk factors are summarized in Table 1 for continuous/discrete variables without normal distribution and in Table 2 for variables with normal distribution. Moreover categorical variables that do not violate the assumption of the Chi-square Test for Independence concerning the “minimum cell frequency” (at least 80% of cells with expected frequencies of 5 or more) are presented in Table 3. Finally, comparison of groups for categorical variables that do violate the assumption of the Chi-square Test concerning the “minimum cell frequency” is shown in Table 4, using Fisher’s Exact Probability Test.

Differences in distribution of age at first live birth were found out between cases and controls with a slight excess of younger control subjects. Thus, median age at first live birth of the controls was 22 years (Range: 35 years) and 25 years for the cases (Range: 22 years); $p=0,021$, Odds ratio= 1,086.

No difference was apparent between study groups in body mass index (BMI), in weight gain after the age of 18 years old, after menopause, and in the last 5 years, in smoking, alcohol consumption, menstrual and reproductive history [exogenous hormone exposure (use of hormone replacement therapy, oral contraceptive pills), age at menarche and menopause, parity, (duration of) breast feeding)] and family history of breast cancer (first degree relatives with history of breast cancer and their age at diagnosis, premenopausal onset and bilateral breast cancer or breast and other associated cancer, and second degree relatives with history of breast cancer and their age at diagnosis, premenopausal onset and bilateral breast cancer), bone density, history of spontaneous fracture and height loss, breast density, history of false positive mammography, performance of previous biopsies, histologic risk factors (atypical hyperplasia, non infiltrative cancer).

DISCUSSION

Because of the multifactorial process in breast cancer development, and the tendency for lifestyle variables to cluster, inconsistent and inconclusive data have emerged on breast cancer risk even from well-designed epidemiological research. Consequently, it is essential to continuously update knowledge on the risk factors and their impact on breast cancer. This could help women make beneficial changes in their behavior that could reduce their breast cancer risk. It is interesting that evidence suggests that more than 50% of cancer incidence could be prevented if knowledge of risk factors was applied to changes in behavior.²

The present case-control study provides results on risk

factors and breast cancer among Greek women in Macedonia. To our knowledge, this is the first epidemiological investigation to assess the possible role of the key risk factors in the etiology of breast cancer in such a sample.

Our findings concur with previous work reporting that young age at first full term pregnancy and live birth has a protective effect.^{3,4} Late age at first birth delays terminal duct proliferation of mammary gland, probably leading to a higher proportion of epithelial cells that are susceptible to carcinogenic insult.⁵

In the present study it was interesting to discover that the whole of the rest key risk factors were found to have no significant effect in breast cancer risk.

We are aware that our research, like all other case-control studies, is subject to certain limitations. Potential biases such as selection biases (non response bias, hospital based bias), and information bias (interview bias, recall bias, reporting bias). Certainly, it is not always possible to attain complete and accurate family history data, whether because of time restrictions or because of family matters such as premature deaths, small family size, and distant or broken families. However, while recall bias are acknowledged, such a setback is expected to be minimized since the same process served to collect information from cases and controls. Furthermore, the probability of obtaining false information on lifetime weight and respective age may be not as much of, as weight gain is a continuous concern for a majority of women, and they can recall their weight and its timing fairly correctly.⁶ Yet, as with most case-control studies, selection and recall bias may have influenced our results.

In addition, the sample size is not large, but it is estimated to provide a confidence level of 95% with a conventional margin of error of 8,63%. (7,8,9,10). Besides, the hospitals where the survey was conducted are the busiest hospitals located in Thessaloniki, and over 80% of the outpatients reside in Thessaloniki which is the biggest city in Macedonia with a population of 1 million. The hospitals accept new outpatients with or without doctor's referral. Therefore, the outpatient population may be considered to reflect a general outpatient population of any hospital in Thessaloniki.

Our study is not the first to present divergent results. Several epidemiological studies on breast cancer risk factors have revealed variations among different nations.¹¹ This may in fact be the reason why the International Agency for

Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) evaluations, which are the gold standard of cancer epidemiology, refer to certain risk factors as of limited or probable evidence, eg. hormone replacement therapy and tobacco smoking.^{12,13}

The discrepancy between our findings and other studies in the literature might be due to different characteristics of Greek women that merit additional exploration. Environmental, geographical, dietary, genetic predisposition or personal factors that were not included in our study may be responsible for the interestingly peculiar results of our study.

In particular, potential risk factors that were not explored include: endogenous hormone exposure,^{14,15,16} physical activity,^{13,17,18,19} exposure to environmental tobacco smoke,^{20,21,22,23,24} occupational exposure to night shift work,^{12,25-34} medical conditions and treatments: use of digoxin,^{12,35-37} diabetes and use of metformin/pioglitazone,³⁸⁻⁴⁴ autoimmune thyroiditis,⁴⁵ use of biphosphonates to treat low bone mineral density,⁴⁶ use of aspirin or other non-steroidal anti-inflammatory drugs.⁴⁷⁻⁵⁰

Nevertheless, a possible explanation of our miscellaneous results might be reflected by a key statistic fact of breast cancer. Notably the age-standardized incidence rates for breast cancer in Greece, along with Bosnia Herzegovina, are the lowest in Europe.⁵¹ This variation, in distinction to other countries, may reflect different prevalence of risk and/or protective factors, since European countries almost certainly use similar, standardized diagnostic tests and screening methods. Since most risk factors were found to have no significant effect in breast cancer development, a special protective factor may account at least in part for our miscellaneous results. One specific characteristic of Greek women may be adherence to the Mediterranean diet. It is widely accepted that diet plays an important role in breast cancer prevention or progression and that dietary modification can induce beneficial effects against breast cancer.⁵²⁻⁵⁷

Unfortunately the dietary pattern was not investigated in the current report. This proved to be an important weakness of our study, since diet is a modifiable factor, which could be used as a protective choice.

However, a future research suggestion arises out of

the research limitations that we have identified in our own critical assessment.

CONCLUSION

Although certain factors are considered to be key factors in the development of breast cancer, we could not find any statistical relationship between these factors and risk of breast cancer, except for age at first live birth.

Our miscellaneous results may be due to specific characteristics of our study population. Further studies are required to test the consistency of our findings in larger sample sizes and hopefully in other study populations.

Table 1
Comparison of patients with breast cancer (n = 53) and control cases (n = 75) according to risk factors

Factors	Controls			Cases			p	O.R	Sig
	N	Median	Range	N	Median	Range			
Age (Years)	75	52	29	53	56	44	0,072	1,037	0,055
Age at first live birth (Years)	62	22	35	47	25	22	0,003	1,087	0,020
Age at menarche (Years)	72	13	7	53	13	8	0,370	1,094	0,478
Age at menopause (Years)	46	49	21	37	50	18	0,108	1,068	0,170
Duration of breastfeeding (Weeks)	61	8	156	45	22	156	0,557	1,005	0,381
BMI	73	29,3575	39,26	52	28,9534	25,24	0,656	0,980	0,519
BMID	58	0,0000	24,61	29	0,0000	13,02	0,363	0,980	0,776
BMIDYOUTH	72	8,4159	35,22	50	8,3666	22,35	0,725	1,012	0,722
BMIDMENOPAUSE	47	2,7528	24,01	35	2,5803	17,49	0,854	1,023	0,666

O.R: odds ratio
 BMI: body mass index
 BMID: body mass index difference in the last 5 years
 BMIDYOUTH: body mass index difference after the age of 18 years old
 BMIDMENOPAUSE: body mass index difference after menopause

Table 2
Comparison of patients with breast cancer and control cases according to risk factors (variables) with normal distribution.

Factors	Controls			Cases			p	O.R	Sig
	N	Mean	Std. Deviation	N	Mean	Std. Deviation			
Age of onset of first degree relative affected with breast cancer (Years)	7	54,1429	11,36410	8	52,8750	13,37842	0,848	0,991	0,834
Age of onset of second degree relative affected with breast cancer (Years)	13	59,8462	12,57541	10	51,8000	10,09730	0,113	0,937	0,122

O.R: odds ratio

Table 3

Comparison of patients with breast cancer and control cases according to risk factors (categorical variables) that do not violate the assumption of the Chi-square Test for Independence concerning the ‘‘minimum cell frequency’’;

Factors		Controls		Cases		p	Pearson Chi-Square Value - Continuity Correction	O.R	Sig
		N	% within controls	N	% within cases				
Menopause	NEGATIVE	30	40,5%	15	28,8%	0,246	1,345	1,682	0,179
	POSITIVE	44	59,5%	37	71,2%				
Hormone substitution / Contraceptives	NEGATIVE	60	81,1%	48	90,6%	0,220	1,502	0,446	0,147
	POSITIVE	14	18,9%	5	9,4%				
Bone density	NEGATIVE	43	78,2%	27	67,5%	0,352	0,867	1,237	0,432
	POSITIVE	12	21,8%	13	32,5%				
First Relative	NEGATIVE	67	90,6%	44	83,0%	0,323	0,977	1,682	0,261
	POSITIVE	7	9,5%	9	17,0%				
Second Relative	NEGATIVE	59	79,7%	41	78,8%	1,000	0,000	1,204	0,529
	POSITIVE	15	20,3%	11	21,2%				
PARITY	NEGATIVE	12	16,2%	6	11,3%	0,602	0,273	0,660	0,438
	POSITIVE	62	83,8%	47	88,7%				
Breastfeeding]	NEGATIVE	15	22,7%	15	29,4%	0,543	0,369	0,706	0,413
	POSITIVE	51	77,3%	36	70,6%				
Previous Biopsy	NEGATIVE	63	86,1%	38	71,7%	0,104	2,649	2,261	0,068
	POSITIVE	11	14,9%	15	28,3%				
Smoking	NEGATIVE	47	63,5%	35	66,0%	0,916	0,011	0,895	0,769
	POSITIVE	27	36,5%	18	34,0%				
Breast Density	NEGATIVE	40	78,4%	23	69,7%	0,519	0,416	1,581	0,368
	POSITIVE	11	21,6%	10	30,3%				

O.R: odds ratio

Table 4

Comparison of patients with breast cancer and control cases according to risk factors (categorical variables) that do violate the assumption of the Chi-square Test for Independence concerning the ‘‘minimum cell frequency’’;

Factors		Controls		Cases		p	Fisher's Exact Probability Test	O.R	Sig
		N	% within controls	N	% within cases				
Nation (Other than Greek)	NEGATIVE	74	98,7%	53	100,0%	1,000	1,000	0,000	1,000
	POSITIVE	1	1,3%	0	0,0%				
Atypical hyperplasia	NEGATIVE	73	98,6%	52	98,1%	1,000	1,404	0,812	
	POSITIVE	1	1,4%	1	1,9%				
Non infiltrative cancer	NEGATIVE	71	96,9%	51	96,2%	1,000	0,928	0,936	
	POSITIVE	3	4,1%	2	3,8%				
False positive mammography	NEGATIVE	72	97,3%	53	100,0%	0,510	0,000	0,999	
	POSITIVE	2	2,7%	0	0%				
Spontaneous fracture	NEGATIVE	74	100,0%	52	98,1%	0,417	-	1,000	
	POSITIVE	0	0%	1	1,9%				
First Relative Menopause	NEGATIVE	1	14,3%	2	33,3%	0,559	0,333	0,427	
	POSITIVE	6	85,7%	4	66,7%				
Second Relative Menopause	NEGATIVE	2	16,7%	1	14,3%	1,000	1,200	0,891	
	POSITIVE	10	83,3%	6	85,7%				
First Relative Bilateral	NEGATIVE	6	85,7%	9	100,0%	0,438	0,000	1,000	
	POSITIVE	1	14,3%	0	0%				
Second Relative Bilateral	NEGATIVE	12	92,3%	9	90,0%	1,000	1,333	0,846	
	POSITIVE	1	7,7%	1	10,0%				
Breast and other cancer in first relative	NEGATIVE	6	85,7%	8	100,0%	0,467	0,000	1,000	
	POSITIVE	1	14,3%	0	0%				
Drinking	NEGATIVE	67	90,5%	50	94,3%	0,520	0,574	0,438	
	POSITIVE	7	9,5%	3	5,7%				

O.R: odds ratio

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