

Breast Cancer Risk in Relation to Most Prevalent IgE Specific Antibodies: A Case Control Study in Greece

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Abstract. Background: This study aims to explore the debatable role of allergy in breast cancer (BC) by using country-specific biological markers, namely levels of the most prevalent allergen-specific immunoglobulin E in Greece. Patients and Methods: Blood samples and clinical information were collected over a 30-month period from 103 women with histologically-confirmed BC and 103 controls from two university hospitals in Athens. Allergen-specific IgE, against the 12 prevailing allergens in Greece were determined; thereafter, a score comprising the sum of the individual values for this battery of serological IgE determinations was created. Bivariate and multiple logistic regression analyses were undertaken using case-control status as the outcome and IgE-scores as the predictor variable, controlling for socio-demographic, gynecological and lifestyle confounders. Results: The serum IgE score seemed to be positively related to BC (OR: ~1.73; CI: 0.95-3.14; p-value: 0.07). A positive correlation between serological evidence and allergic history among controls was also found (p-value: 0.06). Conclusion: This investigation suggests an IgE-mediated allergic response among women with BC in comparison to their controls. The finding needs confirmation by immuno-epidemiological investigation to clarify the directionality of this association and whether laboratory-ascertained atopy can be considered as a risk-marker of susceptibility in the development of BC.

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In Europe, breast cancer (BC) is the most common form of malignancy and the primary cause of death due to neoplasms amongst females (1). Mortality rates from the disease demonstrated an upward trend from 1951 to 1990 and have subsequently declined in most European countries, with the exception of central and eastern Europe (2). Likewise, accumulating evidence from several countries indicates that rising trends in asthma prevalence amongst adults may have plateaued after increasing for decades (3-5), though concerns have been expressed as to what extent these trends reflect a genuine trend.

The association of cancer with allergy has been supported by two opposing hypotheses. The first considers that tumor immuno-surveillance operates more efficiently in those individuals who have allergies and plays a protective role leading to better detection and destruction of malignant cells. The second holds that the immune system can enhance the inflammatory response and favor malignant transformation through mechanisms of repeated tissue repair that result in random pro-oncogenic mutations in actively dividing stem cells (6). Several large epidemiological studies point towards the inverse relation of allergy to colorectal cancer (7-9), brain cancer (10-12) and leukemia (13-17), and positive, not inverse association, with lung cancer (18-24), whereas with respect to the association of allergy with non Hodgkin's lymphoma risk (25-28) and pancreatic cancer (29-34), the results varied notably among different studies.

Current epidemiological data do not provide any insight as to the role of allergy in breast cancer risk development. The inconsistent findings may be partly due to differences in defining allergy and assessing the associated atopic disorders. The aim of the present study was to explore the association between breast cancer and allergic conditions assessed by the determination of country-specific biological markers for atopy, namely allergen-specific immunoglobulin E (IgE) antibodies.

Patients and Methods

Patients and controls. During a 30-month period, newly diagnosed and histologically confirmed cases of breast cancer were identified at the University of Athens teaching hospitals 'E. Venizelou' and 'Laiko'. Among the 118 women who were identified, 103 agreed to participate and were included in the study.

For each breast cancer patient, a woman of similar age concurrently admitted in the same hospitals who either had a mammogram indicating the absence of any detectable masses or who was hospitalized in the orthopaedic department with minor trauma was recruited as a control. The controls had never been diagnosed with any form of cancer. Fifteen of the selected controls were unable or unwilling to collaborate and were properly substituted.

All cases and controls were of Greek nationality and were interviewed by one of four trained interviewers using the same pre-coded questionnaire. Information pertaining to demographic, anthropometric and reproductive variables as well as lifestyle characteristics including alcohol consumption was obtained. A history of allergic disorder was defined as that comprising at least one of the following: asthma, allergic rhinitis, allergic conjunctivitis, pharmaceutical allergy and urticaria. The study protocol was approved by the University of Athens Medical School Ethics Committee and was in accordance with the Helsinki Declaration of 1975 and all participants provided informed consent.

Collection of serum. Fasting blood samples were collected during routine clinical procedures before the initiation of therapy from all cases and controls (no later than 09:00 h). At the time of blood drawing for the determination of allergen-specific IgE, none of the study subjects were taking any medication that could affect immune homeostasis and they were all free of infection.

Measurement of IgE antibodies. To determine the allergen-specific IgE antibodies, blood samples were centrifuged and the sera obtained were stored at -70°C blinded as to case-control status. Frozen samples were transferred to the Department of Immunology and Histocompatibility of the University of Thessaly Medical School in Larissa where allergen-specific IgE levels were determined using an enzyme immunoassay (EIA) (HY-TEC[®], Hycor Biomedical, Inc. Garden Grove, CA, USA). The sensitivity of this assay was 0.35 IU/mL and the intra-assay coefficient of variation was 7%. In particular, serum levels of the specific IgE antibodies against the 12 most prevalent allergens in Greece were measured. Measurements of individual IgE antibodies were subsequently combined in a total serological IgE score indicating the degree of the serologic IgE mediated allergic response.

Statistics. Frequency distributions of cases and controls by the study variables were derived and subsequently the association of the serological IgE score with the history of atopy among controls was examined. To study the possible association of the serological IgE score with breast cancer, the data were modeled through univariate and multivariate unconditional logistic regression models using case/control status as the outcome and the IgE score as the predictor variable in the latter case also controlling for a series of possible confounders, namely age, education, height, BMI, age at menarche, parity, age at menopause and alcohol consumption. The SAS statistical package (SAS Institute Inc. NC, USA) was used in all analyses (35).

Results

The distribution of 103 women with newly diagnosed breast cancer and 103 individually age-matched control women by selected risk factors for breast cancer and by IgE score is shown in Table I. These data are mostly descriptive and not directly interpretable because of mutual confounding, but they reveal most of the established host risk factors for breast cancer. Thus, women with breast cancer were somewhat taller, had an earlier menarche, were more frequently alcohol consumers and were older at menopause compared with the controls. With respect to body mass index (BMI) and parity, data are shown by menopausal status because obesity and nulliparity have different breast cancer risk implications among pre- and postmenopausal women. Concerning postmenopausal women, cases were rather more obese and had their first birth at an older age than the controls.

Table II, shows the association of serological IgE score with a history of atopy among the 103 control women. There is an indication of borderline statistical significance ($p=0.06$) that both history and serological examination point towards a similar underlying process for allergic responses to one or more allergens.

Univariate and multivariate analysis findings regarding the association of breast cancer with the country-specific serological IgE score are presented in Table III. There seemed to be a positive association between serologic IgE-mediated allergic response and breast cancer risk in the univariate analysis which became more substantial after controlling for age, education, height, age at menarche, parity, age at menopause and alcohol consumption (odds ratio: ~ 1.73 ; $p\text{-value}=0.07$).

Discussion

Immune system stimulation towards an IgE-mediated response, and the association it might have with the development of cancer is a highly debatable topic. Any association of allergy/atopy and cancer is dependent on the specific allergic condition and the particular organ site. According to the "worm" and "toxin" hypotheses, the Th2 dependent IgE responses function to destroy and mediate expulsion of a variety of harmful chemicals, micro-organisms and macro-organisms (helminths) before they can exert deleterious effects, including cancer. This hypothesis seems to account for the increased prevalence of allergies in recent years as being an adaptive response to exposure to new pathogens and carcinogens (such as environmental proteins and chemical pollutants) resulting from urbanization and higher population densities (36). In contrast, it is argued that atopy causes chronic inflammation and therefore enhances the risk of cancer development in specific tissues (37). A joint effect of

Table I. Distribution of 103 women with breast cancer and 103 controls by sociodemographic, somatometric and reproductive variables and by the serological IgE score.

Variables	Cases		Controls		p-value
	N	%	N	%	
Age (years)					0.72*
<45	15	14.6	17	16.5	
45-54	31	30.1	28	27.2	
55-64	27	26.2	24	23.3	
65-74	23	22.3	24	23.3	
75+	7	6.8	10	9.7	
Education (years)					0.13*
<6	15	14.6	22	21.4	
6	25	24.3	32	31.1	
9	26	25.2	19	18.4	
12	20	19.4	14	13.6	
13+	17	16.5	16	15.5	
Height (cm)					0.001*
<160	13	12.6	20	19.4	
160-164	22	21.4	55	53.4	
165-169	53	51.5	23	22.3	
170+	15	14.5	5	4.9	
Body mass index (kg/m ²)					0.88*
Premenopausal					
<25.0	20	55.6	21	61.8	
25.0-29.9	12	33.3	8	23.5	
30.0+	4	11.1	5	14.7	
Postmenopausal					0.45*
<25.0	25	37.3	31	44.9	
25.0-29.9	29	43.3	26	37.7	
30.0+	13	19.4	12	17.4	
Age at menarche (years)					0.001*
<13	43	41.7	16	15.5	
13	34	33.0	35	34.0	
14	15	14.6	34	33.0	
15+	11	10.7	18	17.5	
Age at menopause (years)					0.002**
Premenopausal					
≤49	36	35.0	34	33.0	
50+	19	18.4	40	38.8	
50+	48	46.6	29	28.2	
Age at first birth (years)					0.77***
Premenopausal					
nulliparous	11	30.6	8	23.5	
<30	22	61.1	22	64.7	
30+	3	8.3	4	11.8	
Postmenopausal					0.07**
nulliparous	3	4.5	10	14.5	
<30	43	64.2	45	65.2	
30+	21	31.3	14	20.3	
Alcohol consumption (glasses/month)					0.001*
0	15	14.6	47	45.6	
<1	18	17.5	23	22.3	
1-3	27	26.2	23	22.3	
4-7	29	28.1	9	8.8	
≥8	14	13.6	1	1.0	
Serologic IgE score					0.29*
0 (negative)	78	75.7	82	79.6	
1-2.99 (positive)	15	14.6	16	15.5	
3+ (strong positive)	10	9.7	5	4.9	

*P-value derived from Chi-square for trend; **p-value derived from Chi-square for contrast; ***p-value derived from Fisher's Exact test.

Table II. Cross-tabulation of the 103 control women by history of atopy and by serological IgE score.

Serological IgE score	History of atopy				p-value
	No		Yes		
	N	%	N	%	
0 (negative)	69	83.1	13	65.0	0.06*
1-2.99 (positive)	14	13.3	5	25.0	
3+ (strong positive)	3	3.6	2	10.0	

*P-value derived from Chi-square for trend.

Table III. Unconditional logistic regression derived odds ratios (ORs) and 95% confidence intervals (95% CIs) for breast cancer associated with serological IgE score in univariate and multivariate (controlling for age, education, height, BMI, age at menarche, parity, age at menopause and alcohol consumption) models.

Variable: serological IgE score (2 degrees more)	OR	95% CIs		p-value
Univariate model	1.28	0.81	2.04	0.29
Multivariate model	1.73	0.95	3.14	0.07

asthma with specific gene polymorphisms increasing the susceptibility to cancer of specific sites, such as lung cancer has also been reported (38). Logical findings concerning breast cancer and atopy, however, have failed to support either of the two hypotheses and no plausible theory to explain the reported results has been presented.

The association of allergic disease with respect to breast cancer has been examined in previous studies, but the results have not shown any strong positive correlation. Two prospective studies demonstrated a slightly, non-significant, increased risk of breast cancer among women who reported a previous history of allergy (39, 40). In an earlier cohort study, the incidence of breast cancer was significantly enhanced (OR: 2.5, 95% CI 1.01-5.16) among patients with positive skin prick tests (41). This finding though was refuted in a larger cohort study conducted by the same investigators, where the evidence of any association between breast cancer and atopy was not statistically significant (42). In contrast, a population-based case-control study in the United States found that a positive allergic history among women older than 35 years of age was associated with a reduced risk of developing breast cancer (OR=0.77, 95% CI, 0.60-0.99) (43). A prospective study of the Busselton cohort, failed to show an association of breast cancer with allergy/atopy (44). Finally, the most recent large case-control analysis that assessed allergen-

specific IgE positivity in combination with reported diseases related to atopy (asthma, hay fever and atopic dermatitis) also revealed an increased risk of breast cancer associated with atopy that did not reach statistical significance (OR 1.20, 95% CI 0.87-1.66) (45).

The inconsistent and contrasting nature of these findings has been attributed to methodological issues including small numbers of patients, lack of adjustment for possible confounders such as alcohol consumption, and selection biases that might compromise the validity and affect the comparability of the studies (46). Furthermore, each study has utilized a different diagnostic approach for the identification of the allergic patients, including the evaluation of the patients' symptoms and several *in vitro* and/or *in vivo* diagnostic procedures. Each of these approaches might have different sensitivity in identifying allergy and eventually affect the reported results.

Allergic patients as a study population share some unique characteristics that may act as confounding factors in case-control studies that attempt to correlate atopy with breast cancer. Due to their condition, those suffering from an atopic disorder may demonstrate a greater awareness of personal health and be in closer contact with their physicians. Therefore, they might be more enthusiastic to engage in breast cancer screening procedures than the general population and they tend to adopt a healthier lifestyle which might moderate the risk of cancer development. On the other hand, patients with cancer may suffer from immuno-suppression leading to the reduction of symptoms associated with allergy.

The main strength of the present study relates to the undertaking of blind and simultaneous biochemical determinations of specific IgE antibodies. Thus, the analysis was based on a score comprising specific IgEs as a marker of atopic predisposition rather than relying on reported symptoms as a definition of allergy. As in most studies probing the etiology of breast cancer, however, the study was of moderate size, and power limitations impose caution in the interpretation of the results.

In conclusion, the results of the present study could be interpreted as pointing to an association of breast cancer with IgE-mediated allergic disorders. Studies exploring the relationships between risk of cancer development and allergic responses need to utilize firmly standardized criteria in order to improve accurate assessment of the "exposure" under investigation. Further immuno-epidemiological studies may be able to clarify the directionality of the underlying pathophysiological mechanism, namely whether the elevated IgE levels are a consequence of the process of tumor development or whether allergy itself plays a role in the pathogenesis of the disease.

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References

- Boyle P and Ferlay J: Cancer incidence and mortality in Europe 2004. *Ann Oncol* 16: 481-488, 2005.
- Veronesi U, Boyle P, Goldhirsch A, Orecchia R and Viale G: Breast cancer. *Lancet* 365: 1727-1741, 2005.
- Flemming DM, Sunderland R, Cross KW and Ross AM: Declining incidence of episodes of asthma: a study of trends in new episodes presenting to general practitioners in the period 1989-1998. *Thorax* 55: 657-661, 2000.
- Senthilselvan A, Lawson J, Rennie DC and Dosman JA: Stabilization of an increasing trend in physician-diagnosed asthma prevalence in Saskatchewan, 1991 to 1998. *Chest* 124: 438-448, 2003.
- von Hertzen L and Haahtela T: Signs of reversing trends in prevalence of asthma. *Allergy* 60: 283-292, 2005.
- Carrozi L and Viegi G: Allergy and cancer: a biological and epidemiological rebus. *Allergy* 60: 1095-1097, 2005.
- La Vecchia C, D'Avanzo B, Negri E and Franceschi S: History of selected diseases and risk of colorectal cancer. *Eur J Cancer* 27: 582-586, 1991.
- Kune GA, Kune S and Watson LF: Colorectal cancer risk, chronic illnesses, operations and medications: case control results from the Melbourne Colorectal Cancer Study. *Cancer Res* 48: 4399-4404, 1988.
- Negri E, Bosetti C, La Vecchia C, Levi F, Tomei F and Franceschi S: Allergy and other selected diseases and risk of colorectal cancer. *Eur J Cancer* 35: 1838-1841, 1999.
- Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG and Black PM: History of allergies and autoimmune diseases and risk of brain tumors in adults. *Int J Cancer* 99: 252-259, 2002.
- Wiemels JL, Wiencke JK, Sison JD, Mücke R, McMillan A and Wrensch M: History of allergies among adults with glioma and controls. *Int J Cancer* 98: 609-615, 2002.
- Schwartzbaum J, Jonsson F, Ahlborn A, Preston-Martin S, Lonn S, Söderberg KC and Feychting M: Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. *Int J Cancer* 106: 423-428, 2003.
- Nishi M and Miyake H: A case-control study of non-T cell acute lymphoblastic leukaemia of children in Hokkaido, Japan. *J Epidemiol Community Health* 43: 352-355, 1989.
- Soverason RK, Davis S, Thomas DB, Stevens RG, Heuser L and Sever LE: Acute myeloid leukemia and prior allergies. *J Clin Epidemiol* 42: 995-1001, 1989.
- Wen W, Shu XO, Linet MS, Neglia JP, Potter JD, Trigg ME and Robison LL: Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control* 11: 303-307, 2000.
- Schuz J, Morgan G, Bohler E, Kaatsch P and Michaelis J: Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer* 105: 255-260, 2003.

- 17 Spector L, Groves F, DeStefano F, Liff J, Klein M, Mullooly J, Black S, Shinefield H, Ward J and Marcy M: Vaccine Safety Datalink Project: Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. *Eur J Cancer* 40: 579-584, 2004.
- 18 Vena JE, Bona JR, Byers TE, Middleton E Jr, Swanson MK and Graham S: Allergy-related diseases and cancer: an inverse association. *Am J Epidemiol* 122: 66-74, 1985.
- 19 Alavanja MC, Brownson RC, Boice JD Jr and Hock E: Preexisting lung disease and lung cancer among nonsmoking women. *Am J Epidemiol* 136: 623-632, 1992.
- 20 Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, Liff J, Boyd P, Henderson BE and Correa P: Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol* 141: 1023-1032, 1995.
- 21 Huovinen E, Kaprio J, Vesterinen E and Koskenvuo M: Mortality of adults with asthma: a prospective cohort study. *Thorax* 52: 49-54, 1997.
- 22 Mayne ST, Buconsejo J and Janerich DT: Previous lung disease and risk of lung cancer among men and women nonsmokers. *Am J Epidemiol* 149: 13-20, 1999.
- 23 Brenner AV, Wang Z, Kleinerman RA, Wang L, Zhang S, Metayer C, Chen K, Lei S, Cui H and Lubin JH: Previous pulmonary diseases and risk of lung cancer in Gansu Province, China. *Int J Epidemiol* 30: 118-124, 2001.
- 24 Boffet P, Ye W, Boman G and Nyren: Lung cancer risk in a population-based cohort of patients hospitalized for asthma in Sweden. *Eur Respir J* 19: 127-133, 2002.
- 25 Cartwright RA, McKinney PA, O'Brien C, Richards LD, Roberts B, Lauder I, Darvill CM, Bernard SM, Bird CC et al: Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Research* 12: 81-88, 1988.
- 26 Francheschi S, Serraino D, Bidoli E, Talamini R, Tirelli U, Carbone A and La Vecchia C: The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. *Leuk Research* 13: 465-472, 1989.
- 27 La Vecchia C, Negri E and Franceschi S: Medical history and the risk of non-Hodgkin's lymphomas. *Cancer Epidemiol Biomarkers Prev* 1: 533-536, 1992.
- 28 Fabbro-Peray P, Daures JP and Rossi JF: Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control* 12: 201-212, 2001.
- 29 Gold EB, Gordis L, Diener MD, Seltzer R, Boitnott JK, Bynum TE and Hutcheon DF: Diet and other risk factors for cancer of the pancreas. *Cancer* 55: 460-467, 1985.
- 30 Mack TM, Yu MC, Hanisch R and Henderson BE: Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* 76: 49-60, 1986.
- 31 Mills PK, Beeson WL, Abbey DE, Fraser GE and Phillips RL: Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 61: 2578-2585, 1988.
- 32 Farrow DC and Davis S: Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer* 45: 816-820, 1990.
- 33 Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A and Trichopoulos D: Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control* 4: 375-382, 1993.
- 34 Dai Q, Zheng W, Ji BT, Shu XO, Jin F, Zhu JL and Gao YT: Prior immunity-related medical conditions and pancreatic-cancer risk in Shanghai. *Int J Cancer* 63: 337-340, 1995.
- 35 SAS Institute Inc: SAS/STAT User's Guide Version 6, fourth edition Cary NC, 1989.
- 36 Zacharia BE and Sherman P: Atopy, helminths, and cancer. *Med Hypotheses* 60: 1-5, 2003.
- 37 Wang H and Diepgen TL: Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 60: 1098-1111, 2005.
- 38 Seow A, Ng DP, Choo S, Eng P, Poh WT, Ming T and Wang YT: Joint effect of asthma/atopy and an IL-6 gene polymorphism on lung cancer risk among lifetime non-smoking Chinese women. *Carcinogenesis* 27: 1240-1244, 2006.
- 39 McWhorter WP: Allergy and risk of cancer: A prospective study using NHANESI follow-up data. *Cancer* 62: 451-455, 1988.
- 40 Mills PK, Beeson WL, Fraser GE and Phillips RL: Allergy and cancer: organ site-specific results from the Adventist Health Study. *Am J Epidemiol* 136: 287-295, 1992.
- 41 Eriksson NE, Holmen A, Hogstedt B, Mikocz Z and Hagmar L: A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 50: 718-722, 1995.
- 42 Eriksson NE, Mikocz Z and Hagmar L: Cancer incidence in 13811 patients skin tested for allergy. *J Investig Allergol Clin Immunol* 15: 161-166, 2005.
- 43 Hedderston MM, Malone KE, Daling JR and White E: Allergy and risk of breast cancer among young women (United States). *Cancer Causes Control* 14: 619-626, 2003.
- 44 Talbot-Smith A, Fritschi L, Divitini ML, Mallon DF and Knudman MW: Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. *Am J Epidemiol* 157: 606-612, 2003.
- 45 Wang H, Rothenbacher D, Low M, Stegmaier C, Brenner H and Diepgen TL: Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. *Int J Cancer* 119: 695-701, 2006.
- 46 Lindelof B, Granath F, Tengvall-Linder M and Ekborn A: Allergy and cancer. *Allergy* 60: 1116-1120, 2005.

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