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Association between Different Types of Allergy Disorders, Total Immunoglobulin E and Risk of Breast Cancer

Mohammad Shirkhoda, MD[1,2], Reza Ghiasvand, Ph.D.[3], Fatemeh Sadeghi, M.Sc.[1,4*], Mohammad Hassan Bemanian, MD[5], Azam Noormohammadi, M.Sc.[1], Ramesh Omranipour, M.D.[2*] and Kazem Zendehdel, MD, Ph.D.[1]

[1]Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran,
[2]Department of Surgical Oncology, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran,
[3]Oslo Centre for Biostatistics and Epidemiology, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway,
[4]Department of Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran,
[5]Department of Allergy and Clinical Immunology, Rasoul-e-Akram Hospital, Tehran, Iran,

(Corresponding author: Fatemeh Sadeghi and Ramesh Omranipour)
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ABSTRACT: We aimed to investigate the association between history of allergic disorders, total IgE level and risk of Breast Cancer (BC). A case-control study was conducted and 168 BC patients and 165 controls were enrolled. Participants were interviewed in details about history of allergic disorders and allergic symptoms. In addition, total IgE levels was measured. A significant decrease was observed in risk of BC among participants with history of asthma compared to non-asthmatic participants in both univariate (P=0.0083) and multivariate analysis (P=0.035). Total IgE level above 25 IU/ml, was determined as borderline significant associated with BC in univariate analysis (P=0.07). However, the association was not significant in multivariate analysis. The association between atopy, defined by IgE level, and risk of BC may differ from the association investigated through clinically defined diseases such as asthma. Further study is recommended using a larger sample size and application of IgE specific or prick test.

Keywords: Allergy; Atopy, Asthma; IgE; Breast cancer, Developing countries

INTRODUCTION

Breast cancer (BC) is the most common cancer diagnosis and the leading cause of cancer-related death among women worldwide. There were an estimated 1.7 million new cases and 521,900 deaths in 2012 (Torre *et al.*, 2015). Besides, the prevalence of allergy and atopy has increased dramatically in recent decades. It is currently estimated that up to 40% of the people worldwide are sensitive (IgE antibodies) to foreign proteins in the environment (Weinberg, 2011) and asthma occurs in roughly 5 - 15% of the general population (Corren, 1997). However, there is considerable geographic difference in prevalence and types of allergen. It is estimated that in I.R of Iran, 20% of total population reported at least one allergic condition (Entezari *et al.*, 2009).

Many studies have evaluated the association between history of allergy and risk of cancer. A negative association has been reported in cancers of colorectal (Tambe *et al.*, 2015; Kune *et al.*, 2007) and pancreatic (Gomez-Rubio *et al.*, 2015) and a positive association has been reported in asymptotic lung cancer patients (Santillan *et al.*, 2003). While, some reports found no association (Ming *et al.*, 2004; Zhu *et al.*, 2016).

The dual role of allergy in cancer protection or promotion is largely unconfirmed and two fundamental and contradictory theories have evolved to justify this type of association (Turner *et al.*, 2006). The theory of enhanced immune surveillance is such that the immune system is able to detect and eliminate malignant tumor cells more effectively in a hypersensitive state. In contrast, the antigenic stimulation theory supports a positive association between allergy and cancer (Wang and Diepgen, 2005).

Allergy is a chronic inflammatory disease mediated by the IgE-mast cell release of histamine and leukotrienes (Turner *et al.*, 2006). The recurrent injury and repair processes, due to chronic inflammatory condition, could eventually lead to cancer and T-helper 2 (TH2) immune skewing implies an important role (Josephs *et al.*, 2013).

Research regarding the association between allergy or atopy and risk of BC is controversial (Wang *et al.*, 2006; Lowcock *et al.*, 2013). One meta-analysis found no significant association, however, the number of included studies that assessed atopy were small and authors included studies that assessed BC mortality, rather than incidence (Vojtechova and Martin, 2009). Another study reported a negative association between allergy and BC (Wrotek *et al.*, 2009); however Malgorzata E *et.al* demonstrated that the antitumor cytokines including, IL-1β, IL-4, IL-6, and IFN-Y were not involved in a negative relation of allergy and BC and suggested further studies were required (Kowalczewska *et al.*, 2014). These conflicting results may be due to the pleiotropic nature of allergic immunity or to different methods of measurement in epidemiological studies. In all studies, allergic patients were identified only by self-reported information and few studies have used biomarkers to diagnose individuals with atopic tendency. Moreover, to date, all previous studies were conducted in more developed countries. It is proposed that geographic diversity and different flora distribution might mediate results (Peden, 2003). Therefore, further studies in less developed countries are needed. Therefore, we aim to examine the association between allergic disorders, total immunoglobulin E and risk of BC in Iranian population.

MATERIALS AND METHODS

We performed a case-control study during 2014-2015 in Cancer Institute of I.R of Iran including, 168 incident cases and 165 controls. BC is the most common cancer types in this center (Fatemeh Sadeghi *et al.*, 2017). Eligible cases were women with a confirmed core biopsy of BC that had received no anticancer treatment. Cases that had cancer in other organ were excluded. We categorized stages of cancer patients into local, regional and distant metastasis, using SSER staging method. Only patients with local and regional cancers were included in our study. The control group consisted of patients who had referred to the orthopedic, urology, neuro-surgery, and general surgery departments of Imam Khomeini Hospital Complex. Controls had no history of breast biopsy, history of hysterectomy and oophorectomy and no history of other types of cancer. Controls were frequency matched with cases according to age and hospital. A written informed consent was obtained from all participants before they were included in the study. The study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences.

A. Questionnaire

We used a questionnaire to collect information on history of allergy, demographic factors, and potential confounders. including, age, marital status (single, married and widow/div), BMI (postmenopausal and premenopausal), occupation (housewife and employed), education (illiterate, high school, bachelor and postgraduate), family history of breast and ovarian cancer (yes and no), menarche age, menopausal status (yes and no), regular period (regular/usually regular and irregular), parity (yes and no), age at first pregnancy, parity (yes and no), breastfeeding (0, 1-24, 25-48, 49-73 and 73-250 months), history of oral contraceptive pill consumption (yes and no), smoking (yes and no), husband smoking (yes and no) and physical activity (common and moderate/high). A trained nurse interviewed the participants and collected blood samples. Subjects were defined as having a history of allergy if 1) diagnosed by a doctor for asthma, allergic rhinitis, atopic dermatitis, food allergy or drug allergy OR 2) based on The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, rationale and methods (Asher *et al.*, 1995). According to ISAAC questionnaire, asthma was recorded as positive only if the participant answered yes to "Have you had wheezing or whistling in the chest in the last 12 months?" OR "Did a doctor ever tell you that you had respiratory allergies?" Allergic rhinitis was recorded as positive only if the participant answered yes to both "In the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?" AND "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?" Atopic dermatitis was recorded as positive only if the participant answered yes to both "Have you had itchy rash at any time in the last 12 months? AND "Has this itchy rash at any time affected the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?"

B. Total IgE measurement

Blood samples were collected from cases and controls at interview, before the initiation of any treatment. The technician who performed the assays was blind to the case and control samples. All participants were free from the use of immune-regulatory drugs and infectious disease at the time of blood collection. Blood samples were centrifuged and all serum samples were stored at -80 degrees centigrade until ELISA assay.

Total IgE levels > 100 IU/ml are clinically elevated, 25-100 IU/ml are borderline and total IgE level < 25 IU/ml are considered as normal. We considered 25 IU/ml as cut-off and participants were classified as having atopic tendency, if they had IgE level higher than 25 IU/ml.

C. Statistical analysis

Differences in proportions of categorical covariates among cases and controls were determined using chi-square test. Logistic regression was performed and odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to investigate the association between different types of allergy disorder and risk of BC. Multivariate models were adjusted as appropriate for potential confounders including parity, breast feeding time and family history of breast and ovarian cancer, age and smoking.

To study the possible association between serological IgE score and BC risk, logistic regression was performed and multivariate models were adjusted for age, smoking, occupation, parity, breastfeeding time and family history of breast and ovarian cancer. All tests were two-sided and a 5% level of significance was used. All statistical analyses were performed using Stata, version 13 (StataCorp. College Station, TX, U.S.A.).

RESULTS

Mean age of the 168 cases was 45 years and mean age of the 165 controls was 46 years. We found a significant association between family history of breast and ovarian cancer (P=0.0001), parity (P=0.0043), breastfeeding (P=0.0034) and risk of BC (Table 1). However no significant association was found between other characteristics including, age, marital status, BMI, occupation, education, regular period, menopausal status, menarche age, age at first pregnancy, history of oral contraceptive pill consumption, smoking, husband smoking and physical activity and risk of BC. Mean age for participants with IgE below and above 100 IU/ml was 45 and 46 years, respectively. A significant association was found between occupation and total IgE level (P=0.0068) (Table 2). In this study, 23.6% of controls and 12.5% of cases had a history of asthma. In the univariate analysis, we found a significant negative association between a history of asthma and BC (OR: 0.46, 95% CI: 0.26-0.83, P=0.0083). The association remained significant after adjusting for confounders including, parity, breastfeeding, family history of breast and ovarian cancer, age and smoking (OR: 0.46, 95% CI: 0.22-0.95, P=0.035) (Table 3).

Table 1. Selected characteristic of cancer cases and controls, case-control study at Cancer Institute of Iran, 2014-2015.

Characteristics	Cases N (%)	Controls N (%)	P value [1]
Age			**0.8303**
≤ 40 years	51 (32)	58 (35)	
41-49 years	56 (35)	58 (35)	
≥ 50 years	51 (32)	49 (30)	
Family history of breast/ovarian cancer			**0.0001**
Yes	41 (24)	14 (8)	
No	127 (76)	151 (92)	
Parity			**0.0043**
0	19 (12)	18 (12)	
1 – 2	55 (35)	45 (29)	
3 - 5	74 (47)	60 (39)	
6 -11	10 (7)	31 (20)	
Breast feeding (month)			**0.0034**
0	39 (23)	18 (12)	
1 – 24	32 (19)	35 (24)	
25 – 48	46 (28)	31 (21)	
49 – 72	26 (16)	21 (14)	
73 - 250	23 (14)	42 (29)	
Smoking			**0.3357**
Yes	8 (5)	12 (7)	
No	160 (95)	153 (93)	

[1] P-value derived from Chi-square test

Bold values indicate statistical significance

Table 2. Selected characteristic of participant with high and low IgE level, case-control study at Cancer Institute of Iran, 2014-2015.

Characteristics	IgE<100 N (%)	IgE≥ 100 N (%)	P value [1]
Age			0.6866
≤ 40 years	96 (34)	13 (30)	
41-49 years	96 (34)	18 (40)	
≥ 50 years	87 (32)	13 (30)	
Occupation			**0.0068**
Housewife	213 (78)	28 (60)	
Employed	60 (22)	19 (40)	
Smoking			0.060
Yes	14 (5)	6 (12)	
No	268 (95)	45 (88)	

[1] P-value derived from Chi-square test
Bold values indicate statistical significance

Table 3. Univariate and multivariate odds ratios and 95% confidence intervals for breast cancer risk associated with history of allergy disorders, case-control study at Cancer Institute of Iran, 2014-2015.

Disorders	Case N=165	Control N=168	Univariate Model		Multivariate Model [1]	
			OR (95% CI)	P value	OR (95% CI)	P value
Asthma						
No	147 (87.5)	126 (76.4)	1		1	
Yes	21 (12.5)	39 (23.6)	0.46 (0.26-0.83)	**0.0083**	0.46 (0.22-0.95)	**0.035**
Hay fever						
No	141 (83.9)	138 (83.6)	1		1	
Yes	27 (16.1)	27 (16.4)	0.98 (0.54-1.75)	0.9424	1.46 (0 .71-2.97)	0.298
Atopic dermatitis						
No	149 (88.7)	146 (88.6)	1		1	
Yes	19 (11.3)	19 (11.5)	0.98 (0.49-1.92)	0.9530	1.26 (0.51-3.10)	0.614
Food allergy						
No	138 (82.1)	133 (80.6)	1		1	
Yes	30 (17.8)	32 (19.4)	0.90 (0.51-1.57)	0.7191	1.42 (0.68-2.95)	0.34
Drug allergy						
No	143 (90.5)	153 (93.3)	1		1	
Yes	15 (9.5)	11 (6.7)	0.69 (0.30-1.54)	0.3597	0.62 (0.21-1.76)	0.37
All types of disorders combined						
No	112 (66.7)	101 (61.2)	1		1	
Yes	56 (33.3)	64 (38.8)	0.78 (0.50-1.23)	0.3007	0.97 (0.55-1.69)	0.919

[1] Logistic regression model, adjusted for age, breast feeding time (month), parity, family history of breast & ovarian cancer and smoking
OR odds ratio, *CI* confidence interval
Bold values indicate statistical significance

In multivariate analysis, hay fever (OR=1.46, 95% CI: 0.71-2.97), atopic dermatitis (OR=1.26, 95% CI: 0.51-3.1) and food allergy (OR=1.42, 95% CI: 0.68-2.95) tended to be associated with a higher risk of cancer, although none of the associations were statistically significant. In contrast, drug allergy was associated with a decreased risk of BC in both univariate (OR=0.69, 95% CI: 0.30-1.54) and multivariate analyses (OR=0.62, 95% CI: 0.21-1.76) but the associations were not statistically significant.

Total IgE-mediated allergic response (IgE>25) was borderline significant associated with BC risk in univariate analysis (OR: 1.5, 95% CI 0.96 -2.34, P=0.0741) (Table 4). However, the association was not significant in multivariate analysis (OR: 1.56, 95% CI 0.89-2.72, P=0.113).

Table 4. Univariate and multivariate odds ratios and 95% confidence intervals for breast cancer risk associated with serologic IgE Level, case-control study at Cancer Institute of Iran, 2014-2015.

Atopy	Case N=165	Control N=168	Univariate Model		Multivariate Model [1]	
			OR (95% CI)	P value	OR (95% CI)	P value
IgE level						
<25 IU/ml	96 (57.14)	110 (66.7)	1		1	
>= 25 IU/ml	72 (42.9)	55 (33.3)	1.5 (0.96-2.34)	0.0741	1.56 (0.89-2.72)	0.113

Total IgE levels dichotomized; cutoffs of 25 IU/ml

[1] Logistic regression model, adjusted for age, breast feeding time (month), parity, family history of breast & ovary cancer, smoking and occupation

OR odds ratio, *CI* confidence interval

DISCUSSION

In this case-control study, history of asthma was associated with a decreased risk of BC. However, histories of hay fever, atopic dermatitis or food allergy were associated with slightly, non-significant, increased risk. In contrast, drug allergy was associated with a non-significant decreased risk of BC. These findings were independent of age, smoking, parity, breastfeeding and family history of breast and ovarian cancer. It seems that association of allergy and cancer is dependent on the specific allergic condition and the particular organ that is affected. No significant association between IgE level and risk of BC was found.

The association between history of allergic disorders and risk of BC has been investigated in previous studies with controversial results. The most prominent finding of the present study was an inverse association between asthma and BC. Lowcock *et al* found no association between asthma and risk of BC overall among Canadian women; however, asthma was associated with a reduced risk of BC among premenopausal women (Lowcock *et al.,* 2013). In previous studies, asthmatic patients were identified only by self-reported information, while we used the ISAAC questionnaire to consider allergic symptoms for more precise identification. A negative association was reported between asthma and gastric (El-Zein *et al.,* 2010) and ovarian (Elmasri *et al.,* 2010). But, reports in lung (Wang *et al.,* 2009) and thyroid cancers (Meinhold *et al.,* 2010), suggest a positive association. It was proposed that immune response against particular allergen could increase the risk of cancer in the contacted organ (Cipolat *et al.,* 2014) but might have a protective role in other organs due to over-activation of the immune system. In addition, geographic diversity and gene polymorphism could modify the results.

A history of food allergy was associated with a moderately increased risk in our study. In contrast, a history of drug allergy had a mitigating effect. However, both associations were determined as not statistically significant, which might be due to the lack of power in the study. To date, only a few studies have analyzed the effect of food and drug allergies on the risk of cancer and reports show mixed findings. The American glioma case-control study was the first to include food-specific IgE as a biomarker, demonstrating a protective association of IgE-mediated allergy on glioma (Wiemels *et al.,* 2004). Hedderson *et al.* reported a protective effect of food and drug allergies on BC through questionnaire. However, the research found an increased risk among women < 35 years (Hedderson *et al.,* 2003).

Our findings on the association between higher levels of serum total IgE and increased risk of BC was in agreement with the study by Petridou et al. in Greece (Petridou *et al.,* 2007) and Wang et al. in Germany (Wang *et al.,* 2006). Taghizadeh *et al.* found a positive association between total IgE serum level and lung cancer in Dutch population (Taghizadeh *et al.,* 2015). In our study IgE level was measured in patients before cancer treatment to prevent the effects of chemotherapy and radiotherapy and considered potential confounders and multivariate analysis was performed to assess the independent effects of total IgE level on risk of BC.

According to previous research it is suggested that allergic persons typically have high IgE level. Immune system stimulation towards an IgE-mediated response, and the association with the development of cancer is highly controversial. In lymphatic and hematopoietic cancers IgE might indicate an overactive immune system that enhances immune surveillance and results in a decreased risk of cancer (Karagiannis *et al.,* 2003). However, in epithelial type cancers such as breast or prostate cancer, where atopy is locally active, it was proposed high IgE level does not reflect a generalized overactive immune system. It may cause an inappropriate skewing toward Th2 responses. Th2 cytokines, such as IL-4 and IL-13, suppress Th1 cytokine release and lead to an increased risk of cancer (Hoste *et al.,* 2015).

To date, no theory has been able to clarify the association between allergy and BC. Such inconclusive findings could be because of the pleiotropic nature of allergic immunity, specific allergic condition, geographic condition and flora distribution (Hoste *et al.*, 2015; Peden, 2003). To our knowledge, no study has been conducted on the association between allergy history and any type of cancer in less developed countries. Moreover, differences in defining allergy and atopic disorders in studies could influence results. All previous studies relied on self-reported history of allergy disorders. This study was not restricted to self-reported disease and, in addition, an ISAAC questionnaire was used to consider the allergic symptoms for better identification of allergic patients.
This study was limited by use of retrospective data and the sample size was moderate. Moreover, data for allergy disorders and symptoms was based on medical history taken from the patients. Thus, our findings are prone to recall bias and misclassification of exposures.

CONCLUSIONS

Our study suggests that asthma might decrease the risk of BC. In addition, some association was found in other subgroups of allergy disorders, although the results were not statistically significant. Further studies with larger sample size are required to confirm the findings of the present study. The mechanism behind an association between the risk of BC and allergic disorder is likely associated with a complex combination of immunological pathways and other predisposing risk factors. Advances in the understanding of cancer and immunology may give further clues to the role of atopic disorders in the risk of some types of cancer.

LIST OF ABBREVIATIONS

ISAAC (The International Study of Asthma and Allergies in Childhood), BC (Breast Cancer)

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COMPETING INTERESTS

The authors declare no conflict of interest.

REFERENCES

Asher, M. I., Keil, U., Anderson, H. R., Beasley, R., Crane, J., Martinez, F., Mitchell, E. A., Pearce, N., Sibbald, B. & Stewart, A. W. (1995). International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *European Respiratory Journal*, **8**(3): 483-491.

Cipolat, S., Hoste, E., Natsuga, K., Quist, S. R. & Watt, F. M. (2014). Epidermal barrier defects link atopic dermatitis with altered skin cancer susceptibility. *Elife.* 2014; **3**: e01888.

Corren, J. (1997). Allergic rhinitis and asthma: how important is the link? *Journal of Allergy and Clinical Immunology*. **99**(2): S781-S786.

El-Zein, M., Parent, M.-E., Kâ, K., Siemiatycki, J., St-Pierre, Y. & Rousseau, M.-C. (2010). History of asthma or eczema and cancer risk among men: a population-based case-control study in Montreal, Quebec, *Canada. Annals of Allergy, Asthma & Immunology.* **104**(5): 378-384.

Elmasri, W. M., Tran, T. H. & Mulla, Z. D. (2010). A case-control study of asthma and ovarian cancer. *Archives of Environmental & Occupational Health*. **65**(2): 101-105.

Entezari, A., Mehrabi, Y., Varesvazirian, M., Pourpak, Z. & Moin, M. (2009). A systematic review of recent asthma symptom surveys in Iranian children. *Chronic Respiratory Disease.* **6**(2): 109-114.

Sadeghi F, Ardestani A, Mirzania M, Mahmoodzadeh H, Aghili M, Zendehdel K. Travel Burden and Clinical Profile of Cancer Patients Admitted to the Cancer Institute of Iran in 2012. *Archives of Iranian Medicine.* **20**(3): 147.

Gomez-Rubio, P., Zock, J.-P., Rava, M., Marquez, M., Sharp, L., Hidalgo, M., Carrato, A., Ilzarbe, L., Michalski, C. & Molero, X. (2015). Reduced risk of pancreatic cancer associated with asthma and nasal allergies. *Gut*. 2017; **66**(2): 314-22.

Hedderson, M. M., Malone, K. E., Daling, J. R. & White, E. (2003). Allergy and risk of breast cancer among young women (United States). *Cancer Causes & Control*. **14**(7): 619-626.

Hoste, E., Cipolat, S. & Watt, F. M. (2015). Understanding allergy and cancer risk: what are the barriers? *Nature Reviews Cancer*, **15**: 131-2.

Josephs, D. H., Spicer, J. F., Corrigan, C. J., Gould, H. J. & Karagiannis, S. N. (2013). Epidemiological associations of allergy, IgE and cancer. *Clinical & Experimental Allergy*. **43**(10): 1110-1123.

Karagiannis, P., Singer, J., Hunt, J., Gan, S. K. E., Rudman, S. M., Mechtcheriakova, D., Knittelfelder, R., Daniels, T. R., Hobson, P. S. & Beavil, A. J. (2009). Characterisation of an engineered trastuzumab IgE antibody and effector cell mechanisms targeting HER2/neu-positive tumour cells. *Cancer Immunology, Immunotherapy*. **58**(6): 915-930.

Karagiannis, S. N., Wang, Q., East, N., Burke, F., Riffard, S., Bracher, M. G., Thompson, R. G., Durham, S. R., Schwartz, L. B. & Balkwill, F. R. (2003). Activity of human monocytes in IgE antibody-dependent surveillance and killing of ovarian tumor cells. *European Journal of Immunology*. **33**(4): 1030-1040.

Kune, G. A., Kune, S. & Watson, L. F. (2007). Colorectal cancer risk, chronic illnesses, operations and medications: Case-control results from the Melbourne Colorectal Cancer Study. *International Journal of Epidemiology*. **36**(5): 951-957.

Lowcock, E. C., Cotterchio, M. & Ahmad, N. (2013). Association between allergies, asthma, and breast cancer risk among women in Ontario, Canada. *Cancer Causes & Control*. **24**(5): 1053-1056.

Meinhold, C. L., Ron, E., Schonfeld, S. J., Alexander, B. H., Freedman, D. M., Linet, M. S. & De González, A. B. (2010). Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *American Journal of Epidemiology*. **171**(2): 242-252.

Ming, M. E., Levy, R., Hoffstad, O., Filip, J., Abrams, B. B., Fernández, C. & Margolis, D. J. (2004). The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. *Journal of the American Academy of Dermatology*. **50**(3): 357-362.

Peden, D. B. (2003). Air pollution: indoor and outdoor. Middleton's Allergy Principles and Practice (Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, eds). 1529-555.

Petridou, E. T., Chavelas, C., Dikalioti, S. K., Dessypris, N., Terzidis, A., Nikoulis, D. I., Markopoulos, C., Papadiamantis, Y. & Germenis, A. E. (2007). Breast cancer risk in relation to most prevalent IgE specific antibodies: a case control study in Greece. *Anticancer Research*. **27**(3B): 1709-1713.

Santillan, A. A., Camargo Jr, C. A. & Colditz, G. A. (2003). A meta-analysis of asthma and risk of lung cancer (United States). *Cancer Causes & Control*. **14**(4): 327-334.

Taghizadeh, N., Vonk, J. M., Hospers, J. J., Postma, D. S., De Vries, E. G. E., Schouten, J. P. & Boezen, H. M. (2015). Objective allergy markers and risk of cancer mortality and hospitalization in a large population-based cohort. *Cancer Causes & Control.* **26**(1): 99-109.

Tambe, N. A., Wilkens, L. R., Wan, P., Stram, D. O., Gilliland, F., Park, S. L., Cozen, W., Martínez-Maza, O., Le Marchand, L. & Henderson, B. E. (2015). Atopic allergic conditions and colorectal cancer risk in the multiethnic cohort study. *American Journal of Epidemiology*. **181**(11): 889-897.

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J. & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a Cancer Journal for Clinicians*. **65**(2): 87-108.

Turner, M. C., Chen, Y., Krewski, D. & Ghadirian, P. (2006). An overview of the association between allergy and cancer. *International Journal of Cancer*. **118**(12): 3124-3132.

Vojtechova, P. & Martin, R. M. (2009). The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. *Cancer Causes & Control*. **20**(7): 1091-1105.

Wang, H. & Diepgen, T. L. (2005). Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy*. **60**(9): 1098-1111.

Wang, H., Rothenbacher, D., Löw, M., Stegmaier, C., Brenner, H. & Diepgen, T. L. (2006). Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. *International Journal of Cancer*. **119**(3): 695-701.

Wang, X.-R., Ignatius, T. S., Chiu, Y. L., Qiu, H., Fu, Z., Goggins, W., Au, J. S. K., Tse, L.A. & Wong, T.W. (2009). Previous pulmonary disease and family cancer history increase the risk of lung cancer among Hong Kong women. *Cancer Causes & Control.* **20**(5): 757-763.

Weinberg, E. G. (2011). The WAO white book on allergy 2011-2012. *Current Allergy & Clinical Immunology*. **24**(3): 156-157.

Wiemels, J. L., Wiencke, J. K., Patoka, J., Moghadassi, M., Chew, T., Mcmillan, A., Miike, R., Barger, G. & Wrensch, M. (2004). Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Research.* **64**(22): 8468-8473.

Wrotek, S., Kamecki, K., Kwiatkowski, S. & Kozak, W. (2009). Cancer patients report a history of fewer fevers during infections than healthy controls. *Journal of Pre-Clinical and Clinical Research.* **3**: 331-335.

Zhu, J., Song, J., Liu, Z., Han, J., Luo, H., Liu, Y., Jia, Z., Dong, Y., Zhang, W. & Jiang, F. (2016). Association between allergic conditions and risk of prostate cancer: A Prisma-Compliant Systematic Review and Meta-Analysis. *Scientific Reports.* **6**: 35682.