Ann. Acad. Med. Siles. (online) 2017; 71: 371–377
eISSN 1734-025X
DOI:10.18794/aams/67645

PRACA ORYGINALNA
ORIGINAL PAPER

The link between neoplastic and atopic diseases

Związek pomiędzy chorobą nowotworową a alergią atopową

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ABSTRACT

INTRODUCTION: Whether there is a protective or stimulating effect of atopy on the risk of neoplastic disease is an interesting question. Studies that have analyzed the matter to date have proposed various explanations for such an effect. In this study, the prevalence of neoplastic diseases in patients with confirmed atopic diseases compared with a control non-atopic group was analyzed.
MATERIAL AND METHODS: A total of 1451 patients with atopic disease and 1389 control subjects over 35 years of age received a physical examination, a skin-prick test and measurement of IgEs specific to common inhalant allergens. A medical history based on an original questionnaire and analysis of family history for the possible occurrence of neoplastic diseases and allergies were performed. Additionally, tumor markers AFP, CEA, SCC, PSA, Ca15.3, Ca19-9, Ca125, HCG, and CYFRA 21-1 were measured in serum.
RESULTS: The results confirmed no significant difference in the prevalence of most analyzed neoplasms between the groups. Chronic lymphocytic leukemia and chronic myelogenous leukemia were significantly less common in the study group. A negative correlation between the concentration of total IgE in serum and the probability of neoplasm diagnosis in the study group was noted. A higher concentration of serum marker CYFRA 21-1, but without clinical manifestation in patients with atopic disease was observed.
CONCLUSIONS: The occurrence of neoplastic diseases is slightly lower in patients with atopic diseases than in the control group without allergies. There were no significant differences in the analyzed serum tumor markers between the groups.

KEY WORDS
allergy, atopy, total IgE, neoplastic disease

Received: 23.08.2016 **Revised:** 07.12.2016 **Accepted:** 12.12.2016 **Published online:** 03.11.2017

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STRESZCZENIE

WSTĘP: Ochronny lub stymulujący wpływ atopii na ryzyko rozwoju nowotworu pozostaje otwartym pytaniem. Dotychczasowe prace naukowe analizujące temat przynoszą różne odpowiedzi. W pracy badano występowanie chorób nowotworowych u pacjentów z potwierdzonymi chorobami atopowymi w stosunku do grupy kontrolnej bez cech atopii.

MATERIAŁ I METODY: U 1451 pacjentów z chorobą atopową oraz 1389 osób stanowiących grupę kontrolną w wieku powyżej 35 r.ż. wykonano badanie, alergiczne testy skórne, oznaczono stężenie alergenowo swoistych przeciwciał IgE przeciwko najczęstszym alergenom wziewnym. Przeprowadzono analizę dokumentacji medycznej oraz wypełniono oryginalny kwestionariusz zawierający między innymi pytania o ewentualne występowanie chorób nowotworowych i alergii u pacjenta oraz w jego rodzinie. Dodatkowo wykonano oznaczenia następujących markerów nowotworowych w surowicy krwi AFP, CEA, SCC, PSA, Ca 15.3, Ca 19-9, Ca 125, HCG, CYFRA 21-1.

WYNIKI: Wyniki potwierdziły brak istotnej różnicy w częstości występowania większości analizowanych nowotworów pomiędzy badanymi grupami. Odnotowano znacznie mniejszą zachorowalność na przewlekłą białaczkę szpikową oraz przewlekłą białaczkę limfatyczną w grupie badanej. Zaobserwowano ujemną korelację pomiędzy wartością stężenia całkowitej IgE w surowicy krwi a prawdopodobieństwem rozpoznania choroby nowotworowej w grupie badanej. Wśród pacjentów z chorobą atopową obserwowano wyższe stężenie markeru CYFRA 21-1 w surowicy krwi, lecz bez manifestacji klinicznej.

WNIOSKI: Występowanie choroby nowotworowej jest nieznacznie niższe u pacjentów z chorobami atopowymi niż w grupie kontrolnej bez alergii. Nie odnotowano istotnych różnic w analizowanych markerach nowotworowych surowicy krwi pomiędzy grupami.

SŁOWA KLUCZOWE

alergia, atopia, całkowita IgE, choroba nowotworowa

INTRODUCTION

Allergy-related diseases have become more common, which is related to a global rise in allergy frequency in recent decades. Allergy prevalence is estimated to be 10–30% of the global population, depending on the geographical region or type of allergy.

Particular attention should be paid to allergy-related diseases, which stem from atopy and are related to the overproduction of IgE. These diseases include atopic asthma, allergic intermittent or chronic rhinitis or conjunctivitis, and atopic dermatitis.

An interesting and important issue from the clinical point of view is the potential correlation between the occurrence of allergies (atopy) and the risk of neoplastic diseases. Current studies that have analyzed the matter have provided various explanations to the question. The explanations have been based on one of two opposing research hypotheses:

- The first one proposes the protective function of atopies against neoplastic disease via an increase in immunological supervision.
- The second one proposes a relation between atopy and an increased risk of neoplastic diseases, stemming from chronic stimulation of the immunological system [1,2,3].

According to the first hypothesis, the overstimulation of immunocompetent cells, which results from contact with an allergen, causes the production of certain IgE antibodies that may have a cytotoxic influence on neoplastic cells. The second hypothesis assumes that continuous chronic infection accompanying allergy diseases may induce the production of free oxygen radicals, which may encourage oncogenesis. Damage to the oxidative pathways of cells induces the mutation of suppressor genes and posttranslational modifications of proteins responsible for DNA repair processes or apoptosis process control. The transition in the Th1/Th2 balance towards Th2 lymphocytes among allergy patients fosters inhibition of correct production processes of cytotoxic effector cells and simultaneously lowers their ability to eliminate neoplastic cells [3,4].

What these two theories have in common is the field of "allergo-oncology", which analyzes the correlation between the immunological system and the occurrence of neoplastic diseases [5].

The relationship of certain atopic diseases with the potential risk of cancer among such patients has attracted attention. The literature available to date does not provide a clear answer to the question as to whether there is a correlation between atopic dermatitis and neoplastic diseases.

The aims of this study were as follows:

1. To evaluate the prevalence of neoplastic disease in patients with confirmed atopic diseases compared with a control (non-atopic) group based on an ori-

ginal survey and a retrospective analysis of medical records.
2. To determine tumor markers in patients with atopic diseases relative to the control group.

METHODS

Patients

The study included 1451 patients comprising 694 women and 757 men aged 35 to 74 years (mean age, 49.7 ± 13.1 years). These patients were diagnosed in the Allergy Clinic because of suspected inhalation-related allergies. The study group was formed as a result of a screening assessment of 16.500 records. From the resulting pool of patients and through stratified sampling, it was determined that the key population was of those over 35 years of age, and this group was selected as the target group.

The control group consisted of 1389 people with excluded IgE-mediated allergies; the group comprised 664 women and 775 men aged 35 to 78 years (mean age, 46.4 ± 10.8 years). The population details are presented in Table I.

Table I. Characteristics of study population
Tabela I. Charakterystyka badanej populacji

Features	
Females (%)	47.8
Mean age (years)	49.7 ± 13.1
Allergic asthma (%)	32.7
Atopic dermatitis (%)	11.6
Allergic rhinitis (%)	88.1
Multiple diseases (%)	22.1%
Most common allergies (%):	
House dust mites	41%
Grass pollen	39%
Birch	21%
Other inhalant allergens	20%
Mean duration of allergic disease (years)	18.2 ± 11.8

The inclusion criteria were as follows:
1. Over 35 years of age.
2. Inhalant allergy symptoms documented by medical history, skin-prick tests and/or elevated total IgE and/or allergen-specific IgE antibodies against inhalant allergens.
3. The presence of atopic asthma and/or atopic dermatitis and/or allergic rhinoconjunctivitis.

The exclusion criteria were as follows:
1. A lack of consent to participate in the prospective study.
2. The presence of other allergies (i.e., to bee or wasp venom or drug allergies) without confirmation of atopic disease.

A. Prospective procedures
1. Medical history based on the original questionnaire (see Table II).
2. Physical examination with laryngological and dermatological assessment.
3. Allergy procedures.

Determination of IgE concentration

Measurement of the concentration of total IgE and allergen-specific IgE (sIgE) was performed using the Pharmacia CAP system FEIA (Pharmacia AB, Sweden), and the values are shown in kU/L. The following specific IgE allergens were investigated: *D. pteronyssinus*, *D. farinae*, *Aspergillus fumigatus*, *Alternaria tennis*, *Cladosporium herbarium*, dog, cat, grass mix, birch, alder, hazel, and mugwort. IgE values above 0.35 kU/l were considered positive.

Skin-prick tests

Skin-prick tests (Allergopharma, Reinbeck, Germany) to the inhalant allergens mentioned above were performed according to previously published guidelines [6].

Tumor markers

The serum concentrations of selected tumor markers were evaluated in a randomly selected subgroup of patients with a known IgE-mediated allergy and in the control group, which comprised 987 and 1078 respondents, respectively. The subgroups were similar in terms of age and gender. Collectively, we evaluated the following markers in serum: AFP; CEA; SCC; PSA; Ca15.3; Ca19-9; Ca125; HCG; and CYFRA 21-1. All the analyses were performed with 5 ml of blood serum from each patient according to an automatic, immunoenzymatic method (Cobas c311, cpbas e441, Roche, Poland) using commercial kits.

B. All the patients participated in a retrospective evaluation for the following:
1. Diagnosis of a possible neoplastic cancer using code IC-10 in medical records [7].
2. Diagnosis of asthma according to GINA criteria [8], atopic dermatitis according to Hanifin-Rajka [9] criteria or allergic rhinitis according ARIA [10].
3. Analysis of family history and the possible occurrence of neoplastic disease and allergies.

The project received approval from the Bioethics Committee of the University of Silesia, dated 25.02.2014 r, No. CDF/0022 /KB1/18/14.

Table II. Original survey: prevalence of oncological diseases and allergies
Tabela II. Oryginalny kwestionariusz: występowanie chorób nowotworowych i alergii

A. Allergy history

Do you suffer from asthma and/or allergic dermatitis (AD) and/or allergic rhinitis?
NO YES (please specify):
If you suffer from one of the above-mentioned diseases, please complete the survey on this disease
Asthma
1. How do you assess your degree of asthma control?
Controlled asthma
Asthma partly controlled
Uncontrolled asthma
2. Do you receive allergen-specific immunotherapy?
NO YES
3. How long have you been treated for asthma?
4. Severity of asthma – rating by GINA (completed by physician):
I II III IV
Atopic dermatitis
1. How long have you suffered from atopic dermatitis?
2. Please specify the areas of the skin that are affected:
Local changes
30% of skin affected
50% of skin affected
The entire body
3. SCORAD index (completed by physician):
Allergic rhinoconjunctivitis
1. How often during the year does allergic rhinitis occur:
Seasonally (spring-summer)
Year-round
Does your family have or had other conditions such as asthma, allergic dermatitis (AD), allergic rhinitis?
NO YES (please specify)

B. Oncology history

1. Have you suffered from a neoplastic disease in the past?
NO YES (please specify)
2. Are you currently suffering from a neoplastic disease?
NO YES (please specify)
3. In the case of neoplastic disease, please indicate whether the following treatment modalities were used:
Surgical treatment
Chemotherapy (which drugs?)
Radiotherapy
4. Does your family have a history of neoplastic cancer?
NO YES (please specify)
5. Do you suffer from other chronic diseases?
NO YES (please specify)
6. Have you participated in tests for the presence of tumor markers?
NO YES (specify? ..... when? ..... (year)

RESULTS

Assessment of the risk of cancer in patients with atopic disease was based on the survey and medical records including the ICD code.

The results confirmed that there were no significant differences in the incidence of most neoplastic diseases between the groups. However, the incidence of certain hematologic diseases (chronic myeloid leukemia and chronic lymphocytic leukemia) rarely occurred in patients with atopy. Detailed results are shown in Table III. The type of atopic disease had no effect on the degree of neoplasm risk. An influence of the severity of the asthma and/or atopic dermatitis on the risk of developing neoplasm was not observed.

The odds ratio of the presence of different types of neoplastic diseases was slightly decreased in patients with atopic disease (Table IV).

There was a significantly lower concentration of CEA and CA19-9 markers in patients with clinical signs of atopy and a higher concentration of the CYFRA- 21 marker than in the control group. Detailed results are provided in Table V. However, it did not correspond with the clinical symptoms of neoplastic diseases.

There was a negative correlation between the concentration of total IgE in serum and the probability of neoplastic disease diagnosis in the study group $R = -0.67$ ($p < 0.05$). There was no such correlation in the control group. In patients with atopic disease who have a total IgE > 2500 IU/l, the correlation was strong and amounted to -0.88 ($p < 0.05$).

There was no significant correlation between the total IgE concentration and the analyzed markers. Only marker Cyfra-21 had a positive correlation with total IgE: $R = 0.78$ ($p < 0.05$).

Table III. Profile of diagnosed neoplastic diseases in patients with atopic disease and control groups
Tabela III. Profil chorób nowotworowych u pacjentów z chorobą atopową i w grupie kontrolnej

Type of neoplastic disease	Patients with atopic disease n = number of cases	Control group n = number of cases	p value
Acute lymphocytic leukemia	2	3	NS
Acute myeloid leukemia	3	3	NS
Chronic lymphocytic leukemia	2	8	0.04
Chronic myelogenous leukemia	4	11	0.03
Lymphoma	6	6	NS
Bronchial cancer	9	12	NS
Gynecological neoplastic disease (ovarian, uterine and breast cancer)	16	14	NS
Gastrointestinal neoplastic disease (stomach, colon, and esophagus)	11	10	NS
Prostate cancer	9	8	NS
Skin cancer	6	10	NS
Other	8	10	NS
Total	76	95	0.01

Legend: NS – not significant

Table IV. Odds ratio for a particular cancer in patients with atopy
Tabela IV. Iloraz szans na występowanie poszczególnych chorób nowotworowych u pacjentów z atopią

Type of cancer	Odds ratio – OR (95% CI)
Acute lymphocytic leukemia	0.89 (0.83, 1.22)
Acute myeloid leukemia	0.84 (0.81, 1.05)
Chronic lymphocytic leukemia	0.32 (0.18, 0.81)
Chronic myelogenous leukemia	0.58 (0.44, 0.78)
Lymphoma	0.98 (0.69, 1.18)
Bronchial cancer	0.98 (0.83, 1.03)
Gynecological cancer (ovarian, uterine and breast cancer)	1.09 (0.91, 1.10)
Gastrointestinal cancer (stomach, colon, esophagus)	0.87 (0.85, 1.12)
Prostate cancer	0.93 (0.87, 1.01)
Skin cancer	1.03 (0.88, 1.11)

Table V. Comparison of mean concentrations of tumor markers in blood serum in groups
Tabela V. Porównanie średniego stężenia markerów nowotworowych w surowicy krwi pomiędzy badanymi grupami

Markers	Patients with atopic disease n = 987	Control group n = 1078	p value
Mean age	47.6 ± 6.9	45.2 ± 9.9	NS
AFP (N: 0–8.5 ng/ml)	3.22 ± 1.2	2.98 ± 1.72	NS
CEA (N: 0–2.5 ng/ml)	1.05 ± 0.93	1.86 ± 1.7	0.023
SCC (N < 1.5 ng/ml)	1.03 ± 0.41	1.15 ± 0.66	NS
PSA (N: 0–4 ng/ml)	0.78 ± 0.52	0.81 ± 0.43	NS
Ca15.3 (N < 25 IU/l)	7.2 ± 6.8	6.3 ± 5.1	NS
CA19-9 (N: 0–37 j/ml)	11.7 ± 5.63	19.63 ± 8.51	0.012
CA 125 (N < 35 j/ml)	4.2 ± 2.19	3.91 ± 0.61	NS
HCG (N < 5 jm/l)	0.66 ± 0.23	0.56 ± 0.55	NS
Cyfra-21 (N < 3.5 ng/ml)	1.56 ± 0.48	0.76 ± 0.23	0.001

Legend: NS – not significant

DISCUSSION

The results suggest a protective role of atopic diseases for neoplastic diseases.

This phenomenon can be explained as follows. According to one hypothesis, allergic diseases involve a highly active immune system. Excessive stimulation of mast cells, eosinophils, basophils, and T cells following contact with a specific allergen results in the production of specific IgE antibodies that interact with the cell and affect the production of immune factors such as IL-4 and IL-5, which together with IgE antibodies, may affect anti-tumor immunity. These factors may not have a direct effect on tumor cells but may affect vascular permeability, which may be important in tumor induction. IgE may also activate the complement alternative route and form immune complexes that destroy tumor cell clones. Reduced levels of IgE and histamine have been found in patients with neoplastic diseases. IL-12 is an anti-allergic inflammation cytokine that stimulates T cells and NK cells as well as the production of INF gamma, which stimulates macrophages to kill neoplastic cells [3,4].

Perhaps these described reactions explain the lower incidence of chronic leukemia in atopy patients. Similar observations have been previously noted [11].

Despite the different configurations of atopic diseases in the examined patients, there was no correlation between asthma, atopic dermatitis or allergic rhinitis and the prevalence of neoplastic diseases. The literature on this subject is inconclusive. Often, chronic inflammation is one of the first exponents of the existence of oncogenesis. In this regard, does chronic inflammation in asthma predispose one to neoplastic disease? Scholars are divided on the answer to this question. It seems more likely that the presence of large amounts of oxygen free radicals results in asthma and can damage the genetic material of cells and thus contribute to the development of cancer, as mentioned above [12,13]. In contrast, enhanced immune-surveillance in patients with asthma can effectively eliminate transformed cells compared with healthy subjects [14].

A similar problem is unresolved in patients with atopic dermatitis. However, Olsen et al. analyzed 2030 adults, suffering from atopic dermatitis, for the occurrence of cancer. There was an increased risk for cancer in this population, particularly of the skin. There was a total of 67 cancer cases, including 16 skin cancers (basal carcinoma and squamous cell cancers). There were no cases of malignant melanoma, which could indicate a reduced risk of the incidence of this type of cancer among patients suffering from atopic dermatitis [15]. Nevertheless, in the present work we observed no such correlations – none of the analyzed patients with allergies had a malignant melanoma. Denholm et al. confirmed an inverse relationship between asthma and the incidence of lung cancer. In contrast, for chronic bronchitis, emphysema and pneumonia, a positive correlation was found when diagnosed less than 2 years before the diagnosis of lung cancer [16].

Another study of 31330 patients with AD confirmed these previous observations; there were 12 cases of malignant melanoma of 21 expected cases (RR = 0.59).

This finding indicates a reduced risk of the incidence of this type of cancer among people suffering from AD. A positive correlation was noted compared with 57 cases of basal cellular cancer per 40 expected (RR = 1.41) and squamous cell carcinoma of 7 cases per 3 expected (RR = 2.48) [17].

The research on allergic rhinitis and other allergies with a complex clinical picture is equally inconclusive. It appears that the occurrence of allergic rhinitis does not significantly influence the incidence of neoplastic diseases, but the co-occurrence of more than one atopy in a patient triggers a reduction in malignant neoplasm processes [13]. Notwithstanding, some results indicate that patients with atopy show a comparable incidence of selected neoplasms of the skin, lungs and female organs to the control group. On this basis, it cannot be generalized that the risk of neoplastic diseases in patients with atopy is common. This contradiction demonstrates the complexity of the problem.

While analyzing the occurrence of allergies and neoplasms, particular attention must be paid to the phenomenon of atopic disease incidence among patients who have already been diagnosed with neoplastic disease [18]. The observations of this phenomenon are extremely poor, however, they do indicate that the risk of allergies among patients with neoplasms is marginally reduced. Nonetheless, this possibility requires further analysis, including a larger number of such cases. Marker analysis did not answer the question regarding the risk of neoplasms in patients with atopy; the results were similar in both groups. In most cases, the markers did not vary from the norm even in the cases of confirmed cancers. These results confirm the small diagnostic value of these markers in predicting cancer [19].

A limitation of this study was the lack of monitoring of tumor marker trends in blood serum over a prolonged time. However, despite this limit, it appears that the markers do not indicate with certainty the risk of neoplasm incidence.

There were more frequently observed moderate elevated concentrations of CYFRA 21-1 in patients with atopic diseases, but this observation can be explained by the presence of chronic inflammation in asthma and allergic rhinitis in those participants [20]. This marker did not correlate with the incidence of lung cancer in the study group, except in 2 patients who had microcellular carcinoma.

CONCLUSIONS

The occurrence of neoplastic diseases is slightly lower in atopic patients than in the control group without allergies. There is a smaller incidence of morbidity for selected neoplasms of the hematopoietic system. Analysis of the concentration of tumor markers indicated little difference in some of their types between the two groups. There is no evidence linking these differences to the more relevant clinical manifestation of cancer.

Author's contribution

Study design – R. Kozłowska, A. Bożek, J. Jarząb
Data collection – R. Kozłowska, A. Bożek
Data interpretation – R. Kozłowska, A. Bożek
Statistical analysis – R. Kozłowska, A. Bożek
Manuscript preparation – R. Kozłowska, A. Bożek, J. Jarząb
Literature research – R. Kozłowska

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