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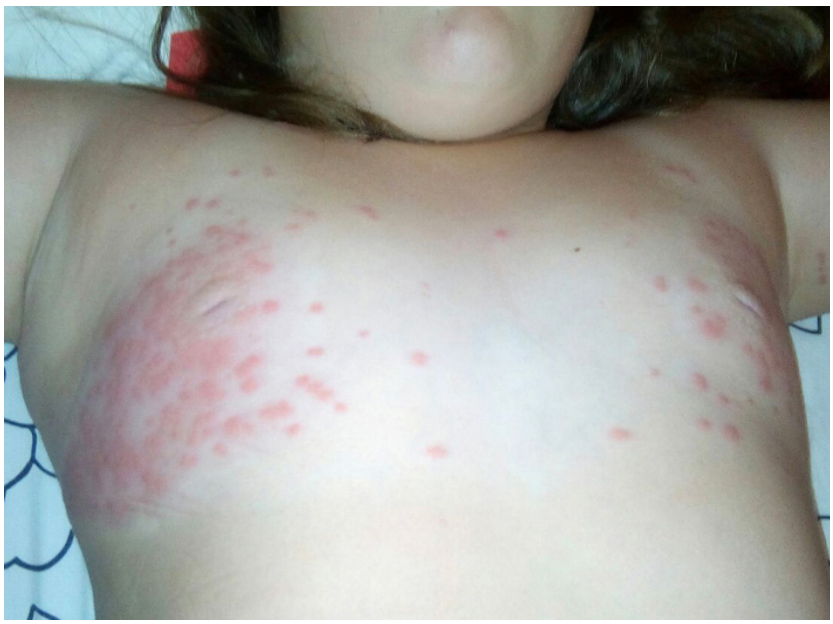

Cutaneous lesions on the body: what is your diagnosis?

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Contents

EDITORIAL

Friend or foe: how intestinal microbiome contribute to health and disease states

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In this issue, Allegra et al. provide an in-depth overview of how the microbiome influences hematologic malignancies. While largely overlooked in the past, the importance of the microbiome for human health is increasingly recognized. Whether convinced by disputes on causality or not, the modern medical doctor needs to remain informed on new insights in microbiome and disease. Several of these aspects will be dealt with here.

In the digestive tract, there is intensive contact between foreign antigens and the microbiome and here, our immune system is constantly exposed to a diversity of molecular microbial components and food. That immune system needs to remain tolerant against non-pathogenic antigens, and at the same time be capable of rapidly responding to potential pathogens to maintain tissue homeostasis. Failure in controlling balanced immune responses contributes to different pathogenic intestinal and systemic conditions.[1] The intestinal epithelium is covered by mucous layers of mucin, which serves as a physical barrier against the microbiome, and secretions of antimicrobial peptides protect intestinal crypts against bacterial overgrowth.[2,3] Secretion of polyspecific low affinity Immunoglobulin A (IgA) and lower quantities of higher affinity specific IgA regulate the composition of the intestinal microbiome.[4] Different pattern recognition receptors, on epithelium and immune cells, such as toll-like receptors, sense microbial components and direct immune responses against the microbiota.[5] Antigen presenting cells in the lamina propria help to promote mucosal tolerance by influencing T-cell differentiation, which is further supported by high numbers of regulatory T cells (Treg cells) in the gut, thereby maintaining tolerance against food and commensal antigens.[6] Also, innate lymphoid cells contribute to maintaining homeostasis at the gut lumen.[7] Early establishment of a healthy microbiome protects against pathogenic processes through prevention of intestinal colonization with pathogens, which has been called colonization resistance.[8,9] Due to recent advances in high-throughput sequencing and analytical tools, analysis of complex genomic bacterial datasets is now feasible, and has yielded an exponential increase of reported associations between disease states and microbiome composition. Whether many may seem indirectly meaningful, some other studies do contribute to completely new insights into how bacteria can drive human disease.

Under dysbiotic circumstances, bacterial products such as LPS and entire bacteria can translocate the epithelial lining, leading to continuous activation of CD4+ and CD8+ T cells and subsequently, autoimmunity.[10] Whereas distorted microbiome early after allogeneic hematopoietic cell transplantation can be identified and associated with development of acute graft versus host disease, the composition of the microbiome can also positively influence immune response, not only in hematopoietic cell transplantation (reviewed by Köhler and Zeiser)[11] but for instance, also in the outcome of cancer treatment. Efficacy of cancer immunotherapy with immune checkpoint antibodies can be diminished with administration of antibiotics, and superior efficacy is observed in the presence of specific gut microbes. This may offer future strategies to identify and correct defects in the microbiome to improve therapeutic efficiency.[12]

One of the reappearing questions concerns whether association between distinct microbiome profiles or bacterial species and diseases states reflect true causal relations, or whether it could merely be explained by changes secondary to inflamed tissues. Several well-designed studies may provide proof in favor of causality. For instance, Manfredo Vieiro et al. report in mice with genetic predisposition to lupus-like disease a translocation of gut pathobiont *Enterococcus gallinarum* to the liver and elsewhere to promote autoimmunity.

Antibiotic treatment reduced autoimmune phenomena and vaccination prevented translocation of this pathobiont. *E. gallinarum* DNA was recovered from liver tissue from patients with autoimmune diseases and *in vitro* assays with human cells proved autoimmune promoting effects, which supports the existence of similar bacterial-driven murine autoimmune processes in humans.[13] The potential of microbiota-mediated modulation of the immune system in humans was recently demonstrated in two patients with therapy refractory immune checkpoint inhibitor-associated colitis. They were successfully treated with fecal microbiota transplantation, with reconstitution of their gut microbiome and a relative increase in the proportion of Treg cells within the colonic mucosa.[14] Further studies are necessary to validate these findings.

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REVIEW

The association between allergic diseases and cancer: a systematic review of the literature

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ABSTRACT

Introduction: Atopic syndrome (allergic rhinitis, asthma and eczema) and food allergies are frequently reported, especially in developed countries. Studies have previously suggested an inverse association between allergic diseases and cancer. The aim of this study was to investigate the association between allergic diseases and different types of cancers by performing a systematic review of the literature.
Methods: A systematic literature search of Ovid Medline, Embase, Web of Science, Cochrane Library and Google Scholar was performed for studies on the association between allergic diseases and cancers.
Results: We identified a total of 5868 articles through our search, with 145 articles describing an association between allergic diseases and cancers. Allergies were associated with reduced risk of brain cancer, pancreatic cancer and melanoma and with possibly reduced risk of lymphatic and hematopoietic cancer, colorectal cancer, urogenital cancers of women and cancers in general. Asthma, but not atopy without asthma, was however associated with increased risk of lung cancer. There is possibly no association between allergic diseases and the risk of breast cancer and prostate cancer.
Conclusion: Overall, allergic diseases are inversely associated with the risk of cancers.

KEY WORDS

Allergic diseases, allergic diseases and cancer, atopy, cancer, malignancy

INTRODUCTION

Immunoglobulin E (IgE)-mediated allergic diseases (hereon called allergies) are frequently reported, especially in developed countries, and result in high morbidity and high costs for healthcare systems.[1] The most commonly reported allergies are atopic diseases (allergic rhinitis, asthma and eczema) and food allergies. The diagnostics and treatment options for patients with allergies have improved significantly in the past decades. Although still controversial, the hygiene hypothesis proposes a decrease in infectious disease in early childhood as the cause of high incidence of allergies and asthma in developed countries.[2] The lack of early infections leads to the stimulation of a T-helper 2 (Th-2) cell-mediated immune response favoring allergic diseases. The genetic susceptibility of the host however, may also play a key role in developing atopic symptoms.[3]
Previous studies have highlighted the potential inverse association between allergies and cancer.[4-6] Currently, the association between allergy and oncology is of high interest and the European Academy of Allergy and Clinical Immunology (EAACI) has established a Task Force to better understand basic immune responses in both fields.[7] Patients with allergic diseases may develop a state of enhanced immune surveillance leading to fewer occurrences of malignancies such as glioma and pancreatic cancer.[8,9] The purpose of this study was to give an overview of the association between allergic diseases and different types of cancers by performing a systematic review of the literature.

METHODS

A systematic literature search was performed to include all articles that addressed an association between allergy and cancer. This systematic review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Outcomes were structured by cancer category. The number of studies reporting a positive, negative or no association was noted. For each category the lowest and highest values of the most frequent risk estimates, such as the relative risk (RR) odds ratio (OR), hazard ratio (HR) and the standardized incidence ratio (SIR) were reported.

Data source

Studies on the association between allergy and cancer were conducted from the following online databases: Embase, Ovid Medline, Web of Science, Cochrane Library and Google Scholar.

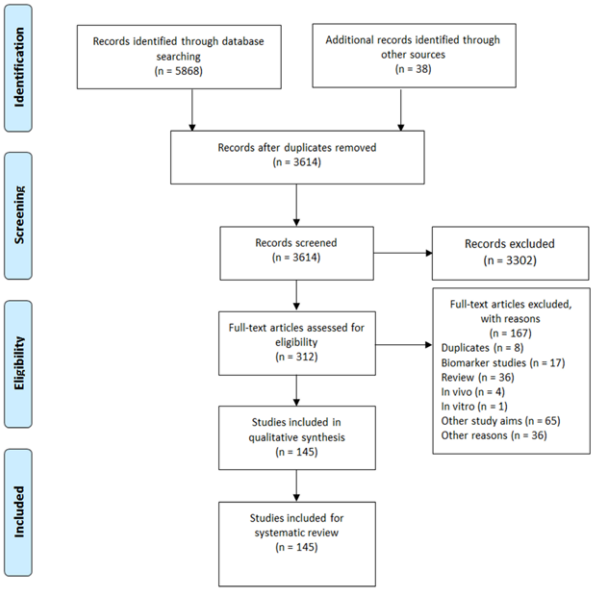
The last search was run on June 2nd, 2017. No filters for date or language were used in the search strategy (see the additional *Appendix* for the full search strategies).

Study selection

The titles and abstracts of all studies were reviewed after extracting duplicates. The studies were evaluated using the following criteria for inclusion: articles in English or English translation, original studies focusing on the relationship between allergy and cancer. Studies focusing on serological parameters such as serum IgE and malignancy, *in vivo* and *in vitro* animal studies, review articles and meta-analysis were excluded. Three reviewers (AFK, LW, RO) independently performed a review of the full text and could reach consensus on the relevance for inclusion of each article.

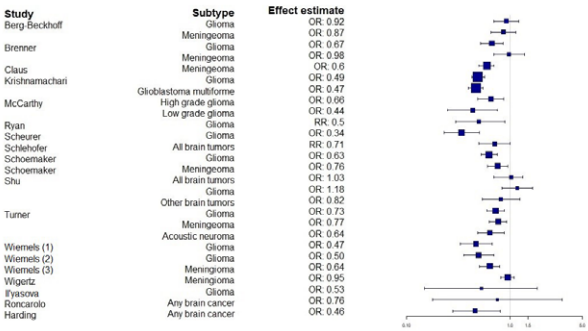
Data visualization

In order to visualize the various risk estimates, we used the R Statistical Software to plot forest plots for all included studies and plotted separate forest plots for the different cancer subgroups. We made forest plots for all study outcomes reported in relative risk (RR), OR, HR and SIR. Studies that reported other outcomes, such as the standardized mortality ratio, are not plotted in the forest plots; neither are studies that did not report 95% confidence intervals. No overall estimates were calculated, as the use of different methods to express risk estimates did not allow us to pool the studies. For the same reason, the degree of heterogeneity of studies could not be calculated.



RESULTS

Of a total of 5868 articles identified by the search, 312 articles publishing an association between allergy and cancer were eligible (*Supplementary figure 1*). After screening, we further narrowed down our selection to 145 articles that reported an association between allergies and malignancies. The main outcomes of this study are shown in *table 1, table 2* (*at the end of this article*) and *figure 1, Forest plots of the association between allergic diseases and cancer types.*



Brain cancer

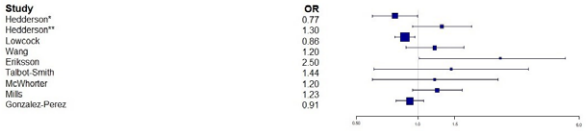
In total, we identified 19 studies describing an association between allergic diseases and brain cancer.

Positive association with brain cancer: no study demonstrated a positive association between allergic diseases and a brain tumor.

Negative association with brain cancer: We included 19 studies reporting the association between allergic disease and brain cancer. Of these, six studies showed no association between allergic diseases and brain cancer;[10-16] 12 studies demonstrated a consistent reduced risk of brain tumors in patients with allergic diseases (OR between 0.34 and 0.76);[11,17-28] and one study identified no association between allergic disease and meningioma, but did show a negative association between allergic disease and glioma. No studies reported a positive association.

Of the 19 studies, 16 examined the association between allergic diseases and brain cancer in adults, while three studies examined this association in children and adolescents.

Conclusion: Allergic diseases are mostly associated with a reduced risk of brain tumors.



* women aged > 35 years

** women aged 35 or less

Breast cancer

In total, eight studies on the association between allergic diseases and breast cancer were included.

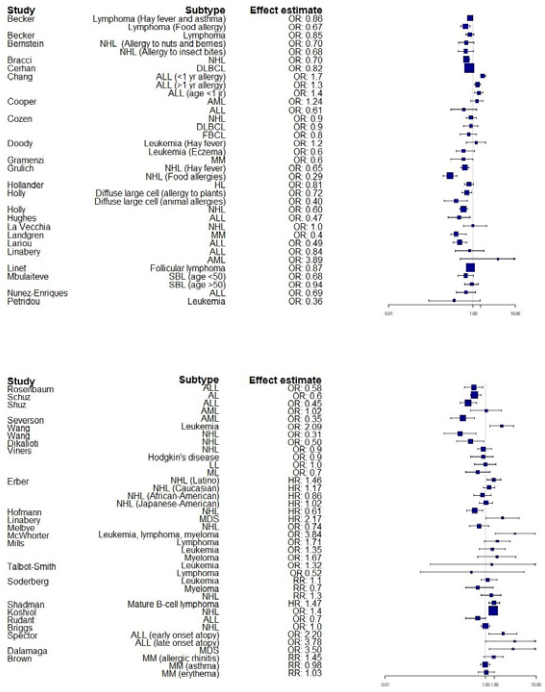
Positive association with breast cancer: only one out of eight studies identified a positive association between allergic diseases and breast cancer (OR 2.5).[29]

Negative association with breast cancer: a negative association between allergic diseases and breast cancer was found in two studies (OR 0.77 and 0.86).[30,31] Hedderson et al. found a decreased risk (OR 0.77) of breast cancer in women aged 35 years or older having a history of allergic diseases.[30] However, in the same study, no association was observed between breast cancer and allergic diseases in women younger than 35 years. The other five studies did not identify a positive or negative association between allergic diseases and breast cancer.[32-36]

Conclusion: In general, allergic diseases do not appear to influence the breast cancer risk in women.

Lymphatic and hematopoietic cancer

We included a total of 47 studies on the association between allergic diseases and lymphatic and hematopoietic cancers. Negative as well as positive associations between allergic diseases and lymphatic and hematopoietic cancers have been published. Of the 47 studies, 20 showed no association, 15 reported a negative association (range OR: 0.29 to 0.87) and eight demonstrated a positive association



(range OR: 1.3 to 3.84); four studies presented different associations for different subgroups.

Positive association with lymphoma: A positive association between allergic diseases and lymphoma was demonstrated in four studies (range OR:1.4-3.84).[34,37-39] A positive association between airborne allergies and development of hematological malignancies, in particular, mature B-cell lymphoma (HR: 1.47) was found in one study.[38] In this study however, the risk of malignancy was increased in women with a history of allergies to airborne allergens of plants, grass or trees, but not in men. Another study showed overall increased risk for non-Hodgkin lymphoma (NHL) in patients with allergic diseases (OR: 1.4).[37] The high risk was mostly associated with erythema and allergic alveolitis, rather than with airborne allergies, and black patients with allergies seemed to be at a higher risk of developing NHL than white patients.

Negative association with lymphoma: A total of 10 studies showed a protective, negative association between allergic diseases and lymphoma (range OR: 0.29-0.87).[40-49] In the study of Becker et al., hay fever and asthma did not influence the risk of lymphoma, and the association between food allergies and lymphoma was negative (OR: 0.67).[47] The only study investigating the association between allergic diseases and NHL in children demonstrated a negative association (OR: 0.50).[48]

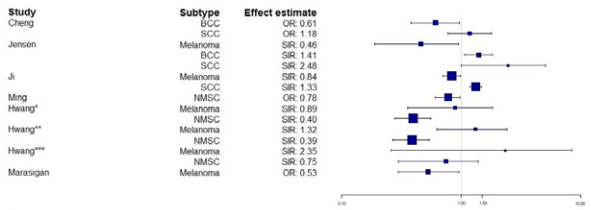
In total, 14 studies however could not find any association between allergic diseases and lymphoma.[33,35,39,47,50-59]

Positive association with other hematological malignancies: Seven studies of other hematological malignancies including lymphatic or myeloid leukemia, multiple myeloma and myelodysplastic syndrome, demonstrated positive associations between allergic diseases and these malignancies (range OR: 1.3-3.5).[34,60-65] In Linabery et al., no association was found between allergic diseases and hematological malignancies, but a clear association was noted between asthma and myelodysplastic syndrome (HR: 2.17).[63] This study was however limited to post-menopausal women.

Negative association with other hematological malignancies: A total of seven studies demonstrated a negative association between other hematological malignancies and history of allergic diseases (range OR: 0.4-0.6).[66-72]

A total of 10 studies (out of 47) examined the association between hematological malignancies and allergic diseases in children. As mentioned earlier, one study studied the association between allergic diseases and NHL and found a protective, negative association (OR:0.5).[48] Another study found a positive association between allergic diseases and acute lymphocytic leukemia (ALL) in children (OR 2.2).[64] The other 10 studies investigated the association between allergic diseases and leukemia in children. Only two studies showed a positive association between allergic diseases and leukemia (OR 1.4-1.7 and OR 2.2 respectively).[60,64] In Spector et al., the early onset atopy was associated with increased risk of ALL, while there was no association between late onset atopy and ALL in children.[64] In five studies, no associations between leukemia and allergic diseases were found.[64,72-75]

Conclusion: Most of the studies demonstrated no association between allergic diseases and lymphatic and hematopoietic cancers. However, there are more studies showing a protective role of allergies than studies with a positive association between allergic diseases and lymphatic and hematopoietic cancers.



* Allergic rhinitis
** Asthma
*** Atopic dermatitis

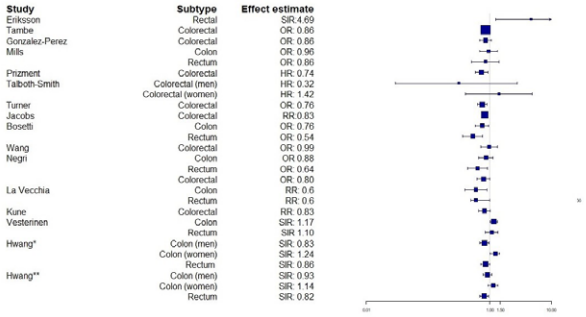
Skin cancer

There is a limited number of studies on the association between skin cancers and allergic diseases available. We included seven studies.

Positive association with skins cancers: In two studies, a positive association between allergic diseases and skin cancer was described; SIR: 1.41 for basal cell carcinoma (BCC), SIR: 1.33 for squamous cell carcinoma (SCC).[76,77]

Negative association with skin cancers: A total of six studies described negative associations between allergic diseases and skin cancers (range SIR 0.39 to 0.84; range OR 0.53 to 0.78).[76-82] In Cheng et al., the risk for developing BCC was decreased (OR: 0.61), while there was no association between allergic diseases and SCC.[78] Two studies found a negative association between atopic dermatitis and non-melanoma scan cancers (NMSC) (OR 0.78 and SIR 0.40).[79,80] Four out of five studies investigating the relationship between allergies and malignant melanoma observed a decreased risk for melanoma (range SIR: 0.46-0.84).[76,77,81,82] In Hwang et al., the risk for developing malignant melanoma was unchanged in patients with allergic rhinitis, asthma and atopic dermatitis.[80]

Conclusion: Allergic diseases appear to reduce the risk for developing malignant melanoma and NMSC.



* Asthma
** Allergic rhinitis

Colorectal cancers

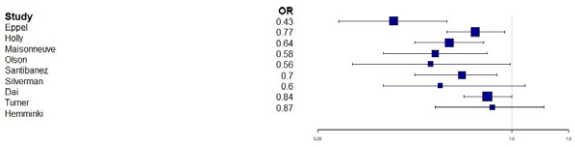
We included 17 studies that evaluated the association between allergic diseases and colorectal cancers.

Positive association with colorectal cancers: Three studies described positive associations between allergic diseases and colorectal cancers (range SIR: 1.17-4.69).[80,83,84] Vesterinen et al. found a positive association between asthma and colon carcinoma (SIR:1.17), but could not identify any association between asthma and rectal carcinoma.[84] In Hwang et al., only a positive association

was seen between asthma and colon carcinoma in women (SIR: 1.24).[80]

Negative association with colorectal cancer: A negative association between allergies and colon cancer was found in nine studies (range OR: 0.54-0.86).[80,85-92] Prizment et al. studied the risk of colorectal cancer only in women and found a negative association (HR:0.74).[86] Negri et al. described only a negative association between allergic diseases and rectum carcinoma, but no association between allergic diseases and colon carcinoma (OR: 0.64).[90] In contrast La Vecchia et al. identified a negative association between allergic diseases and colon carcinoma, yet no association with rectal carcinoma (RR: 0.6).[91]
No associations were observed between allergic diseases and colorectal cancers in 11 studies.[32,34-36,80,84,88,90,91,93,94]

Conclusion: Overall, the risk of colorectal cancer is possibly reduced in patients with allergic diseases.

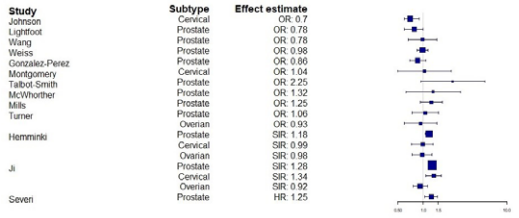


Pancreatic cancer
We identified 10 studies on the association between allergic diseases and pancreatic cancer.

Positive association with pancreatic cancer: No studies were published describing a positive association between allergic diseases and pancreatic cancer.

Negative association with pancreatic cancer: In total, seven studies reported a negative association between allergic diseases and pancreatic cancer (range OR: 0.43-0.77).[9,95-100] In Olson et al., hay fever and allergies to animals were related to a reduced risk of pancreatic cancer, while asthma and other allergies did not appear to influence the risk of pancreatic cancer (OR 0.58).[98] Three other studies did not observe an association between allergic diseases and pancreatic cancer.[87,101,102]

Conclusion: Overall, allergic diseases are associated with a reduced risk of pancreatic cancer.

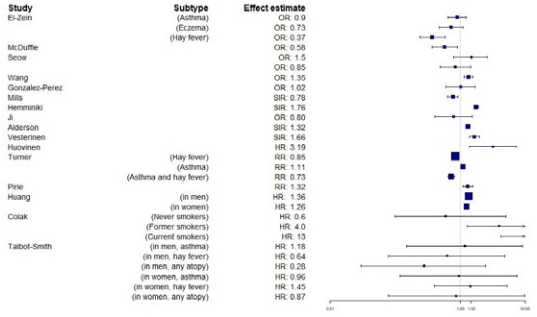


Urogenital cancers
Among urogenital cancers, a total of 12 studies were identified reporting the association between allergic diseases and prostate cancer[32-36,76,81,87,102-105] and seven studies described the association with female urogenital cancers.[76,81,87,102,106-108]

Positive association with urogenital cancers: In total, three studies demonstrated an increased risk of prostate cancer in patients with allergic diseases (range SIR: 1.18-1.64).[76,102,105] Only one study showed a positive association between allergic diseases and cervix cancer (SIR 1.34),[76] however, only the association between asthma and cancer was studied.

Negative association with urogenital cancers: Only one study showed a negative association between allergic diseases and prostate cancer (SMR 72).[81] In eight studies, no significant association was described between allergic diseases and prostate cancer.[32-36,87,103,104] Three studies on uterine leiomyomas, squamous cell cervical cancer, cervix and ovarian cancer showed reduced risks of these cancers in women with allergic diseases.[81,106,107] In Kallen et al. however, only the association between asthma and cervix and ovarian cancer was studied.[81] Four other studies looking at the association between allergic diseases and cervical cancer and ovarian cancer observed no changes in the risk of developing these cancers in women.[76,87,102,108] Ji et al. however, despite observing no general association between allergic diseases and ovarian cancer, did see a positive association between asthma and cervix cancer (SIR 1.34).[76]

Conclusion: In general, there is possibly no association between allergic diseases and prostate cancer in men. Studies on the association between allergic diseases and female urogenital cancers are limited, but favor a protective role of allergies.

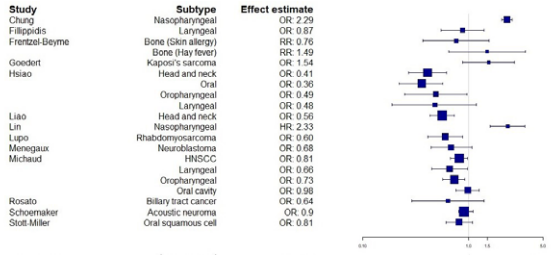


Lung cancer
We included a total of 19 studies, which studied the relationship between allergic diseases and lung cancer.

Positive association with lung cancer: In 10 studies, increased risks of lung cancer in allergic diseases were observed (range HR: 1.26- 13).[36,76,81,84,87,109-113] In Reynolds et al., the lung cancer risk was increased only in men with asthma.[109] In all except for two studies,[114,115] focusing only on examining the associations between asthma (and not other allergic disorders) and lung cancer, showed an increased risk of lung cancer. [33,35,36,76,81,84,87,109-113] In Turner et al., lung cancer mortality was increased in patients with asthma, but reduced in patients with hay fever only or patients with both asthma and hay fever (RR 1.11, 0.85 and 0.73, respectively).[87] In another study, lung cancer incidence was increased in current smokers and former smokers with a history of asthma, but in patients with asthma who never smoked, the cancer risk was unchanged (HR 13, 4.0 and 0.6, respectively).[113]

Negative association with lung cancer: In five studies, negative associations between allergic diseases and lung cancer were found (OR 0.37-0.85).[87,102,115-117] These studies usually examined the association between allergies (not only asthma) and lung cancer, and showed a reduced risk of developing lung cancer. The same applied to studies where, in general, no association was found between allergic diseases and lung cancer.[32,33,35,113-115,118]

Conclusion: Asthma is related with an increased risk of lung cancer, while atopic patients without asthma may be protected.



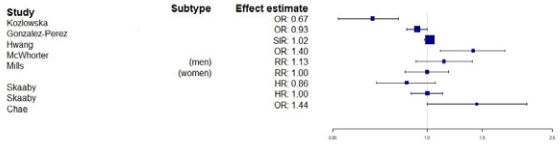
Other cancers

In total, we included 13 studies that studied the association between other cancers and allergic diseases.

Positive association with other cancers: In two studies, a positive association between allergic diseases and nasopharyngeal cancers was observed (OR 2.29 and HR: 2.33).[119,120]

Negative association with other cancers: Four studies found a negative association between allergic diseases and cancers, including head and neck cancers and rhabdomyosarcoma.[121-124] However, no associations were noticed for most of other cancers including laryngeal cancer,[125] neuroblastoma,[119-126] biliary tract cancer,[127] acoustic neuroma,[128] oral squamous cell carcinoma[129] and Kaposi's sarcoma.[130]

Conclusion: Most of the studies published do not show a change of risk for developing cancers in patients with allergic diseases.



Cancer in general

We investigated the risks of developing cancer in 12 studies.

Positive association with cancer: The risk of developing cancer was increased (OR 1.40) in only one study by McWorther.[34] In this study, hives were associated with the strongest cancer risk and the strongest allergy association was with lymphatic-hematopoietic cancers.

Negative association with cancer: In total, five studies described a negative association between allergic diseases and cancer in general [131-135] Six other studies did not find an association between allergic diseases and cancer.[35,36,80,136-138]

Conclusion: Mixed results were noticed, but in general, allergic diseases may reduce the cancer risk.

DISCUSSION

In this systematic review, we described the association between allergic diseases and different types of malignancies. This review delivers a comprehensive overview of the risk of malignancies in patients with allergies.

In this study we demonstrate an inverse association between allergic diseases and most of the cancers. Allergic diseases appear to reduce the risk of brain cancer, pancreatic cancer, melanoma and possibly the risk of lymphatic and hematopoietic cancers, colorectal cancers, female urogenital cancers and cancer in general. The current available studies do not provide sufficient evidence for a protective role of allergic diseases in developing breast cancer and prostate cancer. Asthma appears to increase the risk of lung cancer, however, patients with atopic diseases without asthma possibly do not have an increased risk of lung cancer.

The question of interest is how allergies may cause immunosurveillance. Allergic immunity depends on Th2-cells, basophils, eosinophils, macrophages and the antibodies type IgG1 and IgE.[139] Allergy is a consequence of improved and hyper-responsive immune system, which may possibly recognize dysregulated or damaged cells, including cancer cells, and may efficiently eradicate these cells (immunosurveillance hypothesis). Patients with allergic diseases have thus an adapted immune system, which may protect against cancers.[140] The production of tumor-specific IgE alone, which has antitumor effects of dendritic cells, eosinophils, basophils and mast cells offer better tumor surveillance and reduced risk of cancers.[7] Furthermore, it is suggested that allergic reactions in specific tissues may be able to remove mutagenic triggers before transformation to malignant cells occur (prophylaxis hypothesis).

Despite an inverse association between allergic diseases and cancer, asthma appears to be independently associated with increased risk of lung cancer, after adjustment for smoking habits. The patients with atopic constitution without asthma however, have a possibly reduced risk of lung cancers. Patients with asthma have mostly other subtypes of lung cancer than adenocarcinoma.[141] Despite the protective role of allergies in cancers, patients with asthma are regularly characterized by airway inflammation, which possibly plays a crucial role in the pathogenesis of lung cancer. Chronic inflammatory conditions may promote development of cancer because of oxidative damage resulting in tumor suppressor gene mutations. Different studies have indeed demonstrated a relationship between chronic airway inflammation and lung cancer.[142,143] Furthermore, recurrent treatment with local or systemic glucocorticoids may also lead to better tumor outcomes and increased cancer risk.[6]

A next interesting question addresses the role of allergen immunotherapy in the development of cancer. Studies have suggested that tumor microenvironment may favor switching to a tumor-specific IgG4, a less potent immunoglobulin, instead of IgG1 and IgE.[144] IgG4 antibodies do not have sufficient immunostimulatory capacities, may block the cytotoxic activities of other antibodies and are correlated with shorter survival and disease progression.[144,145] On the other hand, current data also suggest positive correlation between IgG4-related disease and enhanced cancer risk.[146] In allergic patients undergoing allergen-specific immunotherapy, increased IgG4-specific antibodies have been observed and correlate with allergen tolerance.[147] However, to date, no data are available on cancer incidence and mortality in patients being successfully desensitized.

The results of this study may be limited by studies relying on self-reported ascertainment of allergies, different methods of establishing the diagnosis of allergies, retrospective studies and not always adjusting for cofounders. The variety in methodology of the different studies did not permit us to calculate pooled estimates. Furthermore, by classifying all tumors in broad categories such as lung cancer, lymphatic and hematopoietic cancer, we do not consider possible differences between associations in subtypes of tumors. However, a substantial amount of evidence for the inverse association between allergic diseases and malignancies is reported. Exceptions are patients with asthma who have increased risk of lung cancer. Large prospective studies with validated measurement of allergies and data on potentially confounding factors are required for better understanding the association between allergy and oncology.

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DISCLOSURES

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APPENDIX

Search terms used in the medical database for the literature search in this systematic review on the association between allergy and cancer.

Embase.com (2694)

('allergy'/de OR 'atopy'/de OR 'rhinoconjunctivitis'/de OR 'allergic asthma'/de OR 'allergic rhinitis'/exp OR 'atopic dermatitis'/de OR 'food allergy'/exp OR (allerg* OR atopy OR atopic OR rhinoconjunctivit* OR (rhino NEXT/1 conjunctivit*) OR 'hay fever'):ab,ti) AND (oncology/de OR 'neoplasm'/de OR 'malignant neoplastic disease'/exp OR 'precancer and cancer-in-situ'/exp OR 'skin cancer'/de OR 'cancer risk'/de OR 'cancer incidence'/de OR 'digestive system cancer'/exp OR 'breast cancer'/exp OR 'prostate cancer'/de OR 'bladder cancer'/de OR 'thyroid cancer'/de OR 'brain tumor'/exp OR 'lung cancer'/exp OR 'carcinogenicity'/de OR (oncolog* OR allergooncolog* OR neoplas* OR cancer* OR (tumo* NOT ('tumor necrosis factor')) OR malign* OR leukemi* OR leukaemi* OR glioma* OR glioblastoma* OR astrocytom* OR carcino* OR

lymphoma* OR hodgkin OR myeloma OR meningioma* OR melonoma*):ab,ti) AND ('disease association'/de OR 'health hazard'/de OR 'hazard assessment'/de OR 'incidence'/de OR 'population risk'/de OR 'cancer risk'/de OR 'cancer incidence'/de OR 'odds ratio'/de OR risk/de OR 'neoplasm'/exp/dm_et OR 'risk factor'/de OR (((associat*s NEAR/6 (cancer* OR risk* OR disease* OR factor*)) OR ((risk*) NEAR/6 (cancer* OR disease* OR factor*)) OR hazard* OR incidence OR 'odds ratio' OR relationship* OR allergooncolog* OR (allergo NEXT/1 oncolog*)):ab,ti) AND ('observational study'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'health survey'/de OR 'health care survey'/de OR 'epidemiological data'/de OR 'case control study'/de OR 'cross-sectional study'/de OR 'correlational study'/de OR 'population research'/de OR 'family study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'comparative study'/de OR 'follow up'/de OR 'clinical study'/de OR 'clinical article'/de OR 'clinical trial'/exp OR 'randomization'/exp OR 'intervention study'/de OR 'open study'/de OR 'community trial'/de OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/3 (stud* OR survey)) OR (health* NEAR/3 survey*) OR ((case OR cases OR match*) NEAR/3 control*) OR (cross NEXT/1 section*) OR correlation* OR multicenter* OR (multi* NEXT/1 center*) OR 'follow up' OR followup* OR clinical* OR trial OR random*):ab,ti) NOT ([Conference Abstract]/lim) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline ovid (1585)

("Hypersensitivity"/ OR exp "Rhinitis, Allergic"/ OR "Dermatitis, Atopic"/ OR exp "Food Hypersensitivity"/ OR (allerg* OR atopy OR atopic OR rhinoconjunctivit* OR (rhino ADJ conjunctivit*) OR "hay fever").ab,ti.) AND ("Medical Oncology"/ OR "Neoplasms"/ OR exp "Skin Neoplasms"/ OR exp "Digestive System Neoplasms"/ OR exp "Breast Neoplasms"/ OR exp "Prostatic Neoplasms"/ OR exp "Urinary Bladder Neoplasms"/ OR exp "Thyroid Neoplasms"/ OR exp "Brain Neoplasms"/ OR exp "Lung Neoplasms"/ OR (oncolog* OR allergooncolog* OR neoplas* OR cancer* OR (tumo* NOT ("tumor necrosis factor")) OR malign* OR leukemi* OR leukaemi* OR glioma* OR glioblastoma* OR astrocytom* OR carcino* OR lymphoma* OR hodgkin OR myeloma OR meningioma* OR melonoma*).ab,ti.) AND ("Association"/ OR "Incidence"/ OR "Odds Ratio"/ OR exp risk/ OR exp "Neoplasms"/et OR (((associat*) ADJ6 (cancer* OR risk* OR disease* OR factor*)) OR ((risk*) ADJ6 (cancer* OR disease* OR factor*)) OR hazard* OR incidence OR "odds ratio" OR relationship* OR allergooncolog* OR (allergo ADJ oncolog*)).ab,ti.) AND (exp "observational study"/ OR exp "Cohort Studies"/ OR exp "health surveys"/ OR "Health Care Surveys"/ OR "Epidemiological Monitoring"/ OR "Case-Control Studies"/ OR exp "Epidemiologic Studies"/ OR "multicenter study"/ OR "comparative study"/ OR exp "clinical study"/ OR "Random Allocation"/ OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) ADJ6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* ADJ3 (stud* OR survey)) OR (health* ADJ3 survey*) OR ((case OR cases OR match*) ADJ3 control*) OR (cross ADJ section*) OR correlation* OR multicenter* OR (multi* ADJ center*) OR "follow up" OR followup* OR clinical* OR trial OR random*).ab,ti.) AND english.la. NOT (exp animals/ NOT humans/)

Cochrane (150)

((allerg* OR atopy OR atopic OR rhinoconjunctivit* OR (rhino NEXT/1 conjunctivit*) OR 'hay fever'):ab,ti) AND ((oncolog* OR allergooncolog* OR neoplas* OR cancer* OR (tumo* NOT ('tumor necrosis factor')) OR malign* OR leukemi* OR leukaemi* OR glioma* OR glioblastoma* OR astrocytom* OR carcino* OR lymphoma* OR hodgkin OR myeloma OR meningioma* OR melonoma*):ab,ti) AND ((((associat*) NEAR/6 (cancer* OR risk* OR disease* OR factor*)) OR ((risk*) NEAR/6 (cancer* OR disease* OR factor*)) OR hazard* OR incidence OR 'odds ratio' OR relationship* OR allergooncolog* OR (allergo NEXT/1 oncolog*)):ab,ti)

Web of science (1239)

TS=(((allerg* OR atopy OR atopic OR rhinoconjunctivit* OR (rhino NEAR/1 conjunctivit*) OR "hay fever")) AND ((oncolog* OR allergooncolog* OR neoplas* OR cancer* OR (tumo* NOT ("tumor necrosis factor")) OR malign* OR leukemi* OR leukaemi* OR glioma* OR glioblastoma* OR astrocytom* OR carcino* OR lymphoma* OR hodgkin OR myeloma OR meningioma* OR melonoma*)) AND ((((associat*) NEAR/5 (cancer* OR risk* OR disease* OR factor*)) OR ((risk*) NEAR/5 (cancer* OR disease* OR factor*)) OR hazard* OR incidence OR "odds ratio" OR relationship* OR allergooncolog* OR (allergo NEAR/1 oncolog*))) AND ((((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/5 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR
population* OR (national* NEAR/2 (stud* OR survey)) OR (health* NEAR/2 survey*) OR ((case OR cases OR match*) NEAR/2 control*) OR (cross NEAR/1 section*) OR correlation* OR multicenter* OR (multi* NEAR/1 center*) OR "follow up" OR followup* OR clinical* OR trial OR random*))) AND DT=(article) AND LA=(english)

Google scholar (200)

Allergy/allergies/allergic/atopy/atopic/rhinoconjunctivitis/"hay fever" oncology/neoplasms/cancer/malignant/malignancies association/risk/hazard/incidence/"odds ratio"/relationship

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Table 1. *The association between allergies and cancers*

Brain cancer, case control studies				
Reference	**Allergy**	**Type of cancer: statistical value (95% CI)**	**Association**	**Comments**
(10) Berg-Beckhoff	Any allergy (hay fever, eczema, asthma)	Glioma: OR 0.92 (0.70-1.22) Meningioma: OR 0.87 (0.66-1.14)	No association	
(11) Brenner	Any allergy (hay fever, eczema, asthma)	Glioma: OR 0.67 (0.52-0.86), Meningioma: OR 0.98 (0.70-1.38)	Negative No association	
(17) Claus	Any allergy (not specified)	Meningioma OR 0.6 (0.-50.7)	Negative	
(18) Krishnamachari	Any allergy (allergies, asthma, eczema)	Glioma: OR 0.49 (0.43-0.57) Glioblastoma multiforme: OR 0.47 (0.40-0.55)	Negative	
(19) McCarthy	Any allergy (seasonal, medication, pet, food, not specified)	High grade glioma: OR 0.66 (0.49-0.87) Low grade glioma: OR 0.44 (0.25-0.76)	Negative	
(20) Ryan	Any allergy (not specified)	Glioma: RR 0.5 (0.3-0.9)	Negative	
(21) Scheurer	Any allergy (asthma, allergy not specified)	Glioma: OR 0.34 (0.23-0.51)	Negative	Adjusted odds ratio for the use of antihistamines and anti-inflammatory agents among glioma cases and controls
(12) Schlehofer	Any allergy (asthma, eczema, allergy not specified)	All brain tumors: RR 0.71 (0.5-1.0)	No association	
(23) Schoemaker	Any allergy (asthma, hay fever, eczema)	Glioma: OR 0.63 (0.53-0.76)	Negative	
(23) Schoemaker	Any allergy (asthma, hay fever, eczema)	Meningioma: OR 0.76 (0.61-0.96)	Negative	
(13) Shu	Any allergy (asthma, eczema, allergic rhinitis, wheezing)	All brain tumors: OR 1.03 (0.70-1.34), Glioma: OR 1.18 (0.84-1.67), Other brain tumors (PNET, other specified brain tumors, unspecified brain tumors: OR 0.82 (0.54-1.25)	No association	Study with adults and children.
(24) Turner	Any allergy (asthma, hay fever, eczema)	Glioma: OR 0.73 (0.60-0.88), Meningioma: OR 0.77 (0.63-0.93), Acoustic neuroma: OR 0.64 (0.49-0.83)	Negative	
(25) Wiemels	Any allergy (hay fever and food allergy)	Glioma: OR 0.47 (0.33-0.67)	Negative	
(26) Wiemels	Any allergy (hay fever and food allergy	Glioma: OR 0.50 (0.36-0.70)	Negative	
(27) Wiemels	Any allergy (not specified)	Meningioma: OR 0.64 (0.51-0.80)	Negative	
(14) Wigertz	Any allergy (asthma, eczema, hay fever, food allergy, not specified)	Meningioma: OR 0.95 (0.82-1.10)	No association	

(15) Il'yasova	Any allergy (hay fever, medication and food allergy)	Glioma: OR 0.53 (0.15-1.84)	No association	
(16) Roncarolo	Allergic asthma and eczema	Any brain cancer: OR 0.76 (0.18-3.2)	No association	Study in children
(28) Harding	Allergic asthma and eczema	Any brain cancer: OR 0.46 (0.28-0.81)	Negative	Study in children. Reduced risk of malignancy in asthma and combination of asthma and eczema, no reduction of risk in eczema alone.
Breast cancer, case control studies				
Reference	**Allergy**	**Statistical value (95% CI)**	**Association**	**Comments**
(30) Hedderson	Any allergy (hay fever, drug reaction, insect venom, food)	Breast cancer in women aged 35 years or older: OR 0.77 (0.60-0.99), Breast cancer in women younger than 35: OR 1.30 (0.94-1.81)	Negative No association	
(31) Lowcock	Any allergy (hay fever, not specified)	Breast cancer: OR 0.86 (0.77-0.96)	Negative	
(32) Wang	Any allergy (asthma, hay fever, atopic dermatitis)	Breast cancer: OR 1.20 (0.87-1.66)	No association	
(29) Eriksson	Atopy (confirmed with skin prick test)	Breast cancer: OR 2.50 (1.01-5.16)	Positive	
(33) Talbot-Smith	Any atopy	Breast cancer: OR 1.44 (0.61-3.41)	No association	
(34) McWhorter	Any allergy	Breast cancer: OR 1.20 (0.60-2.43)	No association	
(35) Mills	Any allergy	Breast cancer: OR 1.23 (0.94-1.63)	No association	
(36) Gonzalez-Perez	Asthma	Breast cancer: OR 0.91 (0.78-1.06)	No association	Adjusted for age/sex/calendar year/BMI/ alcohol/smoking/prior comorbidities/health services utilization/aspirin/NSAID/ paracetamol
Lymphatic and hematopoietic cancer, case control studies				
Reference	**Allergy**	**Cancer type: statistical value (95% CI)**	**Association**	**Comments**
(47) Becker	Hay fever and asthma; Food allergy	Lymphoma: OR 0.86 (0.73-1.01); Lymphoma: OR 0.67 (0.52-0.85)	No association; Negative	
(59) Becker	Any allergy (not specified)	Lymphoma: OR 0.85 (0.68-1.07)	No association	
(58) Bernstein	Allergy to nuts and berries; Insect bites allergy	NHL: OR 0.70 (0.46-1.05), NHL: OR 0.68 (0.44-1.04)	No association	
(49) Bracci	Allergic rhinitis	NHL: OR 0.70 (0,60-0.83)	Negative	
(46) Cerhan	Any allergy (excluding drug allergies)	DLBCL: OR 0.82 (0.76-0.89)	Negative	Pooled analysis from 19 InterLymph studies

(60) Chang	Any allergy (hay fever, asthma, atopic dermatitis, anaphylaxis and unspecified allergy)	ALL: OR 1.7 (1.5-2.0): in cases of having an allergy less than one year before ALL diagnosis, ALL: OR 1.3 (1.1-1.5): having an allergy more than one year before ALL diagnosis, ALL: OR 1.4 (1.1- 1.7): having allergy before the age of one year.	Positive	Childhood ALL
(148) Cooper	Any allergy	AML: OR 1.24 (0.88-1.73), ALL: OR 0.61 (0.30-1.25)	No association	
(57) Cozen	Any allergy (hay fever, food, animal, insect, dust, medication allergies)	NHL: OR 0.9 (0.7-1.2), DLBCL: OR 0.9 (0.6-1.3), FBCL: OR 0.8 (0.5-1.2)	No association	
(149) Doody	Hay fever; Eczema	Leukemia: OR 1.2 (0.7-2.0); Leukemia: OR 0.6 (0.4-1.1)	No association	Leukemia: AML, CML, AUL, CLL Statistical value for MM, NHL, and the above separately
(61) Gallagher	Any allergy (not specified)	MM: RR 3.1, $p < 0.001$	Positive	Myeloma patients described the symptoms mainly as skin rashes, swellings and hives.
(150) Gramenzi	Any allergy (drug and food allergies, asthma, eczema)	MM: RR 0.6 (0.3-1.0)	No association	
(45) Grulich	Hay fever; Food allergies	NHL: OR 0.65 (0.52-0.82); NHL: OR 0.29 (0.20-0.42)	Negative	
(56) Hollander	Allergic rhinitis	HL: OR 0.81 (0.64-1.03)	No association	
(44) Holly	Allergy to plants; Animal allergies	Diffuse large cell: OR 0.72 (0.55-0.94); Diffuse large cell: OR 0.40 (0.21-0.73)	Negative; Negative	
(43)Holly	Plant allergies	NHL: OR 0.60 (0.48-0.75)	Negative	
(66) Hughes	Hay fever	ALL: 0.47 (0.26-0.85)	Negative	
(55) La Vecchia	Any allergy (drug, food, asthma eczema)	NHL: RR 1.0 (0.6-2.1)	No association	
(67) Landgren	Any allergy (not specified)	MM: OR 0.4 (0.3-0.7)	Negative	
(70) Lariou	Any allergy (respiratory, food, not specified)	ALL: OR 0.49 (0.34-0.72)	Negative	Patient population: children
(73) Linabery	Any allergy (inhaled, food, medication and contact allergies)	ALL: OR 0.84 (0.38-1.85), AML: OR 3.89 (0.50-29.95)	No association	Patient population: children with Down syndrome
(42) Linet	Any allergy (asthma, eczema, hay fever, not specified, excluding drug allergies)	Follicular lymphoma: OR 0.87 (0.80-0.94)	Negative	
(54) Mbulaiteye	Any atopic condition	SBL: Age < 50 years: OR 0.68 (0.45-1.02), Age > 50 years: OR 0.94 (0.64-1.37)	No association	

(74) Nunez-Enriquez	Any allergy (skin allergy, bronchial asthma, rhinitis, not specified)	ALL: 0.69 (0.40-1.17)	No association	Patient population: children with Down syndrome
(71) Petridou	Allergic disease (not specified)	Leukemia: OR 0.36 (0.09-1.43)	No association	Childhood leukemia
(151) Rosenbaum	Any allergy (hay fever, asthma, animal, food-drug-bee, eczema)	ALL: OR 0.58 (0.38-0.88)	Negative	Childhood ALL
(68) Schuz	Any allergy (not specified)	AL: OR 0.6 (0.5-0.8)	Negative	
(72) Schuz	Hay fever	ALL: OR 0.45 (0.31-0.66), AML: OR 1.02 (0.50-2.08)	Negative, No association	Childhood leukemia
(69) Severson	Any allergy (not specified)	AML: OR 0.35 (0.20-0.60)	Negative	
(62) Wang	Any allergy (asthma, hay fever, food or drug allergies, and eczema)	Leukemia: OR 2.09 (1.22-3.58)	Positive	
(41) Wang	Any allergy (hay fever, animal or egg allergy, plant allergy, asthma, eczema)	NHL: OR 0.31 (0.15-0.64)	Negative	
(48) Dikalioti	Any allergy	NHL: OR 0.50 (0.27-0.29)	Negative	Childhood NHL
(53) Vineis	Any allergy	NHL: 0.9 (0.7-1.3) Hodgkin's disease: 0.9 (0.5-1.4), LL: OR 1.0 (0.6-1.6), ML: OR 0.7 (0.4-1.2)	No association for all listed	
Lymphatic and hematopoietic cancer, cohort studies				
(39) Erber	Any allergy (asthma, hay fever, skin, food or not specified)	NHL: HR 1.46 (1.07-2.00): Latinos NHL: HR 1.17 (0.90-1.52): Caucasian NHL: HR 0.86 (0.58-1.27): African American NHL: HR 1.02 (0.75-1.38): Japanese American	Positive, No association, No association, No association	
(40) Hofmann	Any allergy (hay fever, eczema)	NHL: HR 0.61 (0.42-0.87)	Negative	
(63) Linabery	Any allergy (not specified)	Asthma: MDS HR 2.17 (1.01-4.64) No significant association between allergy and lymphoid and myeloid malignancies	Positive	Large study among post-menopausal Caucasian women
(52) Melbye	Any allergy (not specified)	NHL: OR 0.74 (0.48-1.15)	No association	
(34) McWhorter	Any allergy	Leukemia, lymphoma, or myeloma OR 3.84 (1.55-9.51)	Positive	
(35) Mills	Any allergy (hay fever, asthma, plant allergy, bee allergy	Lymphoma: OR 1.71 (0.95-3.09), Leukemia: OR 1.35 (0.75-2.46), Myeloma: OR 1.67 (0.70-4.00)	No association	
(33) Talbot-Smith	Any allergy (asthma, hay fever)	Leukemia: OR 1.32(0.08-21.54), Lymphoma: OR 0.52 (0.05-5.77)	No association	

(51) Soderberg	Any allergy (asthma, hay fever, eczema during childhood or allergic eczema)	Leukemia: RR 1.1 (0.8-1.7), Myeloma: RR 0.7 (0.4-1.4), NHL: RR 1.3 (0.8-2.0)	No association	
(38) Shadman	Allergies to airborne antigens	Mature B-cell lymphoma: HR 1.47 (1.14-1.91)	Positive	Patients who developed malignancies were older ($p < 0.001$) and a moderate risk for lymphoma was seen in women, but not in men.
(37) Koshiol	Any allergy (rhinitis, asthma, dermatitis, erythema, allergic alveolitis)	NHL: OR 1.4 (1.3-1.5)	Positive	Increased risk especially in patients with allergic alveolitis and dermatitis. Furthermore, the risk was slightly higher in black than white patients.
(75) Rudant	Allergic asthma	ALL: OR 0.7 (0.4-1.0)	No association	Childhood ALL
(50) Briggs	Any allergy	NHL: OR 1.0 (0.8-1.2)	No association	
(64) Spector	Atopy	Early onset atopy and ALL: OR 2.20 (1.16-4.16), Late onset atopy and ALL: OR 3.78 (1.00-14.29)	Positive, No association	Association between allergic diseases and ALL in children
(65) Dalamaga	Any allergy	MDS: OR 3.50 (1.19-10.26)	Positive	
Lymphatic and hematopoietic cancer, retrospective studies				
(152) Brown	Allergic rhinitis; Asthma; Erythema	MM: RR 1.45 (0.93-2.25); MM: RR 0.98 (0.79-1.22); MM: RR 1.03 (0.72-1.48)	No association	
Skin cancer, case control studies				
Reference	**Allergy**	**Statistical value (95% CI)**	**Association**	**Comments**
(78) Cheng	Any allergy (animal, insect sting, food, plant, mold, and dust)	Early onset: BCC: OR: 0.61 (0.38-0.97), Early onset: SCC: OR: 1.18 (0.78-1.79)	Negative, No association	
(77) Jensen	Atopic dermatitis	Melanoma: SIR 0.46 (0.19- 0.95), BCC: SIR 1.41 (1.07-1.83), SCC: SIR 2.48 (1.00, 5.11)	Negative, Positive, No association	
(76) Ji	Asthma	Melanoma: SIR 0.84 (0.71-0.99), SCC: SIR 1.33 (1.19, 1.48)	Negative, Positive	
(79) Ming	Atopic dermatitis	NMSC OR 0.78 (0.61-0.98)	Negative	
(80) Hwang	Allergic rhinitis; Asthma; Atopic dermatitis	Melanoma: SIR 0.89 (0.36-1.84), NMSC SIR 0.40 (0.28-0.56); Melanoma: SIR 1.32 (0.63-2.43), NMSC: SIR 0.39 (0.27-0.54); Melanoma: SIR 2.35 (0.26-8.47), NMSC: SIR 0.75 (0.30-1.54)	No association, Negative; No association, Negative; No association, No association	
(81) Kallen	Allergic asthma	Melanoma: SMR 34 (26.3-44.4), Other skin cancers: SMR 76 (65.2-87.7)	Negative, Negative	
(82) Marasigan	Any allergy (atopic dermatitis, asthma, hay fever)	Melanoma: OR: 0.53 (0.30-0.96)	Negative	

Colorectal cancer, cohort studies				
Reference	**Allergy**	**Cancer type: statistical value (95% CI)**	**Association**	**Comments**
(83) Eriksson	Positive skin prick test	Rectal cancer: SIR 4.69 (1.25-12.0)	Positive	
(85) Tambe	Any allergy (asthma, hay fever)	Colorectal cancer: RR 0.86 (0.80-0.92)	Negative	
(36) Gonzalez-Perez	Asthma	Colorectal cancer: OR 0.86 (0.70-1.06)	No association	Adjusted for age/sex/calendar year/BMI/ alcohol/smoking/prior comorbidities/health services utilization/aspirin/NSAID/ paracetamol
(35) Mills	Any allergy (asthma, hay fever, drug allergy, bee allergy)	Colon cancer: RR 0.96 (0.69-1.33), Rectal cancer: RR 0.86 (0.51-1.44)	No association, No association	
(86) Prizment	Any allergy (asthma, hay fever, eczema, skin allergy)	Colorectal cancer: HR: 0.74 (0.59-0.94)	Negative	Patient population: women only
(93) Talbot-Smith	Any allergy (not specified)	Colorectal cancer Men: HR 0.32 (0.03-2.84), Women: HR 1.42 (0.41-4.95)	No association	
(87) Turner	Asthma and hay fever both	Colorectal cancer: OR 0.76 (0.64-0.91)	Negative	
(88) Jacobs	Asthma and hay fever both	RR CPS-I: 0.90 (95% CI, 0.74-1.09), RR CPS-II 0.79 (95% CI, 0.69-0.91), When results combined with meta-analyses: RR 0.83 (0.74-0.92)	No association, Negative, Negative	CPS = cancer prevention study
(34) McWhorter	Any allergy	ROR 1.69 (0.92-3.11)	No association	
Colorectal cancer, case control studies				
(89) Bosetti	Any allergy (not specified)	Colon cancer: OR 0.76 (0.59-0.97), Rectal cancer: OR 0.54 (0.37-0.77)	Negative	History of allergy first diagnosed within five years before cancer diagnosis. Also, negative association when both sexes studied separately.
(32) Wang	Any allergy (hay fever, asthma, atopic dermatitis)	Colorectal cancer: OR: 0.99 (0.73-1.35)	No association	
(90) Negri	Any allergy (allergic rhinitis, asthma, atopic dermatitis)	Colon cancer: OR 0.88 (0.67-1.14), Rectal cancer: OR 0.64 (0.44-0.92), Colorectal cancer: OR 0.80 (0.63-1.00)	No association, Negative, No association	
(91) La Vecchia	Drug allergy	Colon cancer: RR: 0.6 (0.4-0.9), Rectal cancer: RR: 0.6 (0.5-1.0)	Negative, No association	
(94) Kune	Allergies or hay fever	RR 0.83 (0.67-1.03)	No association	
Colorectal cancer, retrospective studies				
(84) Vesterinen	Asthma	Colon cancer: SIR 1.17 (1.02-1.33), Rectal cancer: SIR 1.10 (0.86-1.38)	Positive, No association	

(80) Hwang	Asthma; Allergic rhinitis	Colon cancer: SIR 1.00 (0.88-1.13), SIR Men: 0.83 (0.69-0.99), SIR Women: 1.24 (1.03-1.47), Rectal cancer: SIR 0.86 (0.73-1.01); Colon cancer: SIR 1.02 (0.90-1.15), SIR Men: 0.93 (0.78-1.10), SIR Women: 1.14 (0.94-1.37), Rectal cancer: SIR 0.82 (0.69-0.97)	No association, Negative, Positive, No association (both sexes); No association, No association, No association, Negative (both sexes)	
(92) Vena	Asthma; Hay fever; Asthma; Hay fever	Colon: Men OR 1.33, women OR 0.61; Colon cancer: Men OR 1.27, women OR 1.00; Rectal cancer: Men OR 0.60, women OR 0.82; Rectal cancer: Men OR 1.22, women OR 0.61	Negative	95% CI not included.
Pancreatic cancer, case control studies				
Reference	**Allergy**	**Statistical value (95% CI)**	**Association**	**Comments**
(95) Cotterchio	Atopy	MVOR 0.66 (0.51-0.85)	Negative	
(9) Eppel	Any allergy (hay fever, not specified)	AOR 0.43 (0.29-0.63)	Negative	
(96) Holly	Any allergy (not specified)	OR 0.77 (0.63-0.95)	Negative	
(97) Maisonneuve	Any allergy (asthma, eczema, hay fever, not specified)	OR 0.64 (0.50-0.82)	Negative	
(98) Olson	Any allergy	OR 0.58 (0.40-0.84)	Negative	Hay fever and animal allergies were related to lower risk. No association between other allergies and asthma
(99) Santibanez	Nasal allergies (including hay fever)	OR 0.56 (0.32-0.99)	Negative	
(100) Silverman	Any allergy (hay fever, asthma, eczema, animal allergy, insect bite/sting allergy, dust or mold allergy, drug allergy, household products	OR 0.7 (0.5-0.9)	Negative	
(101) Dai	Any allergy	OR 0.6 (0.4-1.1).	No association	
Pancreatic cancer, cohort studies				
(87) Turner	Hay fever	OR 0.84 (0.71-1.00)	No association	No association between asthma and pancreas cancer or asthma/hay fever and pancreas cancer
(102) Hemminki	Hay fever/allergic rhinitis	OR 0.87 (0.58-1.26)	No association	
Urogenital cancers, case control studies				
Reference	**Allergy**	**Cancer types: statistical value (95% CI)**	**Association**	**Comments**
(106) Gloria-Bottini	Any allergy (asthma, rhinitis and AEDS (Atopic Eczema/Dermatitis Syndrome)	Uterine leiomyomas	Negative	Uterine leiomyomas is lower in allergic than non-allergic women ($p < 0.004$)

(107) Johnson	Any allergy (not specified)	Squamous cell cervical cancer: OR 0.7 (0.6-0.9)	Negative	
(103) Lightfoot	Any allergy (not specified)	Prostate cancer: OR 0.78 (0.60-1.00)	No association	
(32) Wang	Any allergy (asthma, hay fever, atopic dermatitis)	Prostate cancer: OR 0.98 (0.66-1.45)	No association	
(104) Weiss	Any allergy (hay fever, medication, food, dust, animals)	Prostate cancer: OR 0.98 (0.84-1.14)	No association	
(36) Gonzalez-Perez	Asthma	Prostate cancer: OR 0.86 (0.69-1.07)	No association	Estimates are adjusted for age, sex, calendar year, BMI, alcohol intake, smoking status, prior comorbidities (cardiovascular disease, diabetes, osteoarthritis, and rheumatoid arthritis), health services utilization, use of aspirin, NSAID, and paracetamol using logistic regression.
Urogenital cancers, cohort studies				
(108) Montgomery	Hay fever	Cervical cancer: OR 1.04 (0.50-2.17)	No association	
(33) Talbot-Smith	Atopy	Prostate cancer: OR 2.25 (0.94-5.47)	No association	Adjusted for age, smoking status, and body mass index.
(34) McWhorther	Any allergy	Prostate cancer: OR 1.32 (0.62-2.80)	No association	Adjusted for smoking, age and race.
(35) Mills	Any allergy (hay fever, asthma, bee sting, medication)	Prostate cancer: OR 1.25 (0.93-1.69)	No association	Adjusted for smoking and age
(87) Turner	Asthma and hay fever	Prostate cancer: OR 1.06 (0.74-1.53); Ovarian cancer: OR 0.93 (0.60-1.45)	No association; No association	
(102) Hemminki	Hay fever/allergic rhinitis	Prostate cancer: SIR 1.18 (1.06-1.30), Cervix cancer: SIR 0.99 (0.73-1.32), Ovarian cancer: SIR 0.98 (0.74-1.27)	Positive, No association, No association	
(81) Kallen	Asthma	Prostate cancer: SMR 72 (66.7-77.6), Cervix cancer: SMR 52 (38.9-69.1), Ovarian cancer: SMR 52 (42.1-63.1)	Negative, Negative, Negative	
(76) Ji	Asthma	Prostate cancer: SIR 1.28 (1.20-1.36), Cervix cancer SIR 1.34 (1.07-1.66), Ovarian cancer SIR 0.92 (0.76-1.12)	Positive, Positive, No association	
(105) Severi	Asthma	Prostate cancer: HR 1.25 (1.05-1.49)	Positive	Adjusted for age, country of birth, education, body mass index, fat and fat-free mass, smoking, alcohol consumption, and total energy intake.

Lung cancer, case control studies				
Reference	**Allergy**	**Statistical value (95% CI)**	**Association**	**Comments**
(115) El-Zein	Asthma Eczema Hay fever	OR 0.90 (0.65-1.24); OR 0.73 (0.48-1.12); OR 0.37 (0.24-0.59)	No association; No association; Negative	Adjusted for age, sex, education, respondent status, ethnocultural origin, fruit and vegetable consumption and smoking.
(116) McDuffie	Any allergy (house dust mite, animals, mixed molds, mixed weed pollen, mixed tree pollen, mixed grass pollen)	OR 0.58 (0.37-0.91)	Negative	
(117) McDuffie	Any allergy (house dust mite, mixed grain dust, mixed animal dander, mixed molds, mixed weed pollen, mixed tree pollen, mixed grass pollen)	-	Negative	The study used seven common allergens for allergy skin prick test. Historic evidence of allergy was greater in both control groups compared to the cancer groups.
(118) Seow	Any allergy (asthma, allergic rhinitis, atopic dermatitis)	All histological types: OR 1.5 (0.8-2.6), Adenocarcinoma: OR 1.6 (0.9-3.1)	No association	Study population: non-smoking Chinese women
(32) Wang	Any allergy (asthma, hay fever, atopic dermatitis)	OR 0.85 (0.50-1.47)	No association	
(36) Gonzalez-Perez	Asthma	OR 1.35 (1.15-1.59)	Positive	Estimates are adjusted for age, sex, calendar year, BMI, alcohol intake, smoking status, prior comorbidities (cardiovascular disease, diabetes, osteoarthritis, and rheumatoid arthritis), health services utilization, use of aspirin, NSAID, and paracetamol using logistic regression.
Lung cancer, cohort studies				
(35) Mills	Any allergy (hay fever, asthma, bee sting, medication)	OR 1.02 (0.60-1.72)	No association	In cases of asthma alone, the association with lung cancer was also positive. Adjusted for age, sex, smoking history, and time since last physician contact.
(102) Hemminki	Hay fever/allergic rhinitis	SIR 0.78 (0.64-0.93)	Negative	
(81) Kallen	Asthma	All respiratory tract cancers: SMR 105 (97.0-113.4)	Positive	
(76) Ji	Asthma	SIR 1.76 (1.63-1.90)	Positive	
(114) Alderson	Asthma	OR 0.80 (0.41-1.56)	No association	Covariants are not mentioned.
(109) Reynolds	Asthma	Men: relative risk incidence lung cancer is RR 6.3 and mortality is RR 5.3; Women: relative risk incidence lung cancer is RR 1.2.	Positive in men	Adjusted for gender and smoking.
(84) Vesterinen	Asthma	Men: SIR 1.32 (1.22-1.43), Women: SIR 1.66 (1.39-1.98)	Positive	Covariants are not mentioned.
(110) Huovinen	Asthma	Men: HR 3.19 (1.39-7.31)	Positive	Risk of mortality due to lung cancer. Adjusted for age and smoking

(87) Turner	Asthma and hay fever	Only hay fever: RR 0.85 (0.80-0.90); Only asthma: RR 1.11 (1.02-1.20); Asthma and hay fever: RR 0.73 (0.65-0.83)	Negative; Positive; Negative	Lung cancer mortality. Adjusted for gender, race, smoking, education, marital status, body mass index, diabetes, exercise, alcohol drinking, aspirin use, vegetable intake, and fat intake.
(111) Pirie	Asthma	Women: RR 1.32 (1.10-1.58)	Positive	Non-smoker women. Adjusted for age, region, deprivation quintile, height.
(112) Huang	Asthma	Men: HR 1.36 (1.30-1.41), Women: 1.26 (1.18-1.34)	Positive	Adjusted for lung diseases, low income, age, comorbidities, urbanization and geographic area
(113) Colak	Asthma	Never smokers with asthma: HR 0.6 (0.1-5.1), Former smokers with asthma HR 4.0 (1.3-12), Current smokers with asthma HR 13 (4.3-41)	No association, Positive, Positive	Adjusted for age, sex, BMI, allergy, familial predisposition for asthma, childhood asthma, hay fever, or eczema.
(33) Talbot-Smith	Asthma, hay fever or any atopy	Risk of lung cancer Men: Asthma: HR 1.18 (0.15-9.06), Hay fever: HR 0.64 (0.08-4.87), Any atopy: HR 0.28 (0.03-2.49), Women: Asthma: HR 0.96 (0.12-7.48), Hay fever: HR 1.45 (0.40-5.30), Any atopy: HR 0.87 (0.08-9.89)	No association	
Other cancers, case control studies				
Reference	**Allergy**	**Cancer type: statistical value (95% CI)**	**Association**	**Comments**
(119) Chung	Allergic rhinitis	Nasopharyngeal carcinoma: OR 2.29 (2.05-2.56)	Positive	
(125) Fillippidis	Any allergy (not specified)	Laryngeal cancer: OR 0.87 (0.55-1.4)	No association	
(153) Frentzel-Beyme	 Skin allergy (not specified) Hay fever	Bone tumors: RR 0.76 (0.37-1.55), RR 1.49 (0.65-3.43)	No association	
(130) Goedert	Any allergy (not specified)	Kaposi's sarcoma OR 1.54 (0.88-2.70)	No association	
(121) Hsiao	Any allergy (not specified)	Head and neck cancer: OR 0.41 (0.27-0.62), Oral cancer: OR 0.36 (0.22-0.57), Oropharyngeal cancer: OR 0.49 (0.25-0.96), Laryngeal cancer: OR 0.48 (0.19-1.18)	 Negative, Negative, Negative, No association	Original study plus meta-analysis
(122) Liao	Any allergy (allergic rhinitis, skin allergy, food allergy, drug allergy and asthma)	Head and neck cancer: OR 0.56 (0.43-0.73)	Negative	Diagnosis of squamous cell carcinoma of the head and neck, including oral cavity, oropharynx, hypopharynx, larynx.
(120) Lin	Allergic rhinitis Men Women	Nasopharyngeal carcinoma HR 2.33 (1.59-3.40) HR 2.06 (1.31-3.25) HR 3.02 (1.47-6.22)	Positive	

(124) Lupo	Any allergy (Asthma, eczema, hives, not specified)	Rhabdomyosarcoma OR 0.60 (0.41-0.87)	Negative	Patient population: Children
(126) Menegaux	Any allergy (asthma, hay fever, other ear, nose, and throat allergy such as rhinitis and sinusitis, eczema, and other dermatologic allergy as urticaria, contact dermatitis, food dermatitis, or hypersensitivity to drugs)	Neuroblastoma: OR 0.68 (0.44-1.07)	No association	Patient population: among children over 1 year of age
(123) Michaud	Any allergy (not specified)	HNSCC: OR 0.81 (0.67-0.98), Laryngeal: OR 0.66 (0.45-0.97), Oropharyngeal cancers: OR 0.73 (0.57-0.92), Oral cavity cancers: OR 0.98 (0.76-1.26)	Negative, Negative, Negative, No association	
(127) Rosato	Any allergy	Biliary tract cancer: OR 0.64 (0.29-1.40)	No association	Using data from two cc
(128) Schoemaker	Any allergy (history of seasonal or non-seasonal allergic nasal catarrh and conjunctivitis, food allergy, contact allergy or other types of allergy specified by the participant)	Acoustic neuroma: OR 0.9 (0.8-1.1)	No association	
(129) Stott-Miller	Any allergy (not specified)	Oral squamous cell carcinoma: OR 0.81 (0.61-1.08)	No association	
Cancer in general, case control studies				
Reference	**Allergy**	**Cancer type: statistical value**	**Association**	**Comments**
(131) Allegra	Any allergy (hives, eczema, frequent colds, frequent unexplained rashes, hay fever, asthma)	15-fold decrease in prevalence of cancer ($p < 0.01$)	Negative	
(132) Fisherman	Any allergy prevalence	Malignant tumors: 3.2% Control group: 12.9%	Negative	Prevalence of allergy in patients with malignant tumors and control group.
(133) Kozlowska	Allergic rhinitis	OR 0.67 (0.52-0.81)	Negative	
(134) McKee	Seasonal allergy No history of allergy	23.7% at operation for cancer, 25.4% at operation for cancer	Negative	
(135) Pompei	Any allergy prevalence	Tumor-bearing patients 8%, Non-tumor-bearing subjects 16-37%	Negative	Prevalence of allergy in tumor-bearing patients and non-tumor-bearing patients.
(36) Gonzalez-Perez	Asthma	OR 0.93 (0.86-1.00)	No association	Estimates are adjusted for age, sex, calendar year, BMI, alcohol intake, smoking status, prior comorbidities (cardiovascular disease, diabetes, osteoarthritis, and rheumatoid arthritis), health services utilization, use of aspirin, NSAID, and paracetamol using logistic regression.

Cancer in general, cohort studies				
(80) Hwang	Allergic rhinitis	SIR 1.02 (0.98-1.05).	No association	Table 2 in this article shows the SIR's for many types of cancer and allergic rhinitis.
(34) McWhorter	Any allergy (not specified)	OR 1.40 (1.10-1.77)	Positive	The specific allergy type with the strongest cancer risk was hives. The cancer group with the strongest allergy association was lymphatic-hematopoietic (leukemia, lymphoma, myeloma). Also, further determination of colorectal cancer.
(35) Mills	Any allergy (not specified)	Men: RR 1.13 (0.92-1.39), Women: RR: 1.00 (0.85-1.17)	No association	Cancer sites among males include: colon, rectum, prostate, lung, bladder, melanoma, stomach, kidney, lymphoma, leukemia, multiple myeloma, and sarcoma. Cancer sites among females include: colon, rectum, breast, endometrium, cervix, ovary, lung, bladder, melanoma, stomach, kidney, lymphoma, leukemia, multiple myeloma, and sarcoma.
(138) Skaaby	Any allergy (not specified)	HR 0.86 (0.69-1.06)	No association	
(137) Skaaby	Any allergy (not specified)	HR 1.00 (0.89-1.12)	No association	
Cancer in general, retrospective data analysis				
(136) Chae	Rhinoconjunctivitis	OR 1.44 (1.00-2.08)	No association	

CI = confidence interval; OR = odds ratio; RR = relative risk; PNET = primitive neurectodermal tumour; HR = hazard ratio; SIR = standardized incidence ratios; SMR = standardized morbidity rate; ROR = risk odds ratio; MVOR = multi variable odds ratio; AOR = age-adjusted odds ratio; NSAID = non-steroidal anti-inflammatory drugs; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; DLBCL = diffuse large B-cell lymphoma; ALL = acute lymphatic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; AUL = acute undifferentiated leukemia; CLL = chronic lymphocytic leukemia; FBCL = follicular B-cell lymphoma; MM = multiple myeloma; SBL = sporadic Burkitt lymphoma; LL = lymphocytic leukemia; ML = myloid leukemia; MDS = myelodysplastic syndrome; SCC = squamous cell carcinoma; BCC = basal cell carcinoma; NMSC = non-melanoma scan cancer; AEDS = atopic eczema / dermatitis syndrome; HNSCC = head and neck squamous cell carcinoma.

Table 2. *Overview of the studies on the association between allergic diseases and cancer*

Types of cancers	Positive association (reference number)	Negative association (reference number)	No association (reference number)	Conclusion
Brain cancer	-	(11, 17-28)	(10-16)	Allergic diseases are associated with reduced risk of brain cancer
Breast cancer	(29)	(30, 31)	(32-36)	No association between allergic diseases and breast cancer
Lymphatic and hematopoietic cancer	Lymphoma: (34, 37-39) Other hematological malignancies: (34, 60-65)	Lymphoma: (40-49) Other hematological malignancies: (66-72).	Lymphoma: (33, 35, 39, 47, 50-59) Other hematological malignancies: (33, 35, 39, 47, 50-59)	In general, allergic diseases are possibly associated with decreased risk of lymphatic and hematopoietic cancer
Skin cancers	(77)	(76-82)	(77, 78, 80)	Negative association between allergic diseases and melanoma
Colorectal cancers	(80, 83, 84)	(80, 85-92)	(32, 34-36, 80, 84, 88, 90, 91, 93, 94)	The risk of colorectal cancers is possibly reduced in patients with allergic diseases
Pancreatic cancer	-	(9, 95-100)	(87, 101, 102)	Allergic diseases are associated with reduced risk of pancreatic cancer
Urogenital cancers	Prostate cancer in men: (76, 102, 105) Urogenital cancers in women: (76)	Prostate cancer in men: (81) Urogenital cancers in women: (81, 106, 107)	Prostate cancer in men: (32-36, 87, 103, 104 Urogenital cancers in women: (76, 87, 102, 108)	Possibly no association between allergies and prostate cancer. Possibly a reduced risk of urogenital cancers in Women with allergic diseases
Lung cancer	(36, 76, 81, 84, 87, 109-113)	(87, 102, 115-117)	(32, 33, 35, 113-115, 118)	Asthma is related with an increased risk of lung cancer in contrast to atopy without asthma
Other cancers	(119, 120)	(121-124)	(125-130, 153)	No evident association between allergic diseases and other cancers
Cancer in general	(34)	(131-135)	(35, 36, 80, 136-138).	Allergic diseases are possibly associated with decreased risk of cancers

REVIEW

Role of the microbiota in hematologic malignancies

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ABSTRACT

Human beings are inhabited by innumerable microorganisms that interrelate with the host in a reciprocal way, establishing a combined and efficient ecosystem – the microbiota – that can affect healthiness as well as disease. There is evidence that the conformation of the microbiota may influence, and is controlled by, the human immune system.

Microbes existing in human tissues offer a multiplicity of advantages that participate in functional actions in the host through the adjustment of essential processes such as immunity, signal transduction, and metabolism. The imbalance of this microbial structure has been connected with the pathogenesis and progression of cancer. We reviewed the present knowledge of the diverse microbial ecosystems and we investigated their potential link to carcinogenesis, and the possibility of using advantageous microbes in controlling and preventing hematologic malignancies.

KEY WORDS

Microbiota, hematologic malignancies, antibiotics, immune activation

INTRODUCTION

Overview of the human microbiota: characterization and regulation of microbiota

Human beings are inhabited by innumerable microorganisms that interrelate with the host in a reciprocal way, establishing a combined and efficient ecosystem – the microbiota- that can affect healthiness as well as disease.[1,2]

The term 'gut microbiota' indicates the masses of microorganisms living in the intestine. Most microorganisms inhabit the more distal portions of the intestinal area, where their bio-mass exceeds 10^{11} cells per gram content.[3] Nevertheless, all cavities that connect to the outside and body surfaces are populated by mutable and personalized ecosystems of viruses, fungi, archaea, bacteria and protozoa.

The relationship between the host and the microbiota is symbiotic. The host offers a vital habitat for the microbiome, whereas microorganisms participate in host health via synthesis of essential amino acids, short chain fatty acids (SCFAs) and vitamins.[4-6]

In a recent study, Sonowal et al. showed that small molecules related to indole and originating from commensal microbiota act in different phyla to augment healthy aging. The action of indoles on health span depends upon the aryl hydrocarbon receptor, a conserved sensor of xenobiotic small molecules. In older animals, indole stimulates genes associated with oogenesis and, accordingly, prolongs reproductive span. These results are improving efforts of developing therapeutics based on microbiota-derived indole to decrease frailty in humans.[7]

The microbiota is distinguished by its unremitting dynamic renewal of microbiota.[8] The different microbiota inhabiting human surfaces are not casually developed. They are the result of several elements, such as age, environmental conditions, lifestyle, smoking habit, antibiotics therapy, genetic factors and contact with pathogenic organisms.[9-20] A substantial change in diet modifies microbial configuration within just 24 h of commencement, with a return to baseline two days after diet suspension.[21] Moreover, the gut microbiome of animals nourished with a high-sugar or high-fat diet is more disposed to circadian rhythm disruption.[22]

Numerous diets, including vegan, gluten-free, omnivore, Western and Mediterranean, have been investigated for their

ability to regulate the gut microbiota. In numerous studies, a diet high in animal fat and protein, but low in fiber, causes a pronounced reduction in numbers of beneficial *Eubacterium species* and *Bifidobacterium.*[23-25] Furthermore, host circadian clock and hormonal status alter gut microbial ecology through nourishment and diurnal rhythms; jetlag and long-distance voyage cause the disturbance of this clock, and can therefore alter the gut microbiota.[26,27]

The initiation of novel tools has strongly impacted the interpretation of the controlling systems by which microorganisms and hosts interrelate to provoke a health or disease condition in the host. Next generation

Table 1. *Microbiota and cancer*

Type of tumor	Microbe involved or suspected in carcinogenesis	Pro-carcinogenesis mechanism
Hepatocellular carcinoma	HBV, HCV	Oncogenic activation
Cholangiocarcinoma	Helminth (*O. viverrini, C. sinensis*)	Augmented cell growth Reduced apoptosis Up-regulation of Bcl-2, Down-regulation of p27, Augmented cell invasion
Gallbladder cancer	*Helicobacter spp., S. typhi*	Mucosal alterations, inflammation, weakening and mucosal dysplasia
Pancreatic cancer	*Streptococcus mitis, Neisseria elongate*	Mucosal alterations, inflammation, weakening and mucosal dysplasia
Esophageal squamous cell carcinoma	HPV	Oncogenic activation
Gastric cancer	*Klebsiella pneumoniae, Lactobacillus colehominis, Acinetobacter baumani, Helicobacter pylori*	Mucosal alterations, inflammation, weakening and intestinal metaplasia
Head and neck carcinoma	*Parvimonas*, HPV	Modifications with clinical-pathologic characteristics
Lung cancer	Proteobacteria, genus *Thermus, Legionella spp., Mycobacterium tuberculosis*, all species causing pneumonia, Firmicutes	Mucosal alterations, inflammation, weakening and mucosal dysplasia
Breast cancer	Gut microbiome	Alteration of enterohepatic circulation of estrogen
Endometrial cancer	*A. vaginae,* Porphyromonas sp.	Increased vaginal pH
Cervical cancer	HPV	Oncogenic activation
Acute lymphoblastic leukemia	*Prevotella, Bacteroides Roseburia, Ruminococcus 2, Anaerostipes, Coprococcuss, Faecalibacterium, Aerococcaceae and Carnobacteriaceae,* Firmicutes, *Lactobacillales, Abiotrophia, Granulicatella, Bacilli*	Dysregulation of the immune system through IL-6, HLA-DR+CD4+ and HLA-DR+CD8+ T cells
Hodgkin lymphoma	Gut microorganisms during childhood	Immunological alterations: < Th1 and > Th2, > IgE, < NK, < T-CD8+
Non hodgkin lymphoma	*Helicobacter spp.*, gut microorganisms, *Chlamidia psitacci, Campylobacter jejuni, Borrelia bergdorferi, Streptococcus bovis*; HCV, HTLV-1	Abnormal DNA replication due to increase of B lymphocyte growth Oxidative stress Oncogenic activation
Chronic lymphatic leukemia	Anti-gram-positive antibiotics	Antagonism of antitumor activity of cisplatin [causes ROS-mediated-cell death] and cyclophosphamide [that activates T-helper antitumoral response]

HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV = human T-cell leukemia virus-1; ROS = reactive oxygen species.

sequencing and methods connected to metabolome analysis, such as mass spectrometry, are critical for evaluating the microbiota structure and investigating the metabolic, functional and genetic action of the microbiota.[28-30]

Carcinogenesis and microbiota

Oncomicrobes comprise organisms that can directly injure DNA and modify host cellular processes.[31-33] Several well-recognized oncomicrobes are viruses, which introduce oncogenes into host genetic material. Interestingly, several bacteria have elaborate competitive tactics which can harm DNA of contending organisms. Unfortunately, these same processes can also modify host DNA, resulting in mutations and perhaps, to carcinogenesis. Bacterial DNA can incorporate into human genomes, principally the mitochondrial genome, through an RNA intermediate, and this occurs more commonly in cancerous rather than healthy tissues.[34] DNA mutations may also be caused by toxins generated by bacteria,[35,36] and bacterial proteins can initiate signaling actions in host pathways that control cell growth.[37,38]

Nevertheless, few microorganisms are identified as oncomicrobes (see *table 1*). This may partly be due to difficulties in recognizing microorganisms as the causal mediators of carcinogenesis. The causal agent may be absent from the cancer site due to an environmentally-driven population of organisms, or the microbe may have started host cellular injury by a "hit and run" action after only short interaction with the host tissue.

There is increasing evidence that the conformation of the microbiome may influence, and is controlled by, the human immune system.[39] An unbalanced microbial structure been connected with reduced immune competence, predisposition to infections and inflammatory diseases.[40,41] Experiments performed using germ-free animals propose that microbiota directly stimulate local intestinal immunity through their actions on toll-like receptor (TLR) expression,[42] differentiated T cells, antigen presenting cells and lymphoid follicles,[43,44] as well as by modifying systemic immunity by augmented systemic antibody production and splenic CD4+ T-cells.[45,46]

Microorganisms and microbial elements such as lipopolysaccharide (LPS) can up-regulate TLRs, which can provoke an activation of nuclear factor-kB (NF-kB), which is critical for controlling tumor-associated inflammation,[47,48] invasion, growth, survival and immunosuppression.[49] Bacterial LPS has also been demonstrated to hasten cell proliferation by c-Jun N-terminal Kinase activation.[50]

Remarkably, T-helper cell 17 (Th17) differentiation from naïve T-cells seems to be dependent on the segmented filamentous bacteria. Experiments have demonstrated that Th17 are lacking in the small-intestinal *lamina propria* of germ-free mice, which is their primary differentiation location, while modifications in the gut microbiota are closely related to important variations in Th17/Regulatory T-cell (Treg) balance, possibly mediated by epigenetic mechanisms. This is proven by emergent data connecting an unbalanced microbial structure to epigenetic modifications.[51-53]

Administration with segmented filamentous bacteria provoked an augmentation in production of interferon (IFN) gamma, interleukin-10 (IL-10), and IL-17,[54] while administration of *Sphingomonas yanoikuyae* provoked a modification in immune cells. *Bacterioides fragilis* induces a Th17 response in animals, which was then demonstrated to be necessary for tumorigenesis, while administration with human commensal bacterium *Bifidobacteriom longum*, *Bacteroides thetaiotaomicron* or both caused an increase in the production of the IFN-gamma- and TNF-alpha pathways.[55]

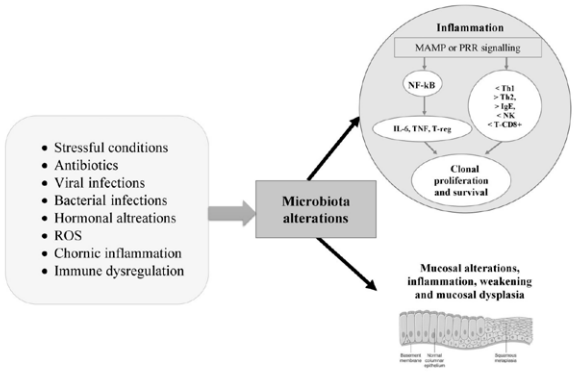
As previously mentioned, gut flora can also control host immunity by epigenetic changes. For example, microbial-originated butyrate reduces histone deacetylases 6 and 9, which results in higher numbers of Treg cells and enhanced acetylation in the promoter of the *FOXP3* gene.[56,57] Metabolic relationships and dietary elements can in some way induce tumor expansion. Metabolic end products may include pro-carcinogenic factors that promote cancer growth.[58] Contact with these elements, referred to as the "exposome," can influence oxidative stress and DNA stability in a host, increasing the danger of developing tumor.[59,60] (see *figure 1*). Several carcinogenic factors can be produced by the cometabolism of xenobiotics by bacterial β-glucuronidases.[61] Significant examples comprise the metabolism of azoxymethane[62] and irinotecan.[63] Similarly, production of harmful metabolites is connected with microbial catabolism of dietary proteins. These putrefactive activities in the bowel provoke the production of N-nitroso elements that cause DNA damage via alkylation.[64,65] The metabolism of aromatic amino acids also causes the production of phenols, indoles, p-cresol and phenylacetic acid.[66] Polyamines are a diverse group of toxic elements and catabolism of the main polyamines is connected with oxidative stress and tumors[67] (see *table 2*).

Chemotherapy and microbiome

Chemotherapy can harm normal cells of the intestinal system and possibly cause gastrointestinal (GI) problems.[68] The cytotoxic actions of these therapies provoke a supplementary immunosuppression, which causes febrile neutropenia and bloodstream infections. Furthermore, the usage of prophylactic and therapeutic antibiotics alters the GI microbiome.[69]

Galloway-Peña et al. studied intra-patient temporal microbiota changeability and its clinical impact on tumor subjects during chemotherapy.[70] These patients presented

Figure 1. *Microbiota and carcinogenesis*



MAMP = microbe-associated molecular pattern

Table 2. *Microbioma and carcinogenesis*

Agents	Action	References
Toxins	DNA mutation Breaks in double stranded DNA	35, 36
Bacterial proteins	Signaling action: Wnt/Beta-catenin IFN-gamma TNA-alpha	37, 38, 55
Microbial elements [Lipopoly-saccharide]	NF-kB, c-Jun/JNK	47, 48, 49, 50
Butyrate	Acetylation in the promoter of the FOXP3 gene; Methylation in the promoter of proinflammatory genes	56, 57
Oncomicrobes	Reduced immunocompetence: Modification of TLR expression T-cells Antigen presenting cells	40, 41, 42, 43, 44, 45
Metabolites: phenols, indoles, phenylacetic acid, polyamines	DNA damage via alkylation Oxidative stress	65, 66, 67

an elevated level of intra-subject temporal instability of oral and fecal bacterial multiplicity. Days on antibiotics were substantially connected with extended temporal variability of oral bacterial multiplicity and microbiome structure. These results indicate that an increased variability was connected with adverse clinical prognosis. Moreover, the data show the relevance of longitudinal microbiome analyses.

Unfortunately, direct interaction with bacteria can influence the effectiveness of chemotherapeutic agents.[71] Mass spectrometry and high-performance liquid chromatography analysis demonstrated that contact with the bacteria determined a biotransformation of certain chemotherapy drugs. The ability of bacteria to reduce the antitumor effect of gemcitabine and to increase that of the prodrug CB1954 was demonstrated *in vivo*.[72] Hence, data in experimental models propose a complicated interaction between numerous chemotherapeutic agents and microbiota.

Exhaustive mechanistic studies *in vivo* have been reported for platinum compounds and cyclophosphamide (CTX).[73,74] CTX, prescribed for therapy of hematologic diseases and solid cancers, harms the small intestine epithelium causing migration of several microorganisms into lymph organs. This barrier breech provokes a T-helper cell-mediated anticancer response and augments drug effectiveness.[73] The antitumor action of platin treatment is radically reduced in germ-free mice or in mice in which gut bacteria have been reduced by broad-spectrum antibiotics.[74] Combined with experimental results that *Lactobacillus acidophilus* supports the anticancer action of cisplatin, clinical data propose the possibility that probiotic bacterial species may promote antitumor action while inhibiting some of the toxic side effects of particular drugs[75-77] (see *table 3*). The intestinal chemotoxicity of methotrexate is due in part, by activation of TLR4 by microbial products such as Cif, as secreted toxin from *Pseudomonas aeruginosa*. Activation of TLR2 protects

Table 3. *Microbioma and chemotherapy*

Agent	Drug	Effect on tumor action	References
E.coli	Gemcitabine	Reduced	72
E. coli Parabac-teriodes distasonis	Doxorubicin	Reduced	72
Lactobacillus acidophilus	Cisplatin	Reduced	75, 76
Germ free mice	Platin	Reduced	74

the mucosa against methotrexate-induced damage by augmenting the expression of the ABC transporter multidrug resistance protein 1 (MDR1; also known as P -glycoprotein and ABCB1), which controls the efflux of xenobiotics from intestinal epithelial cells.[78]

Microbiota and immunotherapy

Improvements in treatments and immunotherapies have generally discounted microorganisms as a part of the tumor therapy, until recently. The intestinal microbiome has been discovered to modify responses to tumor immunotherapy.[79]

Vetizou et al.[80] and Sivan et al.[81] demonstrated that the efficiency of immune checkpoint inhibitors (ICIs) in therapy is reliant on the host microbiota and that the ICIs responded poorly in animals raised under germ-free situations. The authors discovered that, in the presence of microorganisms, host antigen-presenting cells stimulate IFN γ-generating T-cells. Vetizou et al. studied how the curative efficiency of cytotoxic T-lymphocyte-associated protein 4 blockade, as mediated by ipilimumab, might also be caused by elements of the gut microbiota.[82]

It is now clear that primary resistance to immune checkpoints can be attributed to an abnormal gut microbiome composition. Fecal microbiota transplantation (FMT) from cancer patients who responded to immune checkpoints into germ-free or antibiotic-treated mice ameliorated the antitumor effects of programmed cell death 1 protein (PD-1) blockade, whereas FMT from non-responding patients failed to do so. Oral supplementation with *Akkermansia. muciniphila* after FMT with non-responder feces restored the efficacy of PD-1 blockade in an IL-12-dependent manner by increasing the recruitment of $CCR9^{+}CXCR3^{+}CD4^{+}$ T lymphocytes into mouse tumor beds.[83] Moreover, in melanoma patients undergoing anti PD-1 immunotherapy, significant differences were observed in the diversity and composition of the patient gut microbiome of responders versus non-responders. Analysis of patient fecal microbiome samples showed significantly higher alpha diversity and relative abundance of bacteria in the *Ruminococcaceae* family in responding patients.[84]

Microbiota and bone marrow transplantation

Hematopoietic stem cell transplantation (HSCT) is frequently used as curative therapy in patients with hematological diseases. The microbiome could be implicated in local and systemic complications after HSCT. Antibiotic-caused loss of lower gut diversity has been suggested as an independent predictor of unfavorable outcome, while progress of graft-versus-host disease (GVHD) appears to be a main contributor to mortality.[85,86] Lately, microorganisms of the genus *Blautia* were identified as the connection between modifications in microbiota structure, onset of GVHD and a favorable outcome.[87,88] In fact, increased amounts of bacteria belonging to the genus *Blautia* were associated with reduced GVHD lethality. *Blautia* abundance was also associated with improved overall survival.[87] The role of the intestinal microbiota and its potential influence on clinical outcomes for patients undergoing allogeneic HCT (allo-HCT) has been investigated in recent years.[89-91]

Acute GVHD (aGVHD) might reduce the chances of successful allogeneic bone marrow transplantation. Present pathophysiologic hypotheses of aGVHD include proinflammatory cytokines and bacterial LPS as main triggers for aGVHD. LPS originates principally from Gram-negative bacteria and can pass in circulation via the damaged mucosal barrier after the conditioning regimen. Probiotic microorganisms have been proven to modify the components of the intestinal microflora and thus mediate anti-inflammatory actions. It has been suggested that changing the enteric flora using the probiotic microorganism *Lactobacillus rhamnosus* GG would improve aGVHD.[92,93] Analyses of fecal specimens taken from recipients of allo-HCT around the time of engraftment have shown that a reduced intestinal microbiome diversity is associated with significantly worse survival outcomes, and that the alterations in the microbiota composition may influence important clinical outcomes such as aGVHD and disease relapse.[94-96]

It has been hypothesized that approaches to restore a patient's microbiome diversity after HCT may improve outcomes after HCT. Although approaches in restoring microbiome diversity are still investigational, FMT from a healthy individual promise to be a remarkably effective therapy.[97] FMT refers to the infusion of fecal suspension from a healthy donor into the gastrointestinal tract of a patient in order to restore the microbiota and cure the disease. Manipulation of the intestinal microbiota by FMT may influence the immune system and improve immune-mediated enteritis such as gut aGVHD.[98]

Moreover, bloodstream infection (BSI) is one of the biggest causes of death among cancer patients. A study stated that gut domination, described as the occupation of at least 30% by a specific bacterial taxon, is connected with BSI in subjects undergoing allo-HSCT. These data suggest that the intestinal microbiota can recognize high-risk subjects before HSCT and that management of the intestinal microbiota to prevent BSI in high-risk subjects could be a useful treatment.[99]

Finally, a common side effect of myeloablative therapy used during HSCT treatment is GI mucositis.[100] A model, created by Sonis, illustrated a process for bacterial infection due to GI mucositis after HSCT.[101] It comprises an ulcerative stage with increased permeability and harm to the gut mucosal barrier. This stimulates microbial translocation, described as the migration of

microorganisms from the GI tract to extra-intestinal places, such as the blood.[102]

Antibiotics, microbiota and cancer

The discovery that a persistent usage of antibiotics can stimulate some tumors in cancers such as esophageal, gastric and pancreatic cancers,[103] suggests an association between antibiotics, microbiota and cancer.

In fact, there is an indirect indication that an unbalanced microbial structure provoked by antibiotic treatment can augment the incidence of some tumors. An epidemiological study (125,441 cases and 490,510 matched controls) suggests that the use of antibiotics may also influence the occurrence of breast cancer (macrolides, penicillin, cephalosporins, sulphonamides and tetracyclines).[103,104] These data propose that some antibiotics are carcinogenic (tetracyclines inhibit replication of mitochondrial DNA) or that they cause changes in the structure of the microbiota that promote the growth of cancers. However, these results have to be cautiously interpreted because they referred to solid tumors, and the iterative use of antibiotics may denote the existence of immune alterations that could be the main cause of microorganism infections and increased tumor frequency.

Nevertheless, antibiotics can enhance the growth of tumors in animals. This has been demonstrated for the therapy of proto-neu transgenic animals in which tumors appear with ciprofloxacin plus metronidazole.[105,106]

Diet, probiotics and microbiota

There is outstanding interest in the manipulation of the microbiome as a possibility to reduce the incidence of cancer. The intrinsic relationship between microbiome, diet and health demonstrates a possible improvement of our health if we modify our diet.[107,108] Indeed, the American Cancer Society has indicated that diets might be responsible for 30% of tumor cases in developed states and 20% in developing nations.[109]

Reports indicate that diet modifies the structure of the gut flora, and this can impact on the immune response.[110,111] On the other hand, eating particular types of foods (fish, fruits, poultry and vegetables) may prevent several tumors.[112-115]

Metabolism of food can also cause the production of bioactive molecules with chemo-protective activities. Carbohydrate fermentation provokes the production of the short chain fatty acids acetate, butyrate and propionate. These substances can act with free fatty acid receptors in the gut epithelia to influence immune processes, such as the production of cytokines.[116] Other researchers have demonstrated that butyrate can increase the number of formations of tight junction proteins through the modulation of AMP-activated protein kinase.[117] Butyrate also has anti-carcinogenesis actions, principally by two means: the stimulation of G-protein-coupled receptors 41 and 43 and the reduction of histone deacetylase. Some of the described actions of butyrate are improvements of specific pro-apoptotic gene expression in tumor cells and the reduction of the pro-inflammatory pathway of NF-kB.[118,119]

Moreover, there is epidemiological evidence supporting chemo-protection derived from the intake of vegetables and fruits, which have been ascribed to secondary metabolites, such as polyphenols and glucosinolates.[120] Polyphenols are powerful anti-oxidants, but experiments have demonstrated that they are not able to achieve bioactive levels in the blood.[121,122] These elements can also modulate immune responses by modification of the intestinal microbial structure.[123,124]

Probiotics can live in the gut and stimulate the recuperation of regular intestinal microbiota; the most well-known probiotics are *Bifidobacteria* and *Lactobacillus*.[125]

Probiotics increase the immune response through augment of natural killer cell (NK) cytotoxicity and the stimulation of phagocytes.[126] The effectiveness of NK cells can also be augmented when a mixture of probiotics and dextran is utilized.[127] Furthermore, the increase of probiotics seems to increase the production of immunoglobulins IgM and IgA, thus fortifying the adaptive immune response.[128-132]

Bifidobacteria and Lactic acid bacteria are able to induce the secretion of elements that reduce inflammation by downregulating IL-8 production, NF-kB-dependent gene expression and concentrations of macrophage-attracting cytokines.[133-136] Morita et al. also demonstrated a significant augmentation of the expression of IL-6, IL-10, and IL-12 after the stimulation of macrophages with *Lactobacillus acidophilus*.[137] Nutritional supplements with probiotics have been used to increase immune system activity in elderly people.[138,139] Li et al. showed that Prohep - a new probiotic mix - reduces cancer development in an animal model.[140] Probiotics change the intestinal bacterial structure so that it comprises specific advantageous microbes, such that *Oscillibacter* and *Prevotella*, known fabricators of anti-inflammatory substances, which are able to decrease Th17 polarization and stimulate the differentiation of Treg/Tr1 cells in the intestine.

Microbiota and hematologic malignancies

Acute Lymphoblastic Leukemia (ALL)

Rajagopala et al. compared the GI microbiota constitution of adolescent and pediatric leukemia subjects with their healthy relatives.[141] They identified modifications in the microbiota composition of leukemia subjects during chemotherapy by evaluating samples taken before and

after treatment at variable time points throughout the treatment. Their results supply relevant data on GI microbiota structure in immunocompromised patients and suggest that the baseline microbiota of these patients is significantly different from their healthy siblings.

The microbiota structure of patients and siblings are dominated by components of *Prevotella*, *Bacteroides* and *Faecalibacterium*. The microbiota diversity of the patient groups was substantially lower than that of the controls. It was possible to differentiate between the leukemia subjects and the controls based on their microbiota composition. The principal taxa comprise *Roseburia*, *Ruminococcus2*, *Anaerostipes* and *Coprococcus* with moderately higher abundance in the controls.[141]

Information regarding the oral microbiota in leukemia subjects is lacking and mostly inadequate. Among some patients, leukemia first presents in the oral cavity.[142,143] Oral symptoms that commonly arise in leukemia subjects include gingival enlargement and bleeding, candidiasis, oral ulceration and periodontitis[144-146] and oral microorganisms are implicated in the onset of such problems.[147] Specific oral microorganisms have been shown to contribute to septicemia, which might delay antineoplastic therapy or even put the subjects' life at risk.[148-153] Consequently, a suitable therapy for oral lesions could result in a more satisfactory outcome of both oral and systemic complications.

However, Wang et al. studied the structure of the supragingival plaque microbiota of ALL pediatric subjects and of the healthy controls.[154] The oral microbiota of leukemia subjects had less diversity related to controls. Microorganisms grouped into two main clusters, patients and controls, with diverse composition. Variations of specific taxa comprising the families *Aerococcaceae* and *Carnobacteriaceae*, *Phylum Firmicutes*, the order *Lactobacillales*, the genera *Abiotrophia* and *Granulicatella* and the class *Bacilli* were correlated with leukemia status. Nevertheless, it was demonstrated that the complexity of oral microbiota was not significantly diverse between leukemia subjects and controls until beginning of antineoplastic therapy. This contradiction might be ascribed to the methods employed to study oral microbiota. At the time of the study, oral microorganisms might have already undergone selection after ALL was detected, with some microorganisms inhibited and others prospering.[155]

However, the studies of oral microorganisms in ALL subjects, however, provided the possibility of recognizing potential microorganisms correlated with systemic infections in leukemia subjects. Results propose two taxonomical lineages (*Firmicutes/Bacilli/ Lactobacillales/ Aerococcaceae/Abiotrophia*, and *Firmicutes/Bacilli/ Lactobacillales/ Carnobacteriaceae/Granullicatella*) that are much more copious in the supragingival plaque of ALL subjects than controls. This suggests that advantageous situations existed for their growth in the oral space of ALL subjects and could be responsible for an increased risk of bacteremia in leukemia subjects.

Abiotrophia and *Granulicatella* have been involved in endocarditis, otitis media, central nervous system infections, cholangitis and arthritis.[156-159] Previous researchers have found that oral microorganisms are responsible for local infections and for 25-50% of systemic infections.[160]

Finally, adult survivors of ALL have health problems that arise years after termination of treatment. Chua et al. evaluated the anal microbiota structure of adult survivors of childhood ALL and controls. They recognized a modified population with decreased microbial diversity in tumor survivors, who also display signals of immune alteration comprising enhanced T-cell activation. The microorganism population among ALL survivors was enriched for *Actinobacteria* and depleted of *Faecalibacterium*, consistent with corresponding plasma levels of C-reactive protein and IL-6 and HLA-DR+CD4+ and HLA-DR+CD8+ T cells. They established a relationship between dysbiosis and immune alteration in adult ALL survivors. Actions that could reestablish microbial diversity may improve development of late effects of childhood ALL survivors, particularly chronic inflammation-related comorbidities.[161]

Acute myeloid leukemia (AML)

Bacterial infections and their complications are one of the most frequent and critical treatment-related toxicities in subjects with AML. Gram-positive cocci, principally the heterogeneous *Viridans streptococci*, are the most usually isolated microorganisms in patients with AML.[162] However, many elements of the microbiota could play a positive role towards leukemic disease. The oral bacterium, *Aggregatibacter actinomycetem comitans*, generates a leukotoxin (LtxA) that is specific for white blood cells by interacting with lymphocyte function antigen-1 (LFA-1) on susceptible cells. Kachlany et al. valuated the *in vitro* and *in vivo* anti-leukemia action of the toxin. LtxA destroys malignant cell lines and primary leukemia cells from AML subjects, while healthy cells are moderately resistant to LtxA-mediated cytotoxicity. Levels of LFA-1 in Jurkat cell lines correlated with killing by LtxA and the toxin especially destroyed cells presenting the activated form of LFA-1. In a severe combined immune deficiency mouse model for human leukemia, LtxA had powerful therapeutic action resulting in long-term survival of the LtxA-treated mice.[163]

Interestingly for patients with erythroleukemia, a rare form of AML, kefir, a beverage obtained by the incubation of kefir grains with raw milk may be an effective therapy. Kefir grains are a symbiotic complex of diverse kinds of yeasts and bacteria, especially lactic acid bacteria, which

congregate in a mostly carbohydrate matrix, called kefiran. In recent years, the action of kefir on some cancers has been investigated. Jalali et al. demonstrated that kefir caused apoptosis and necrosis in an acute erythroleukemia cell line (KG-1), by reducing growth. The study suggested that kefir may have the potential to be an effective therapy for erythroleukemia.[164]

Furthermore, numerous bacterial toxins are being investigated as potential anti-leukemia agents, either for their direct effects or to release therapeutic proteins against leukemia. LukS-PV, an element of Panton-Valentine leukocidin (PVL) produced by *S. aureus*, has certain anti-leukemia actions such as inducing leukemia cell differentiation and apoptosis, thus making LukS-PV an encouraging novel treatment strategy for leukemia.[165]

PVL is a staphylococcal synergohymenotropic exotoxin belonging to the pore-forming toxin family. PVL causes lysis of human polymorphonuclear neutrophils, monocytes and macrophages. Several works have proven that LukS-PV is able to cause leukemia cell differentiation.[166] LukS-PV provoked differentiation by stimulating the extracellular-signal-reduced kinase (ERK) signaling pathway and c-JUN/c-FOS in human acute myeloid leukemia cells.[167,168]

B and T lymphomas

Adolescent/young adult Hodgkin lymphoma (AYAHL) is associated with reduced exposures to infections. Similarly, a study of AYAHL survivors suggested fewer early childhood fecal-oral exposures compared with health controls, and patients have immunological alterations. AYAHL is related to suppressed Th1 activity and an increase of Th2 response.[169]

Extension of gut microorganisms during childhood[170,171] correspond with a change from a Th2 to a mature Th1-governed immune profile.[170] Increased concentrations of Th2 cytokines and IgE in AYAHL subjects reduced cytotoxic T-cells and NK cells in Hodgkin lymphoma[172] suggest the failure to make this Th2-to-Th1 change. These data suggest the possibility that the gut microorganisms may impact AYAHL.[173,174] Cozen et al. explored whether fecal microbial diversity varied between AYAHL survivors and co-twin controls. In this small investigation, AYAHL survivors seem to have a reduction of rare gut microorganisms. Further study is required to clarify if decreased microbial diversity is a result of Hodgkin lymphoma, its therapy or a specific hygienic environment.[173-176]

About 12% of all human tumors are related to oncogenic viruses such as Epstein Barr Virus, Herpes Human Virus 8 and Human T-cell leukemia virus type 1.[177] The occurrence of virus-related cancers, principally lymphomas, varies geographically and is induced by higher temperatures and environmental factors.[178-201]

Oxidative stress provoked by gut microorganisms can affect carcinogenesis and influence numerous pathways correlated with lymphomagenesis.[195-201]

Mucosal-associated lymphoid tissue (MALT) lymphomas are supposed to derive in the marginal zone and are connected with the presence of *Helicobacter*.[202-205] This correlation was first revealed in an animal model infected with *H. felis*, an intimate relative to *H. pylori* and 154 days post-infection, 25% of mice had lymphoepithelial alterations while none of the controls did.[206] An *H. pylori* infection was initially recognized in gerbils and displayed an augmentation in intestinal metaplasia.[207] Since then, H. *pylori* infections have been recognized in animal models.[208,209]

H. pylori was classified as carcinogenic to humans (Group I carcinogen) in 1994 by an International Agency for Research on Cancer (IARC) Working Group based on the data from a small number of papers that studied gastric carcinoma.[210] In 2009, a new Working Group evaluated significantly more results and confirmed that chronic infection with *H. pylori* is a Group 1 carcinogen with appropriate evidence that the infection causes gastric carcinoma and low-grade B-cell gastric MALT lymphoma.[211]

Gastric MALT lymphoma (GML) is strictly associated with *H. pylori* infection. In a retrospective evaluation of 144 consecutive patients admitted with GML, eradication treatment was extremely effective in causing complete remission (CR) and long-term prognosis was satisfactory. At multidisciplinary care stage EI, 92% of subjects received an *H. pylori* eradication therapy; 83% achieved CR after a mean period of seven months, and 86% remained in CR after a mean follow-up time of 105 months.[212]

A correlation was also hypothesized for other types of lymphomas. Numerous works described that most early-stage gastric diffuse large B-cell lymphoma (DLCBL) is *H. pylori*-dependent. Notably, DLCBL could possibly be treated by *H. pylori* eradication. Unlike MALT lymphoma, however, DLCBL may rapidly increase if it is unresponsive to *H. pylori* eradication. Consequently, detecting biomarkers that may predict an *H. pylori*-dependent status of gastric DLCBL is indispensable. Kuo et al. from Taiwan proposed that the expression of cytotoxin-associated gene A (Cag A) and CagA-signaling molecules p-SHP2 and p-ERK in malignant B cells is associated with *H. pylori* dependence.[213] The same authors demonstrated that activating the B-cell-activating factor (BAFF) pathway upregulates NF-kB and causes BCL3 and BCL10 nuclear translocation in *H. pylori*-independent gastric DLCBL tumors with evidence of MALT. Moreover, they showed that the autocrine BAFF signal transduction pathway contributed to *H. pylori* independence in gastric MALT lymphomas without the t.11;18q21;q21 translocation.[214]

H. helmanii also contribute to MALT lymphoma which is preceded by endothelial venule-like vesicles, which are connected with lymphocyte enrollments.[215] These models of microorganism-induced lymphoma however, appear to have variable results and may implicate bacterial and host elements.[216,217]

Other microorganisms such as *Chlamydia psitacci*, *Campylobacter jejuni* and *Borrelia bergdorferi* may also have an increase in the incidence of the disease in lymphoma progress.[218]

Infection of *Borrelia burgdorferi* may be causally related to B-cell non-Hodgkin lymphoma, as reported in one of two reports in Scandinavia.[219,220] *Chlamydia psittaci*, the agent of the zoonotic infectious disease psittacosis, has been found in MALT lymphomas in several non-gastrointestinal structures,[221] while *Streptococcus bovis* has been connected with hematopoietic diseases such as chronic myelogenous leukemia, and chronic lymphocytic leukemia.[222]

Intriguing results originated from animals defective in the Ataxia telangiectasia-mutated gene (Atm-/- mice), which exhibit a high occurrence of thymic lymphoma.[223] They are hypersensitive to modifications in microorganism content.[224] Barlow et al. discovered that *Atm-/-* animals that were moved into more sterile situations lived longer and have a reduced lymphoma penetrance. In contrast, when they were relocated to standard specific-pathogen-free situations, their life and tumor latency decreased.[225]

Chronic Lymphocyte Leukemia (CLL)

A recent study in CLL subjects connected the efficiency of antineoplastic therapy with the use of antibiotics that alter intestinal microbiota. Pflug et al. assessed the effect of antibiotics on progression-free survival (PFS) and overall survival (OS).[226] Among 800 CLL subjects, those receiving anti-Gram-positive antibiotics attained a substantially lower overall response rate (ORR). In the same study, authors evaluated patients with relapsed lymphoma. Of 122 patients with relapsed lymphoma, those treated with anti-Gram-positive antibiotics achieved a significantly lower ORR. Patients with anti-Gram-positive antibiotics progressed significantly earlier than others. The multivariate analysis demonstrated that the use of anti-Gram-positive antibiotics was independently associated with reduced PFS and OS.[226]

More than 30% of CLLs can be classified based on their expression of stereotypic B-cell receptors (BCRs), strongly proposing that specific antigens are implicated in the onset of CLL. Unmutated CLLs, containing Ig heavy chain variable (IGHV) genes in germline configuration express low-affinity, poly- and self-reactive BCRs. Nevertheless, the antigenic specificity of CLLs with mutated IGHV-genes (M-CLL) is still elusive. In a study, Hogeeboom et al. reported a new subset of M-CLL, presenting stereotypic BCRs highly specific for β-(1,6)-glucan, a major antigenic determinant of yeasts and filamentous fungi. β-(1,6)-glucan binding depended on both the stereotypic Ig heavy and light chains, as well as on a definite amino acid in the IGHV-CDR3. Reversion of IGHV mutations to germline configuration decreased the affinity for β-(1,6)-glucan, suggesting that these BCRs are really affinity-selected for their cognate antigen. Moreover, CLL cells presenting these stereotypic receptors grow in response to β-(1,6)-glucan. With this data it is attracting to hypothesize on the possibilities for pathogen-targeted treatments for this group of subjects.[227]

CONCLUSION

The microbiome is currently accepted as a specific organ with separate metabolic abilities that surpass the liver's metabolism by a factor of 100. The microbiome is able to influence hematologic malignancies via several ways, including directly through metabolites and toxins, or indirectly via the innate and adaptive immune system.[228] However, a number of issues remain unresolved and only further research will clarify whether it is sufficient to administer a single species of bacteria to achieve results or whether it is better to give a mixture of microorganisms, or if by modifying an individual's microbial composition, we can improve the effectiveness of immunotherapy.[229-230] In addition, FMT could help manage critical illness such as acute leukemias. In fact, in the critical care setting, several elements such as use of antibiotics, aberrant nutrition, bloodstream infections, bowel ischemia and abnormal bowel motility, strongly contribute to intestinal dysbiosis, and FMT therapy should be investigated.[231,232] Further studies are needed to clarify the rationale of FMT for cancer management such as reconstruction of intestinal microbiota, amelioration of bile acid metabolism and modulation of immunotherapy efficacy.

Substances with probiotic and prebiotic capacities may represent a novel approach to change microbiota structure with beneficial effects on tumor development. Targeted treatment on the microbiome by pre-or probiotics may be used for tumor prevention and particular alterations of the microbiome may be implemented as an adjuvant treatment to augment the effectiveness of current tumor therapies of chemotherapy and immuno-therapy.

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CASE REPORT

Post-transfusion purpura in a woman with acute myeloid leukemia

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SUMMARY

Post-transfusion purpura (PTP) is a rare, but severe transfusion reaction in which both donor and autologous platelets are sequestered due to immunization against HPA-1a antigens in HPA-1a negative recipients (HPA: human platelet antigens). We describe a patient who developed PTP during induction therapy for acute myeloid leukaemia. The pitfalls, delays in diagnosing and therapy options of this serious transfusion reaction are discussed.

KEY WORDS

Post transfusion purpura, HPA-1a, refractoriness, acute leukemia

What was known on this topic?
PTP is a rare but severe transfusion reaction, for which case reports have been previously reported. However, these case reports are mostly about PTP in relatively healthy individuals without co-morbidities.

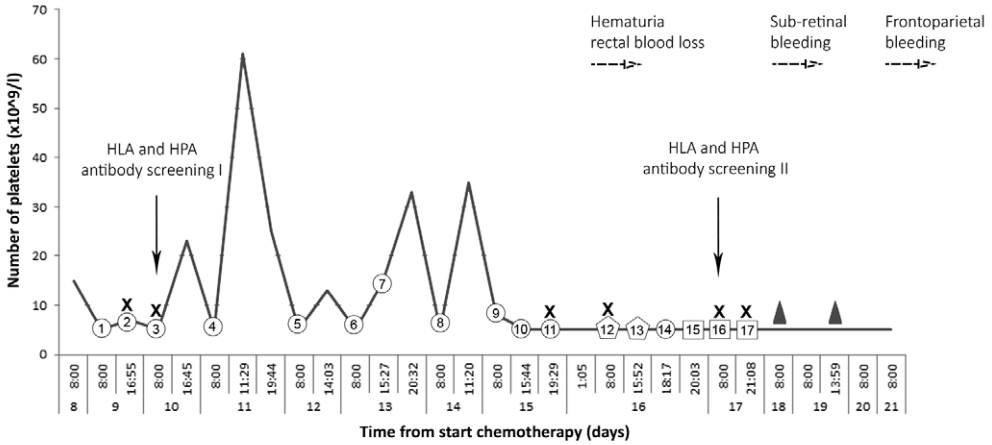
What does this add?
While PTP has been described in several case reports, none of them have described PTP in a patient with AML. We describe the pitfalls and delays of the diagnosis of PTP in a patient with AML, complicating diagnosis and treatment.

INTRODUCTION

Post-transfusion purpura (PTP) is a severe transfusion reaction that was first described in 1961.[1] The incidence of PTP is estimated at 1:50.000-100.000 transfusions.[2] PTP typically occurs after whole blood transfusion in women who have had a first immunization reaction during pregnancy, but also in subjects who have had previous transfusions. PTP is characterized by antibody formation against Human Platelet Antigens (HPA), which are lacking on platelets of the recipient. This nearly always results from immunization against HPA-1a-antigens in HPA-1a-negative subjects but occasionally, immunization against other HPA antigen types occurs.[3-5] The prevalence of HPA-1a-negative individuals in the Caucasian population is about 2%.[6] Characteristically, PTP presents 5-10 days after transfusion of blood products with deep thrombocytopenia (< 10 x 10^9/l), fever, shivering from cold and refractoriness to platelet transfusions.[7] Most patients recover spontaneously within weeks, but for patients with a secondary high bleeding risk, PTP is associated with a mortality rate of 10-20%.[8]

The mechanism of PTP is not precisely known. Both the transfused donor platelets and the patient's autologous platelets are destroyed. This 'innocent bystander' effect may be explained by the fact that autologous platelets absorb immune-complexes against allogeneic HPA-antigens through interaction with the Fc-receptor and are subsequently sequestrated in the spleen.[1,3,8,9] Another hypothesis suggests the production of platelet autoantibodies next to the HPA-1a alloantibodies.[1,9,10] A third hypothesis suggests absorption of soluble HPA-antigens in donor plasma or preservative on autologous platelets, which subsequently react with HPA antibodies.[2,5] We describe a suspected PTP in a patient receiving chemotherapy for acute myeloid leukaemia (AML) and discuss the complexity of diagnosis and therapy.

Figure 1. *Timeline (x-axis) after starting chemotherapy and platelet counts (y-axis). The numbers represent platelet transfusions. The numbers in circles represent conventional platelet transfusions, the numbers in polygons represent plasma-depleted transfusion and the numbers in squares represent Human Leucocyte Antigen- (HLA-) and Human Platelet Antigen (HPA)-compatible transfusions. X represents transfusion reactions. (Days 9 and 10: transfusion reactions on erythrocyte transfusions; days 15, 16 and 17: transfusion reactions on platelet transfusions). Triangles (day 18 and 19) represent Intravenous Immuno Globulin (IVIG) administrations.*



CASE REPORT

A 57-year old woman, mother of two children, presented with AML (Hb: 5.7 g/dl; leukocytes: 139 x 10^9/l; platelets: 78 x 10^9/l). During induction chemotherapy, multiple platelet concentrates and red blood cell units were transfused (*figure 1*). On days 9 and 10, red blood cell infusion was accompanied by fever and shivering. Clemastine and prednisolone were administered which reduced these symptoms. Therefore, preceding all subsequent transfusions, clemastine and prednisolone were administered. While platelet transfusions 1-3 were administered without a transfusion reaction, the corrected count increments (CCI) after one and 24 hours (CCI-1 and CCI-24) were zero. Therefore, Human Leukocyte Antigen (HLA) and HPA antibody screening and genotyping were performed. Genotyping showed that the patient was negative for the HPA-1a antigen and no HLA nor HPA antibodies were found. Furthermore, imaging ruled out splenomegaly. Platelet transfusions 4, 7 and 8 resulted in a CCI-1 > 2.5, however, platelet counts decreased to < 5.0 x 10^9/l within 24 hours, resulting in nose bleeds and hematomas. After platelet transfusion 11, the platelet count remained < 5.0 x 10^9/l, and transfusion reactions no longer responded to administration of clemastine and prednisolone. Febrile reactions were observed only after transfusions. There was no sign of infection. The plasma solution of the platelet concentrates 12 and 13 was substituted by platelet additive solution in an attempt to prevent transfusion reactions. But both transfusions resulted in a CCI-1 of zero. At this moment, platelet transfusions were mandatory because of hematuria and rectal bleeding. Because of suspicion of an immunological cause, HLA and HPA antibody screening was repeated on day 17 and HPA-1a and HLA-matched donor platelet concentrates were transfused; however, no increase in platelet count was observed (transfusions 15-17). On day 18, the patient developed a sub-retinal bleeding. At that moment, the second antibody analysis revealed strong reactive HPA-1a antibodies and multiple HLA antibodies. Therefore, PTP was suspected and transfusions were stopped and administration of intravenous immunoglobulins (IVIG) was started. Two days after starting IVIG, the patient developed a lethal frontoparietal bleeding due to persisting thrombocytopenia.

DISCUSSION

Since thrombocytopenia has several causes, finding the right diagnosis may be challenging. During AML treatment, thrombocytopenia most commonly is disease or therapy-related. Therefore, diagnosing PTP can be difficult and delayed.

The corrected count increment after one hour (CCI-1) is an important tool to discriminate between immunological (CCI-1 < 7.5) and non-immunological (CCI-1 > 7.5) causes for platelet transfusion refractoriness. In case of an immunological cause, specification of HLA or HPA alloantibodies and/or platelet glycoprotein reactive

antibodies can provide valuable information on the cause. Here, despite decreased CCI-1 values, no HLA and HPA antibodies were found in the first analysis. It appears that, especially in case of an HPA-1a-negative patient, reanalysis of antibody screening should be considered when an immunological cause of thrombocytopenia is clinically suspected, because increase of HLA or HPA antibody titers may be delayed and result into a negative laboratory test.

Thrombocytopenia in AML is common and can mostly be attributed to chemotherapy, inadequate response to platelet transfusions, sepsis and HLA or (rarely) HPA alloimmune antibodies. Furthermore, the differential diagnosis includes heparin-induced thrombocytopenia, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and medication-induced thrombocytopenia. Apart from chemotherapy, this patient did not use any medication known to cause thrombocytopenia, neither did she receive heparin. No signs of sepsis or infection were observed. DIC and TTP were ruled out by normal laboratory findings for activated Partial Thromboplastin Time, Prothrombin Time, fibrinogen and absence of fragmentocytes. Although chemotherapy definitely contributes to thrombocytopenia, here we could discriminate HPA-1a type antibodies, which is very suggestive for PTP in HPA1a-negative individuals. In case of PTP, prophylactic platelet transfusions, even compatible with HPA and HLA antigens, are contra-indicated.[11] IVIG is the primary choice of treatment, since it has response rates of 75-95% and a rapid onset of action.[11,12] Alternatively, steroids may be administrated together with IVIG, although responses appear unpredictable.[13] Plasmapheresis, which is occasionally considered as a second line treatment, results in improved platelet counts within 2-4 days in 80% of patient cases.[14,15] Unfortunately, in our patient, administration of IVIG and corticosteroids did not result in an increase of the platelet count and plasmapheresis could not be applied because rapid deterioration led to her demise.

CONCLUSION

PTP, in particular in patients treated for AML, may not be easily recognized. This delay may be fatal as is illustrated in our patient. When clinically suspected, PTP should not be excluded in platelet transfusion refractory HPA-1a-negative patients without detectable HPA-1a antibodies. However, even with timely recognition, PTP has a high mortality rate, especially in high-risk patients, like our patient with AML.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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CASE REPORT

Macroscopic hematuria as presenting symptom of celiac disease

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ABSTRACT

A 47-year old man was admitted for macroscopic hematuria and spontaneous hematomas. Laboratory results showed a prolonged partial thromboplastin time (PTT), a prolonged activated partial thromboplastin time (APTT) and a severe vitamin K deficiency. The underlying cause proved to be vitamin K malabsorption due to previously undiagnosed celiac disease, possibly provoked by oral antibiotic administration.

KEY WORDS

Celiac disease, hematuria , coagulation, vitamin K deficiency, malabsorption

What was known on this topic?
Celiac disease can manifest in a variety of ways, including impaired coagulation. A study (Cavallaro et al., 2004) showed that adults with untreated celiac disease can have a significantly prolonged prothrombin time.

What does this add?
This case report shows that a severe bleeding can be the presenting symptom of previously undiagnosed celiac disease.

CASE DESCRIPTION

A 47-year old man was admitted to our hospital with new onset macroscopic hematuria. He had no significant medical history, nor did he have any risk factor or family history for bleeding disorders. Our patient reported general discomfort since a few weeks, including some days of diarrhea. Four days prior to hospital admittance, he had been treated with doxycycline for two days for suspected Lyme disease. On physical examination, we observed an underweight man (body mass index 17.9 kg/m^2). Furthermore, spontaenous hematomas on both feet were observed. Moreover, when removing his watch, another hematoma developed instantly at this site. His urine contained blood and urine analysis showed > 50 erythrocytes per view. The primary serum laboratory results showed a normocytic anemia [hemoglobin 5.5 mmol/l, hematocrit 0,28 l/l, MCV 84 fl], as well as severely prolonged PTT (over 180s) and APTT (104s). His thrombocyte count, creatinine level and haptoglobin were within normal ranges. The primary differential diagnosis included (1) disseminated intravascular coagulation (DIC), (2) coagulation factor deficiency (as a result of exogenous vitamin K antagonist administration, malabsorption, low vitamin K intake or due to the recently administrated antibiotics), (3) acquired factor antibodies and (4) hepatic failure. Additional serum tests showed a normal value of factor 1 and liver tests within the normal range, excluding DIC and liver failure from the differential diagnosis. Second, both primary and late mix tests showed a significant shortening of coagulation time, ruling out direct factor inhibitors. Thus, by exclusion, prolonged coagulation times were the result of a factor deficiency. Additional testing demonstrated an extremely low level of factor VII (2%) and a slightly decreased factor V level (53%). Serum vitamin K was 0.01 nmol/l. Coumarin-derived anticoagulants were not found in our patient's serum. Extensive additional questioning revealed that our patient had experienced aberrant stool and stomach aches for years. More additional laboratory tests showed decreased levels of vitamin B12 [less than 61 pmol/l], folic acid [6.7 nmol/l] and albumin [30.3 g/l]. As celiac disease is the most common malabsorption disorder, we tested both anti-transglutaminase IgA antibody (over 128.0 U/ml) and deamidated gliadin antibodies (48 U/ml). Celiac disease was confirmed by gastroduodenoscopy with biopsies, which revealed nearly complete villous atrophy

with crypt hyperplasia and intra-epithelial lymphocytosis (Modified Marsh Classification III C). The introduction of a gluten-free diet led to full recovery of coagulation and hematuria. Therefore, no additional diagnostic tests were performed. In conclusion, a 47-year old man presented with macroscopic hematuria and spontaneous hematomas due to extremely low levels of vitamin K caused by celiac disease-based malabsorption.

DISCUSSION

Vitamin K is an essential fat-soluble vitamin. There are two forms of vitamin K. One is present in food and absorbed in the small intestine; the other is of bacterial origin and absorbed in the colon.[1] The food-derived vitamin K is protein bound, separated by pancreatic enzymes and solubilized into micelles by bile salts before absorption. Vitamin K is then incorporated into chylomicrons, which migrate via the intestinal lymphatics and the portal system to the liver.[2]

In hepatic cells, vitamin K is essential for synthesizing coagulation factors. It is an active coenzyme needed for carboxylation of carboxygluatamic acid, which is present in coagulation factors VII, IX, X, and prothrombin. Carboxylation enhances the affinity of these factors for the phospholipids on the platelet surface and thus promotes coagulation. In the presence of a vitamin K deficiency, carboxylation of the abovementioned factors will be limited which causes an increase in coagulation time.[2] Among others, vitamin K deficiency can occur as a result of malabsorption.[3]

Celiac disease is the most common cause of malabsorption in Europe and North America.[4] In celiac disease, exposure to dietary gluten causes inflammation of the mucosa, crypt hyperplasia and villous atrophy in the small intestine. Abstention of dietary gluten induces improvement of these aberrancies.[5] Usually, celiac disease is diagnosed in patients with diarrhea and weight loss, which is observed in 85% and 57% of celiac patients, respectively.[6] To the best of our knowledge, this is the first European case and the second case worldwide, of macroscopic hematuria as the presenting symptom of celiac disease. Of note, one study investigated the prevalence of prolonged PT in adults with untreated coeliac disease.[7] From a total of 390 celiac disease patients, 72 patients (18.5%) showed prolonged PT.

Our case shows that severe and potentially life-threatening spontaneous bleeding can be the sole presenting symptom of celiac disease. Most probably, our patient has suffered from malabsorption throughout his life due to celiac disease, which has led to reduced vitamin K uptake in the small intestine. Possibly, the administration of doxycycline disrupted the microbiome in the colon and thus reduced the residual uptake of vitamin K to a critical low level.[8] Avoiding dietary gluten led to recovery of the small intestine and improved absorption of vitamin K.

Early recognition of the underlying cause of severe bleeding could prevent undesirable outcomes such as hemorrhagic stroke or gastrointestinal bleeding. Therefore, in cases of patients with spontaneous bleeding and extended coagulation parameters in accordance with vitamin K deficiency, malabsorption based on celiac disease should be considered.

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PHOTO QUIZ

Yellow nail syndrome with complete triad

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Figure 1. *Visual inspection of the patient's hands*

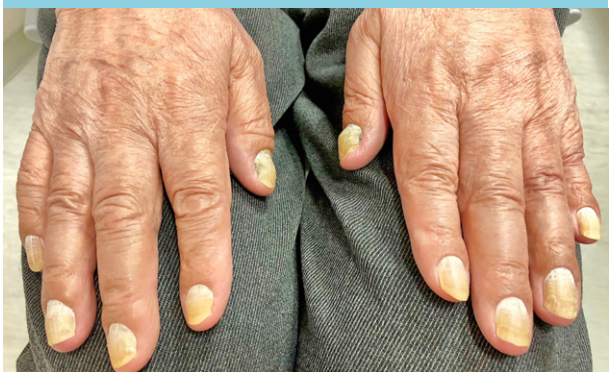
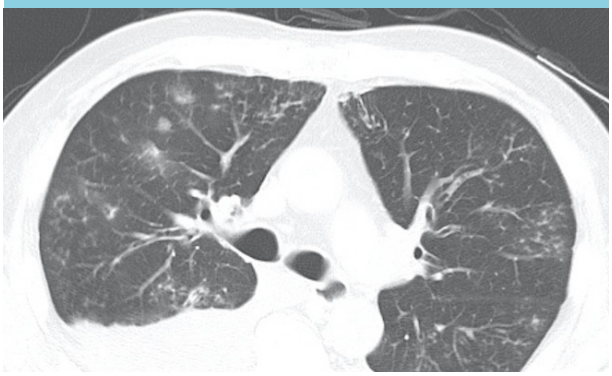


Figure 2. *Chest computed tomography scan*



CASE REPORT

A 77-year old man presented with a month history of edema on both legs. Diffuse panbronchiolitis (DPB) was diagnosed a year prior to his current symptoms and was treated with erythromycin, but the treatment was discontinued due to poor adherence. He had no sinus manifestations and did not recognize discoloration of his nails until he visited our hospital. He had non-pitting edema on both of his legs with Stemmer's sign, and auscultation revealed decreased breath sounds in both lower lung fields. Additionally, the color of his finger and toe nails were yellow (*figure 1*). Chest computed tomography scan showed newly developed bilateral pleural effusion with previous diffuse micronodules in bilateral lung fields. (*figure 2*). Blood laboratory testing was normal, including interferon-γ release assay, and pleural effusion was exudative with lymphocyte dominant exudates, while adenosine deaminase was within the normal range. Echocardiography was normal. He was not taking any drugs where side effects could relate to yellow nails, and trial antifungal therapy (efinaconazole) did not alter discoloration of his nail.

WHAT IS YOUR DIAGNOSIS?

See page 87 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 86)

YELLOW NAIL SYNDROME WITH COMPLETE TRIAD

DISCUSSION

Yellow nail syndrome (YNS) is a rare disorder first described in 1927 and diagnosed based on a triad associating yellow nail discoloration, lower limb lymphedema, and respiratory manifestations including bronchiectasis, pleural effusion (usually lymphocyte-rich exudates) and rhinosinusitis with unknown pathogenesis.[1] YNS usually occurs in adults over 50 years old and there is no gender preference. F. Maldonado et al. retrospectively analyzed 41 YNS patients and revealed that 26 patients (63%) presented with lymphedema as the main manifestation; all but one patient had chronic respiratory manifestations.[2] The classic triad was simultaneously present in 27-60% of patients with the syndrome.[3]

YNS was most plausible cause of leg edema in this case. When YNS is diagnosed, it is important to exclude other possibilities such as heart failure, hypothyroidism, renal failure, liver cirrhosis, tuberculous pleuritis and other disorders related to yellow nail (onychomycosis, drugs such as D-penicillamine, bucillamine), but in our case, there were no findings that indicated such a differential diagnosis. The long-term outcome for YNS is not well known, but prognosis may be poor and relation to cancer has been shown in small sets of patient groups.[2] Since there is no evident specific therapy to date, the prescribed therapy is usually selected based on manifestation of patient symptoms.[2] L. Valdes. et al. reported that the most effective treatments for symptomatic pleural effusion appear to be pleurodesis and decortication/pleurectomy, since a total of 81.8% patients showed partial or complete response.[4]

In our current case, decreased bilateral micronodules were obtained after reintroduction of daily erythromycin. Yellow nail, pleural effusion and leg edema were then stable without any other symptoms.

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PHOTO QUIZ

Neutrophil hypersegmentation ironed out

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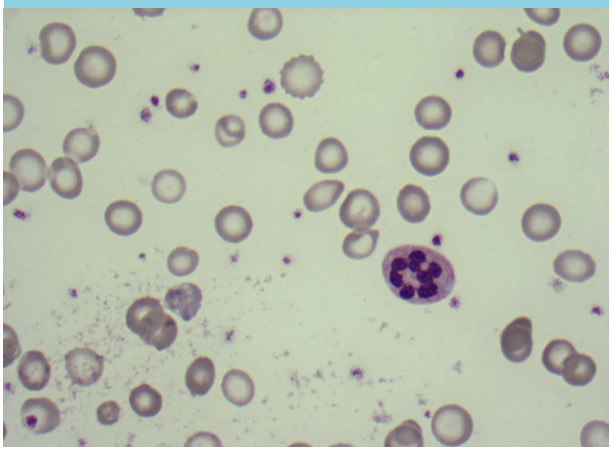
CASE REPORT

A 56-year old man of Egyptian descent was brought to our emergency room because of collapse preceded by subacute dyspnea and chest and back pain. His medical history included hypertension, hypercholesterolemia and two percutaneous coronary interventions six years and one year ago. We saw a pale man in distress, requiring 15 liters of oxygen via a non-rebreathing mask. He was clammy and had a sinus tachycardia of 100 beats/min with a blood pressure of 120/70 mmHg.

Blood gas analysis revealed lactate acidosis with pH 7.14, and a haemoglobin of 1.7 mmol/l. Therefore, two units of filtered erythrocytes were rapidly administered before cross-matching, with further transfusions given until a hemoglobin concentration of 5.0 mmol/l was achieved. There were no signs of external blood loss. A computed tomography scan of his thorax and abdomen did not reveal a bleeding site or other abnormalities. Meanwhile, further laboratory results indicated a mean corpuscular volume (MCV) of 66 fL, but no signs of hemolysis. The direct antiglobulin test did not demonstrate agglutination. A manual blood count was performed (see *figure 1*).

Figure 1. *Microscopic image of the manual blood count of our patient*



WHAT IS YOUR DIAGNOSIS?

See page 89 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 88)

NEUTROPHIL HYPERSEGMENTATION IRONED OUT

DIAGNOSIS

The manual blood count revealed rouleaux formation, anisochromasia, anisoplania, hypochromasia, polychromasia, but no reticulocytosis. Further, 18% of all neutrophils showed five or more segments, which is designated as neutrophil hypersegmentation; one neutrophil had eight segments (see *figure 1*).

Thalassemia was considered because of patient's descent, but his haemoglobin concentration had been 8.1 mmol/l with an MCV of 92 fL a year before. The iron levels were low, whilst folate and vitamin B12 concentrations were normal. Hence, we established a diagnosis of serious iron-deficiency anemia.

It later became clear that he had been eating poorly for the past six months, mostly drinking tea, and had unintentionally lost weight because of significant psychosocial stress. There had been no accompanying symptoms.

Gastrointestinal evaluation revealed no macroscopic or microscopic abnormalities. PCR for *T. whipplei* was negative.

After erythrocyte transfusions, the patient was discharged with a prescription for ferrofumarate and dietary advice. At follow-up six and 12 months later, he maintained a hemoglobin-level of 10 mmol/l, with complete recovery of iron stores.

Iron deficiency anemia is characterized by a low MCV and decreased serum concentrations of iron, ferritin and decreased transferrin saturation. In this patient, neutrophil hypersegmentation was observed, traditionally a sign of folate or cobalamin deficiency, which were both excluded in this patient. Normal segmentation of neutrophils is mediated by cytoskeletal proteins, and facilitates migration.[1] Neutrophil hypersegmentation is defined as the presence of ≥ 5% five-lobed neutrophils, or any number with six or more lobes. Folates stimulate synthesis of purines and thymidylate, important elements in the formation of DNA and RNA. They also enhance methylation reactions of DNA and RNA through methionine. Therefore, folate-deficiency results in compromised synthesis of nuclear DNA. Cytoplasm and other nuclear components are nevertheless still generated, causing hypersegmentation by accumulation.[2] Heavy chain ferritin, a part of the iron-storing protein ferritin, stimulates an important step in the synthesis of thymidylate and methionine from tetrahydrofolate.[3] Low ferritin levels therefore cause hypersegmentation by impaired methionine generation. Indeed, hypersegmentation was previously observed in iron deficiency anemia by others.[4]

In conclusion, neutrophil hypersegmentation is not only a feature of folate or cobalamin deficiency, but can also be seen in iron deficiency.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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PHOTO QUIZ

Cutaneous lesions on the body

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Figure 1. *Papular and erythematous lesions on body areas covered by the swimsuit several hours after contact with seawater.*

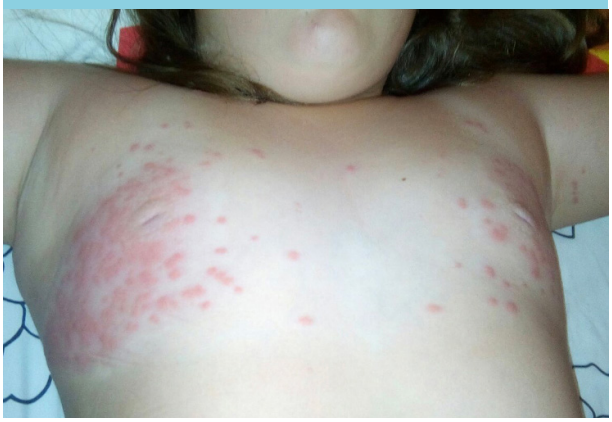
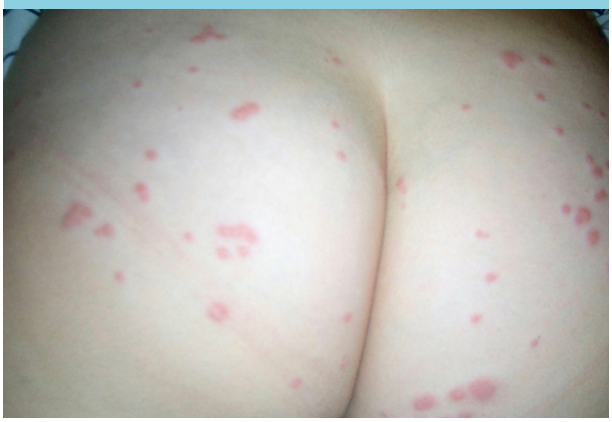


Figure 2. *Maculo-papular lesions were located in areas covered by the swimsuit.*



CASE REPORT

An 8-year old female with no relevant history of previous illnesses was seen in the first week of July because of pruritic cutaneous lesions on her body in areas covered by a new bikini. The lesions appeared after swimming at a beach in Cantabria, Spain, and after having the wet fabric in contact with her skin for several hours. The patient showed neither fever nor any other systemic symptoms.

Physical examination showed an eruption consisting of papulo erythematous lesions of 1-3 mm in diameter, grouped but not converging, located on breasts, sides, back and buttocks, excluding the skin not covered by the swimsuit (*figures 1 and 2*).

A cutaneous biopsy showed a spongiotic and superficial perivascular dermatitis with lympho-histiocytes and many eosinophils. A blood test including food allergens test to milk, egg and anti-transglutaminase antibodies, as well as epicutaneous tests (standard, coloring, textile fabrics from her own swimsuit) did not suggest any pathology. The patient experienced a significant improvement with topical corticosteroids and oral antihistamines leading to a complete recovery and clearing in a period of two weeks.

WHAT IS YOUR DIAGNOSIS?

See page 91 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 90)
CUTANEOUS LESIONS ON THE BODY

DIAGNOSIS

Seabather´s Eruption

According to the clinical evolution and the complementary tests, the possibility of contact dermatitis was dismissed, as well as other sea dermatoses, and Seabather's Eruption was stated as the suspected principal diagnosis.

Seabather's Eruption consists of pruritic papular and erythematous lesions that appear on body areas covered by a swimsuit. Most cases reported belong to geographic areas with warm climates, mainly the Caribbean.[1]

Clinically, lesions can be urticariform or maculo-papular not converging but grouped, appearing in the first hours after contact with seawater, that tend to resolve themselves spontaneously, but may persist for two to 14 days after initial appearance.

Etiology of these lesions is still uncertain. Scientific literature appoints to the larvae of different species of coelenterate (jellyfish, sea anemone, coral and hydra) who have cells with urticating philaments (nematocistes) that deliver their venom and generate this dermatosis. Swimming suits, due to a mechanical phenomenon, perpetuate the contact between the etiopathogenic agent and the skin, leading to this typical location of the lesions.[2] Histopathological studies are in general, unspecific, resembling in many cases, the sting of arthropods. The main differential diagnosis is with swimmer itch (in which uncovered parts of the body are affected after swimming in fresh water), as well as other sea dermatoses (jellyfish sting, contact dermatitis by algae, etc). Similarly, diagnosis may be difficult if symptoms are considered with contact dermatitis due to reactions with the swimsuit fabrics or dyes.

Seabather's Eruption therapy is symptomatic based on topical corticosteroids and oral antihistamines. There is no way to prevent Seabather´s Eruption except to stay out of the water. Patients should be advised that this condition can worsen in fresh water.

An emerging and alarming problem identified by the Dermatological Scientific community is climate change and an increasing number of cases of Seabather´s eruption all along the American Atlantic coast due to an increasing rise of temperatures should be emphasized;[3] new cases have also occured in the last few years in the Cantabrian Sea, mainly in summer. Rising temperatures could facilitate the biology and life cycles of these larvae.[4]

We consider the Seabather´s Eruption knowledge of great interest, not only for the reported cases, but in anticipation of the possibility of a higher number of native cases in the coming years.

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LETTER

Potential predatory journals are colonizing the ICMJE recommendations list of followers

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ABSTRACT

Background. The International Committee of Medical Journal Editors (ICMJE) has expressed its concerns about predatory journals using the list of ICMJE Recommendations (ICMJE-R) followers to "gain the appearance of legitimacy." We assessed the presence of potential predatory journals on the ICMJE-R list and their adherence to ICMJE recommendations.

Methods. A random sample of 350 journals from the estimated 3,100-3,200 biomedical journals listed as ICMJE-R followers was chosen. Data collected from the ICMJE and journal webpages in English were: adherence to six ICMJE-R policies/requirements, year of journal's listing as ICMJE-R follower, discipline covered, publisher and its country of origin and existence of article processing charge. Potential predatory journal was considered as one open access journal not being a member of a recognized listing in COPE, DOAJ, OASPA, AJOL and/or INASP.

Results. Thirty-one percent of journals were considered to be potentially predatory; 94% of them were included in the ICMJE-R list in 2014-2018. Half were published in the United States and 62% were devoted to medicine. Adherence to five of the six policies/requirements was infrequent, ranging from 51% (plagiarism) to 7% (trial registration). Seventy-two percent of journals mentioned a policy on authors' conflicts of interest. Information on article processing charge was available for 76% journals and could not be found for 22%. Authorship policy/instructions were significantly more present in journals with publishers from India than from the USA (53% vs 30%; p = 0.047), with no differences in the other five policies.

Conclusion. Predatory journals should be deleted from the ICMJE-R list of followers to prevent misleading authors. ICMJE-R following journals need to be reevaluated with pre-defined published criteria.

INTRODUCTION

The term 'predatory journals' was coined by Jeffrey Beall in 2008, who also created a list of potential predatory journals and publishers.[1] Although there is not an agreed definition of the term 'predatory journal',[2] it could be assumed that these are open access journals that publish poor quality articles, with poor or no peer-review process, owned by publishers providing no transparent editorial services. Their main objective is financial gain by article processing charges to authors.

The total number of articles published by some 8,000 predatory journals rose from 53,000 in 2010 to 400,000 in 2014.[3] This was accompanied by an increasing interest on this subject. From 2012 to 2017, the number of articles mentioning predatory journals in five bibliographic databases rose from 5 to 140, respectively, totaling 324.[2] Although most predatory journals are located in developing countries, notably India and Turkey, many are edited in the USA and other western countries.[4] The use of predatory journals has spread all over the world: researchers from 146 countries (out of 193 countries belonging to United Nations) have published in predatory journals.[4] This is particularly important in Europe where the implementation of Plan S in 2020 will increase the percentage of research published to be immediately open access:[5] investigators must know how to distinguish scholarly journals from predatory journals.

Although there are organizations dealing with the ethics and quality of scholarly publishing, such as COPE (Committee of Publication Ethics), ICMJE (International Committee of Medical Journal Editors) or WAME (World Association of Medical Editors), predatory journals pose serious issues to academic journals.[6] In their aim to gain more prestige among researchers, many predatory journals claim to be members (or followers) of respectful organizations such as ICMJE. This is why the ICMJE has

expressed its concerns about predatory journals using the list of ICMJE Recommendations (ICJME-R) followers to "gain the appearance of legitimacy."[7]

The aim of this study was to assess the current presence of potential predatory journals on the ICJME-R list and their theoretical adherence to ICMJE-R.

Table 1. *Random sample of 108 potential predatory journals[a] listed as followers of the International Committee of Medical Journal Editors (ICMJE) Recommendations. Presence of 6 specific policies and requirements accessible in journals' websites, disciplines covered, year when the journals were included as followers of the ICMJE Recommendations and country of origin of journals' publishers. All data as of May 5, 2018.*

	Yes *n (%; 95% CI)*	*No* *n (%; 95% CI)*
Policies (or statements)[b,c]		
Authorship instructions	43 (40; 31-50)	65 (60; 50-69)
Authors' conflicts of interest	78 (72; 63-80)	30 (28; 20-37)
Plagiarism	55 (51; 41-61)	53 (49; 39-59)
Requirements[b,c]		
Participant's informed consent	37 (34; 26-44)	71 (66; 56-75)
Research Ethics Committee approval	34 (31: 23-41)	74 (69; 59-77)
Clinical trial registration	8 (7; 3-14)	100 (93; 86-97)
Disciplines covered		
		n (%; 95% CI)
Disciplines	Medicine	67 (62; 52-71)
	Multidisciplinary	24 (22; 15-31)
	Pharmacy	7 (7; 3-13)
	Other 5[d]	10 (9; 5-16)
Year of inclusion as followers in the ICMJE recommendations list		
		n (%; 95% CI)
Year of inclusion in ICMJE recommendations list	2014-2018[e]	102 (94; 88-98)
	2011-2013	5 (5; 2-10)
	Not provided	1 (1; 0-5)
Country of journals' publishers		
		n (%; 95% CI)
Country[f]	USA	54 (50; 40-60)
	India	36 (33; 25-43)
	UK	8 (7; 3-14)
	Other 5[g]	10 (9; 5-16)

n = number of journals. 95% CI = 95% confidence interval
(a) These journals are not members of COPE, DOAJ, OASPA, AJOL or INASP's journals online platform for journals of certain Asian and Central America countries.
(b) Provided in the journal's website or through the publisher's website, but excluding their access through professional bodies (e.g., ICMJE, DOAG, OASPA, COPE or WAME) whose websites were provided on some journals' websites.
(c) Mention of these policies and requirements, even if they fall short from what the ICMJE-R mentioned, was considered as compliance.
(d) Other disciplines: Nursing (n = 3), Odontology (n = 2), Alternative medicine (n = 2), Health (n = 2), Biotechnology (n = 1).
(e) 15 journals in 2014; 25 in 2015; 22 in 2016; 33 in 2017; 7 in 2018 (up to February 18, 2018)
(f) 51 different publishers published 99 journals (9 journals were published by themselves)
(g) China (n = 4), Canada (n = 2), Turkey (n = 2), Algeria (n = 1), Lebanon (n = 1)

MATERIALS AND METHODS

We chose a random sample of 350 journals from the estimated 3,100-3,200 biomedical or health-care journals listed as ICJME-R followers in February 2018 (a journal listed as an ICJME-R follower claims to adhere to the ICJME recommendations).[8] Data collected from the ICMJE and journal websites in English included: adherence to the six main ICJME-R polices/requirements, year of journal's listing as ICJME-R follower, discipline covered, publisher and its country of origin, and existence of article processing charge. The ICJME-R policies (or statements) were those referring to authorship, author's conflict of interest and plagiarism; whereas the ICJME-R requirements were on participant's informed consent, research ethics committee approval and clinical trial registration.

Following the well-respected educational initiative 'ThinkCheckSubmit', potential predatory journals were considered those not being members of a recognized industry initiative, such as COPE, DOAJ (Directory of Open Access Journals), OASPA (Open Access Scholarly Publishers' Association), AJOL (African Journals Online) or INASP (International Network for the Availability of Scientific Publications).[9] As others have done before,[10,11] we checked the inclusion of both the journal and publisher on the updated Beall lists.[12]

RESULTS

This analysis revealed that 31% (108/350) of journals had characteristics of potential predatory journals. *Table 1* shows that most of them were included in the ICJME-R list of followers in the last four years (94%; 102/108). In four years, the annual number of new followers increased 120% from 15 (2014) to 33 (2017). Half (54/108) were published by publishers in the USA and 62% (67/108) were devoted to medicine. Adherence to five of the main policies and requirements considered was scarce, ranging from 51% (plagiarism) to 7% (trial registration). The policy on authors' conflicts of interest was the only commonly (72%) mentioned policy. Only three journals stated that they followed all six policies and requirements, and 11 (10%) had no public evidence of following these policies. Information on an article processing charge was publicly available for 82 (76%) journals, could not be found for 24 (22%) and two journals specifically stated that there was no article processing charge.

Table 2 shows the comparison between American and Indian journals. Authorship policies (or instructions) were significantly more present in journals with publishers from India than from USA (53% vs 30%; p = 0.047), with no differences in the other five policies and requirements. Eighty percent (86/108) of potential predatory journals were included in the up-dated Beall's lists of potential predatory publishers or journals.[12]

Table 2. *Random sample of 108 potential predatory journals[a] listed as followers of the ICMJE recommendations. Comparison between American and Indian journals: policies and requirements. All data as of May 5, 2018.*

	Present in American journals (n = 54) n (%; 95% CI)	*Present in Indian journals (n = 36) n (%; 95% CI)*
Policies (or statements)[b,c]		
Authorship instructions	16 (30; 18-44)*	19 (53; 35-70)*
Authors' conflicts of interest	38 (70; 56-82)	24 (67; 49-81)
Plagiarism	25 (47; 33-60)	14 (39; 23-57)
Requirements[b,c]		
Participant's informed consent	16 (30; 18-44)	14 (39; 23-57)
Research Ethics Committee approval	13 (24; 13-38)	14 (39; 23-57)
Clinical trial registration	2 (4; 0-13)	2 (6; 1-19)

(a) These journals are not members of COPE, DOAJ, OASPA, AJOL or INASP's journals online platform for journals of certain Asian and Central America countries.
(b) Provided in the journal's website or through the publisher's website, but excluding their access through professional bodies (eg, ICMJE, DOAG, OASPA, COPE or WAME) whose websites were provided on some journals' websites.
(c) Mention of these policies and requirements, even if they fall short from what the ICMJE-R mentioned, was considered as compliance.
*p = 0.047 (Chi-square)

DISCUSSION

Our study provides evidence that many potential predatory journals may indeed be gaining legitimacy by being included as ICJME-R followers and that this is a recent phenomenon. Although Beall considered 2012 to be the year when predatory publishers exploded,[1] our results show that potential predatory journals needed two more years to start the race to list themselves as followers of the ICJME-R, reaching a maximum of 31% (33 of 108) of new followers in 2017. Potential predatory journals are also colonizing other databases to gain respectfulness. Hence, PubMed includes articles published by potential predatory journals and the percentage of potential predatory journals increased significantly in only one year. Thus, in 2016, between 11% and 20% of PubMed journals in rehabilitation, neuroscience and neurology were potentially predatory journals, whereas in 2017 these percentages rose to 16%-25%.[13]

There were two limitations to our study. The first is that among the elements that 'ThinkCheckSubmit' advises to check to assess if a journal could be potentially predatory, we checked only the three that were objective and feasible – the article processing charge, easily identifiable publisher and journal being a member of a recognized industry initiative – and we left out those being subjective and non-feasible, such as knowledge of colleagues about the journal, having a recognized editorial board or having articles indexed. For 22 journals, we were not able to identify the article processing charges. However, it is well known that many predatory journals only inform on the fees to be paid once the article has been accepted for publication.[1,2] Finally, two journals explicitly stated that they will not charge any article processing fee; however, both journals and publisher were not included in any of the five recognized industry initiatives[9] and both journals belonged to a publisher (AME Publishing Company, Hong Kong) that was included in the Beall list of potential predatory publishers.[12] The second limitation was that we did not check the accuracy of the six policies and requirements since all, except that referring to authorship policy, can only be checked by submitting a manuscript. This is why we always refer to 'potential' predatory journals.

Publishing in predatory journals is unethical.[11] Potential predatory journals on the list of ICMJE-R followers do not provide public evidence that they actually adhere to ICMJE-R, so it is questionable whether ICMJE should keep this list. They should be deleted from the ICMJE-R list of followers to prevent misleading authors. ICMJE-R followers need to be reevaluated with pre-defined published criteria, similar to the procedure undertaken by DOAJ and OASPA, and these quality checks should be applied to all future applications. A similar approach has been suggested to ensure that PubMed is free of predatory journal articles: journal candidates should satisfy the three MEDLINE preapplication requirements and should be a member of DOAJ, OASPA, COPE or WAME.[14] Finally, a third way to address this scientific publishing problem – of special relevance to biomedicine, the topic of interest to most predatory journals[10]– is to generate a list of respectful journals. This has been the approach taken by urologists who are creating a 'green list' of reputable journals within their specialty.[15] As of December 2018 there were 57 journals included in the 'Urology green list', all of them complying with several criteria such as, for instance, being a member of a professional organization, having a reputable publisher and editorial board, transparent manuscript submission and peer review process or membership or affiliation with COPE.[16]

SUPPLEMENTAL FILE

All the data collected for this study are available from the corresponding author, and is available upon request from the corresponding author.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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