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No association between omalizumab use and risk of cancer: a nationwide registry-based cohort study

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DEAR EDITOR, Omalizumab is a monoclonal antibody that targets free IgE, inhibiting its interaction with the IgE receptor. It is administered subcutaneously to treat antihistamine-unresponsive chronic urticaria (CU), allergic asthma that is inadequately controlled with inhaled corticosteroids, and nasal polyps inadequately controlled by nasal corticosteroids.^{1,2}

A recent study using VigiBase, the World Health Organization's global database of individual case safety reports,³ reported that omalizumab may be associated with a higher risk of malignancies. The increased risk was found for leukaemia, malignant melanoma, and breast, lung, prostate, colon and thyroid cancers. We examined the incidence and risk of cancer in all patients treated with omalizumab in Denmark for CU and asthma. In Denmark omalizumab is only administered at hospitals.

We used The Danish National Patient Registry⁴ that contains prospectively collected data on diagnoses from all hospital admissions and outpatient contacts at all Danish hospitals, and from a number of private clinics, since 1978, using the International Classification of Diseases codes. Treatment procedure codes from the Danish National Patient Register⁴ with hospital-based pharmacological treatment (biological therapies) were used, and individual-level linkage across nationwide administrative registries was done with the unique personal identification number assigned to all Danish citizens.⁵ All Danes from 1 January 1997 and onwards were identified, and patients with CU or asthma were included (source population) (further data are available at <https://figshare.com/articles/figure/Figures/17705027>). Cohort entry (index) was defined as the time of the first omalizumab administration, and all participants were followed until migration, death or 31 December 2018, whichever came first. Participants ever treated with omalizumab (exposed) were individually age- and sex-matched with the source population not treated with omalizumab (unexposed), in a 1 : 10 ratio. Patients with a cancer diagnosis before index were excluded. The incidence rates per 1000 person-years of a cancer between exposed and unexposed participants were calculated, and crude and adjusted (age, sex, diagnosis of CU or asthma) hazard ratios (HRs) were estimated with a Cox regression model. A P-value of <0.05 was considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata statistical software, release 13.0 (StataCorp LP, College Station, TX, USA).

Table 1 Risk of cancer in participants with urticaria or asthma treated with omalizumab (exposed) vs. never treated with omalizumab (unexposed)

Neoplasm	Exposed (n = 1444)		Unexposed (n = 14 397)		Crude HR		Adjusted HR ^a	
	Events	IR (95% CI)	Events	IR (95% CI)	HR (95% CI)	P-value	HR (95% CI)	P-value
Any cancer ^b	21	43.39 (28.28–66.54)	245	50.67 (44.71–57.43)	0.89 (0.57–1.40)	0.632	0.92 (0.58–1.47)	0.741
Chronic urticaria	8	24.68 (12.34–49.36)	37	40.29 (29.19–55.62)	0.61 (0.28–1.32)	0.214	0.45 (0.21–0.98)	0.044
Asthma	13	81.27 (47.19–139.97)	208	53.10 (46.35–60.83)	1.44 (0.82–2.52)	0.202	1.36 (0.77–2.39)	0.281
Bladder	0	–	7	1.43 (0.68–3.01)	–	–	–	–
Brain	0	–	4	0.81 (0.31–2.17)	–	–	–	–
Breast	<3	4.09 (1.02–16.37)	53	10.86 (8.29–14.22)	0.39 (0.09–1.64)	0.203	0.48 (0.11–2.08)	0.332
Female genitalia ^c	<3	2.04 (0.29–14.54)	17	3.48 (2.16–5.59)	0.65 (0.08–4.97)	0.685	0.81 (0.09–6.64)	0.847
Gastrointestinal ^d	5	10.25 (4.26–24.62)	32	6.54 (4.62–9.25)	1.58 (0.61–4.11)	0.340	1.42 (0.51–3.96)	0.500
Head and neck ^e	<3	4.09 (1.02–16.38)	9	1.83 (0.95–3.53)	3.24 (0.65–16.08)	0.149	2.56 (0.46–13.98)	0.278
Hodgkin lymphoma	<3	2.04 (0.29–14.53)	0	–	–	–	–	–
Keratinocyte	0	–	9	1.83 (0.95–3.53)	–	–	–	–
Kidney	0	–	7	1.43 (0.68–3.00)	–	–	–	–
Leukaemia	3	6.14 (1.98–19.04)	<3	0.40 (0.10–1.63)	13.76 (2.29–82.48)	0.004	24.27 (3.66–160.79)	0.001
Lung	0	–	35	7.15 (5.14–9.97)	–	–	–	–
Malignant melanoma	<3	4.09 (1.02–16.38)	21	4.29 (2.80–6.58)	0.86 (0.20–3.71)	0.849	1.26 (0.27–5.82)	0.769
Myeloma	0	–	3	0.61 (0.19–1.90)	–	–	–	–
Non-Hodgkin lymphoma	<3	2.04 (0.28–14.53)	12	2.45 (1.39–4.32)	0.83 (0.11–6.47)	0.864	0.53 (0.06–4.48)	0.564
Prostate	<3	2.05 (0.28–14.52)	25	5.11 (3.45–7.57)	0.37 (0.05–2.75)	0.332	0.36 (0.05–2.90)	0.343
Thyroid	<3	4.09 (1.02–16.37)	7	1.43 (0.68–3.00)	2.78 (0.58–13.43)	0.201	3.29 (0.58–18.57)	0.176

HR, hazard ratio; IR, incidence rate per 1000 person-years; CI, confidence interval. ^aAdjusted for sex, age, diagnosis of chronic urticaria or asthma. ^bAny cancer: a composite outcome referring to any new primary cancer. ^cFemale genitalia: cervix, endometrium, ovary. ^dGastrointestinal: colorectal, gallbladder, liver, oesophagus, pancreas, stomach. ^eHead and neck: nasal, oral, larynx, pharynx.

The study cohort comprised a total of 1444 participants treated with omalizumab (998 women, 446 men) with a mean (SD) age of 40.6 years (± 16.1) of which 1009 (69.9%) had CU, 370 (25.6%) had asthma, and 65 (4.5%) had CU and asthma. The mean duration of exposure to omalizumab was 2.1 years. The unexposed age- and sex-matched control group consisted of 14 397 participants (9961 women, 4436 men) with a mean age of 40.5 years (± 16.0) of which 2891 (20.1%) had CU, 11 430 (79.4%) had asthma, and 76 (0.5%) had CU and asthma. The mean follow-up time was 3.4 years in both groups. A total of 266 cancers (97 men, 169 women) were observed: 21 (1.5%) among exposed and 245 (1.7%) among unexposed, adjusted HR 0.92 [95% confidence interval (CI) 0.58–1.47; $P = 0.741$] (Table 1). Also, the risk of cancer was not increased in stratified analyses based on a diagnosis of CU or asthma; however, the risk of leukaemia was increased, with adjusted HR 24.27 (95% CI 3.66–160.79; $P = 0.001$) in exposed compared with unexposed patients. The association was not significant after excluding all cancer cases occurring within the first year of omalizumab initiation, with adjusted HR 7.00 (95% CI 0.27–178.87; $P = 0.239$), indicating protopathic bias.

In conclusion, we did not find an increased risk of cancer associated with omalizumab used for CU or asthma in this nationwide registry-based cohort study. Our study is limited by the

lack of power to assess some specific cancers, and future studies confirming the long-term safety of omalizumab are warranted.

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Data availability: data are available only on request owing to privacy/ethical restrictions.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 List of codes used in the study.

Surveying the attitudes of dermatologists regarding climate change

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DEAR EDITOR, Anthropogenic climate change affects our environment through higher temperatures, poorer air quality, polluted waters and increased extreme weather events. These changes in our environment negatively influence the health of the population.¹ The integument is not spared by climate change. Higher temperatures, decreased ozone protection, increased airborne pollutants and decreased protection against ultraviolet radiation (UVR) can cause flares of atopic dermatitis, pemphigus, lupus and other inflammatory diseases, and increased rates of skin cancer.² Changing climate also influences the geographic distribution of vector-borne infections.² Although these consequences on dermatological diseases have been described, assessments of dermatologists' attitudes towards climate change have been limited.³

We designed an online questionnaire to characterize the viewpoints and actions of practising dermatologists with respect to climate change (Table 1). The survey was distributed electronically to the membership of dermatological organizations

including the American Society of Dermatologic Surgery, the Medical Dermatology Society, the American Society of Dermatopathology, the Society for Pediatric Dermatology, the Society for Investigative Dermatology, the American Academy of Dermatology's Climate Change Expert Resource Group, and the Association of Professors of Dermatology. Institutional Review Board approval was obtained at the Albert Einstein College of Medicine prior to data collection (2020-12558).

A total of 148 responses were obtained; 94.5% of respondents were from the USA and 83.6% practised in an academic setting. An overwhelming majority of our participants reported a belief that global climate change is occurring [$99.3\% \pm 1.3\%$ (percentage $\pm$ 95% confidence interval)] and that it is caused by human activities ($93.9\% \pm 3.9\%$); $79.6\% \pm 6.5\%$ of respondents reported a belief that climate change has started to affect or will affect their patients through climate-driven phenomena such as increased exposure to UVR ($80.1\% \pm 6.5\%$), changes in patterns of vector-borne illnesses ($78.7\% \pm 6.6\%$) and social displacement ($67.1\% \pm 7.6\%$; Table 1).

These beliefs contrast with a low sense of self-efficacy among our respondents, indicative of a 'practice gap', as only a minority reported that they would feel comfortable discussing climate change with their patients ($37.2\% \pm 7.8\%$), while others stated that they would like to be better informed on the issue prior to discussing it with patients ($31.1\% \pm 7.5\%$). Many also felt that they have a responsibility to bring awareness of the health effects of climate change not only to patients ($77.2\% \pm 6.7\%$), but to other providers ($84.6\% \pm 5.8\%$) and policymakers ($88.6\% \pm 5.1\%$). Our participants also reported some modifications in their personal or professional lives, including altering methods of energy consumption ($75.7\% \pm 6.9\%$), waste disposal ($68.9\% \pm 7.5\%$) and travel ($54.7\% \pm 8.0\%$). Many of our respondents, $81.8\% \pm 6.2\%$, indicated that they would like to read more about the dermatological effects of climate change in scientific journals (Table 1).

Although our conclusions are limited by the potential for response bias, they suggest that there are dermatologists in the USA, particularly in academic areas, who are cognizant of global climate change and its effects on our patients, while desirous of further education on its dermatological ramifications. These findings are similar to those reported by previous surveys of healthcare providers.^{3,4} Consequently, there continues to be unfulfilled interest in education and advocacy regarding climate change, suggesting a 'practice gap' even among dermatologists. While it is not possible to calculate a response rate due to the study design and membership overlap between dermatological organizations, it is likely low (~10%) given that this survey likely reached hundreds of dermatologists. Low participation may be due to lack of prioritization of this issue by many survey recipients or survey fatigue particularly heightened during the pandemic. There is great opportunity to close this 'practice gap' and raise awareness through more efforts to provide resources and actionable items regarding climate change to physicians by professional organizations and journal publications. Further studies are needed to examine