

Atopic dermatitis is not a protective factor for melanoma but asthma may be

Enes Hajdarbegovic · Nasirah Atiq ·
Robert van der Leest · Bing Thio · Tamar Nijsten

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Abstract

Background There is evidence from cohort studies for an inverse association between atopic dermatitis and asthma and cutaneous melanoma. However, these studies have been too heterogeneous and did not show statistically significant results. Also, this association has not been compared to traditional melanoma risk factors.

Objectives To test for associations between history of atopic disorders and melanoma life-time prevalence, and for associations between atopic disorders and melanoma prognosis.

Methods Validated questionnaires from the European Community Respiratory Health Survey and International Study of Asthma and Allergies in Children protocol on life-time prevalence of atopic disorders were sent to 280 patients with histopathologically confirmed melanoma. The control group consisted of their spouses. The skin photo-type was also assessed using a validated questionnaire.

Results One hundred and eighty-four melanoma patients and 169 controls responded to the questionnaire. The life-time prevalence of atopic dermatitis and hayfever was not different in melanoma patients (8.7 % vs. 8.2, $p = 0.890$ and 15.2 vs. 18.3 %, $p = 0.432$, respectively). Asthma was non-significantly lower in melanoma patients (3.8 vs. 8.2 %, $p = 0.075$). Atopic melanoma patients did not differ from non-atopic patients in terms of Breslow thickness, metastases and second melanomas.

Conclusion Atopic dermatitis is not a protective factor in cutaneous melanoma but a history of asthma may be.

Keywords Melanoma · Atopy · Atopic dermatitis · Hayfever · Asthma · Risk factor

Background

Cutaneous melanoma is one of the most aggressive malignant tumours and is virtually incurable after metastasis. It is known for its rapid growth and the ability to metastasize early via the lymphatics and the blood vessels. The incidence of melanoma in the USA is 3.0 and in Europe 2.2–19.2 per 100,000, and has been rising in the past 30 years [1, 2]. The conventional risk factors for development of melanoma are fair skin, history of melanoma in the index patient or their family members, having clinically atypical moles, sunburn and exposition to UV radiation [3, 4]. Because knowledge of the traditional risk factors has not led to effective prevention programs, it is worthwhile looking into alternative risk factors [5]. Atopic disorders—atopic dermatitis, hayfever and atopic asthma—have been of interest in epidemiological studies as a risk and a protective factor for cancer. These studies have shown lower prevalences of different types of cancer in atopic individuals [6, 7]. In two cohort studies with more than 31,000 patients with atopic eczema, a decreased prevalence of malignant melanoma, albeit of borderline significance, was found, with totals of 6 and 12 melanoma patients, respectively [8, 9]. In three prospective studies, children with atopic dermatitis had significantly fewer nevi, which was assumed to reduce the risk of melanoma [10–12]. On the other hand, a health survey in 3,308 Australians revealed an increased prevalence of melanoma

E. Hajdarbegovic (✉) · N. Atiq · R. van der Leest · B. Thio · T. Nijsten
Department of Dermatology and Venerology, Erasmus Medical Centre, Burgemeester 's Jacobplein 51, Gk-315, 3015 NL Rotterdam, The Netherlands
e-mail: e.hajdarbegovic@erasmusmc.nl

[27 cases with hazard ratio 2.39, 95 % confidence interval (CI) 1.00–5.70] in men with hayfever [13]. In contrast, another German case–control study from 1988 with 331 melanoma patients demonstrated that melanoma patients were less likely to report atopic symptoms (4.2 vs. 10 %) [14]. The effect of asthma has also been assessed in a cohort of hospitalized asthmatics. The standardized incidence of melanoma was found to be decreased in a ten-year period in the 1970s in Sweden, but only 72 melanoma cases occurred [15]. This was also found in another large cohort study with the same methodology of 64,346 asthma patients [16]. However, this finding was not consistent for all decades and was not found in patients with multiple admissions for asthma. These previous studies have been heterogeneous, registry-based and focused on a single atopic disorder while assessing the incidences of multiple cancers simultaneously. From their data we cannot conclude whether atopic disorders are a risk factor for development or progression of cutaneous melanoma.

Patients and methods

Study population

The melanoma patients were recruited from the department of Dermatology and Venereology of the Erasmus Medical Centre in Rotterdam. They comprised 280 Dutch Caucasian patients diagnosed with a cutaneous melanoma between 2000 and 2010, extracted from our administrative registry. The diagnosis was histologically confirmed in all patients by certified pathologists. The control group consisted of the melanoma patients' spouses. All subjects were sent identical questionnaires concerning atopic manifestations and their treatment. Melanoma patients and their spouses were also sent a questionnaire assessing their skin phototype. The choice of this control group was made because of availability and because of the match in ethnic, socio-economic and external factors without genetic bias. Because atopic disorders are largely genetically determined and are usually seen in childhood, it is not to be expected that this exposure is of any influence on partner choice later in life. The medical ethical committee at Erasmus Medical Center provides a waiver for single-subject questionnaire-based studies. This study has been conducted in accordance with the Declaration of Helsinki.

Patient-reported atopic disease and skin type

The subjects were approached through a postal survey. Non-responders were contacted a second time. They were sent a questionnaire comprising questions from the European Community Respiratory Health Survey and

International Study of Asthma and Allergies in Children protocol [17, 18]. Subjects were considered to have asthma if they positively answered the question “Have you ever been diagnosed with asthma by a doctor?” and if the answer to the question “How old were you when you were diagnosed with asthma?” was less than 25 years, in order to prevent misclassification of subjects with chronic obstructive pulmonary disease. Diagnosis of atopic dermatitis was made in patients with eczema diagnosed by a physician, with an onset before age 25 and duration of more than 1 year. For diagnosis of hayfever, patients had to answer affirmatively the question “Have you ever had hayfever?” and they would have to have it before the age of 25. Because atopic disorders wane after childhood, we deemed patients diagnosed before the age of 25 to be atopic. This also prevents inclusion of chronic pulmonary obstructive disease patients as asthmatics. In addition, other forms of dermatitis are more likely after the age of 25. To assess the Fitzpatrick skin type the patients filled in the Fitzpatrick skin type questionnaire [19]. This allows the comparison of the effect of atopy with a conventional risk factor which is a skin phototype lower than 3.

Statistics

For sample size calculations, we assumed a prevalence of 20 % of atopic disorders in our control group, as we have found previously [20], and expected half of this proportion in melanoma patients [14]. For a power of 80 % and an alpha level of 0.05, a sample size of 135 cases and 135 controls was required. The chi-squared test was used to test for statistical differences in proportions. The logistic multiple regression analysis was performed in standard fashion where all variables with $p < 0.20$ from the univariate analysis were included. In order to be able to assess and compare the effect size of individual determinants, the variables were analysed by the enter method. All data were analysed using IBM SPSS version 19.0 (Chicago, Illinois 2011).

Results

Demographic characteristics

A total of 184 (61 %) Dutch melanoma patients and 169 (56 %) of their spouses responded to the questionnaire. (Table 1). The control subjects were younger (53 vs. 57 years, $p = 0.001$) and more frequently male (53 vs. 41 %, $p = 0.001$). The family history of atopy did not differ across the groups. Melanoma patients had a skin phototype lower than 3 more frequently than controls (60 vs. 36 %, $p < 0.001$). The median Breslow-thickness of

Table 1 Subject characteristics

	Melanoma patients	Controls	<i>p</i> value
Number	184	169	
Mean age, years (SD)	57 (14)	56 (14)	0.274
Male sex	75 (41 %)	86 (51 %)	0.056
Family history of atopy	95 (52 %)	79 (47 %)	0.359
Skin phototype <3	108 (60 %)	60 (36 %)	<0.001
Breslow thickness median (mm)	1.1 IQR [0.66–2.00]	–	–
Metastases	23 (13 %)	–	–
Second melanoma	29 (16 %)	–	–

SD standard deviation, *IQR* interquartile range, *Metastases* lymphatic or distant site metastases, *Second melanoma* new primary cutaneous melanoma

Table 2 Life-time prevalence of atopic features in melanoma patients versus controls

	Melanoma patients	Controls	<i>p</i> value
Number	184	169	
Asthma	7 (3.8 %)	14 (8.2 %)	0.075
Current inhalator use	7 (3.8 %)	11 (6.5 %)	0.249
Atopic dermatitis	16 (8.7 %)	14 (8.2 %)	0.890
Current topical corticosteroid use	26 (14.1 %)	19 (11.2 %)	0.416
Hayfever	28 (15.2 %)	31 (18.3 %)	0.432
Current use of antihistaminics	22 (12.0 %)	23 (13.6 %)	0.642
Any atopic disorder	44 (24.0 %)	45 (26.6 %)	0.557

our patients was 1.1 mm [IQR 0.66–2.00]. Twenty-three of them had metastases and 29 had a second melanoma. The two control group components did not differ with regard to demographic characteristics or atopic features.

Atopic features

There were no statistically significant differences in atopic eczema, hayfever and the use of disease specific medication across the groups (Table 2). Melanoma patients reported less frequently to have asthma but this was not statistically significant (3.8 vs. 8.2 % $p = 0.075$). In the univariate regression analysis the strongest association was found between melanoma and high risk skin phototype i.e. skin phototypes 1 and 2 (OR 2.69, 95 % CI [1.74–4.14]) (Table 3). Nevertheless, history of asthma seemed to be inversely associated with melanoma OR 0.44 95 % CI [0.17–1.11] but this was not statistically significant. High risk skin phototype remained the most important risk factor in the multiple regression analysis adjusted OR 2.60. 95 % CI [1.66–4.05].

Table 3 Standard uni- and multi-variate regression analysis for risk of melanoma

	Unadjusted OR for melanoma with 95 % CI	Adjusted OR for melanoma with 95 % CI
Age	1.01 (1.00–1.03)	1.01 (1.0–1.03)
Male sex	0.66 (0.44–1.01)	0.72 (0.46–1.12)
Skin phototype <3	2.69 (1.74–4.14)	2.61 (1.67–4.07)
Asthma	0.44 (0.17–1.11)	0.53 (0.20–1.41)
Atopic dermatitis	1.05 (0.50–2.23)	n/a
Hayfever	0.80 (0.46–1.40)	n/a
Any atopic disorder	0.87 (0.54–1.40)	n/a

Variables with $p > 0.20$ were omitted from multivariate analysis. Variables with $p < 0.20$ are shown in **bold**

OR odds ratio, 95 % CI 95 % confidence interval

Table 4 Atopic versus non-atopic melanoma patients

	Atopic melanoma patients	Non-atopic melanoma patients	<i>p</i> value
Number of patients	44	140	
Age (years), mean (SD)	54 (14)	59 (14)	0.035
Age at diagnosis (years), mean (SD)	48 (15)	52 (15)	0.309
Male sex	16/44	59/140	0.309
Skin phototype <3	30/43	78/138	0.085
Breslow thickness (mm), median (IQR)	1.00 (0.51–2.02)	1.10 (0.70–2.00)	0.722
Metastases	5/44	18/140	0.514
Second melanoma	8/44	21/140	0.384

SD standard deviation, *IQR* interquartile range, *Metastases* lymphatic or distant site metastases, *Second melanoma* new primary cutaneous melanoma

Atopy in melanoma patients

For the analysis of the effect of atopy on prognostic parameters of melanoma we compared melanoma patients with, eczema, hayfever or asthma to patients who reported none of these atopic disorders. Atopic melanoma patients were younger on the average than the non-atopic patients (54 vs. 59 years, $p = 0.035$) (Table 4). Nevertheless, atopic patients did not differ from non-atopic patients in terms

of Breslow-thickness, metastases and second melanomas. However, high risk skin types were more prevalent in atopic patients (70 vs. 57 % $p = 0.085$). The seven asthmatic melanoma patients did not differ from the non-asthmatic in terms of Breslow thickness: 0.9 mm [interquartile range (IQR) 0.4–2.4] vs. 1.1 mm (IQR 0.7–2.0). Grouping the patients according to atopic dermatitis and hayfever status yielded essentially the same results.

Discussion

Our findings indicate that atopic dermatitis and hayfever are not a protective or a risk factor for melanoma. Asthma, however, may be associated with a lower risk of melanoma, as found in previous studies [15, 16]. Although they were more prevalent, hayfever and atopic eczema did not show any association with melanoma. In comparison, having a high-risk skin phototype was found to be significantly associated with melanoma and its effect on the odds ratio was much greater than the effect of having an atopic disorder. Atopic disorders were also not associated with prognostic factors for melanoma like Breslow thickness and metastasis. The greatest limitation of our study is the low number of cases, although our study sufficiently excludes a large effect from atopic dermatitis and hayfever. A bigger study is necessary to confirm the findings in patients with asthma. In addition, the retrospective setup may introduce selection bias because of the lethality of melanoma. However, a case-control methodology is preferred because of the high prevalence of atopic disorders, i.e. exposure, and relatively low prevalence of melanoma. Also, there is not a more practical way to ascertain atopy, as it is mostly found during childhood. It is noteworthy that atopic melanoma patients had lower skin phototypes than non-atopic patients, which is actually expected to increase their chance of having a melanoma. It also means that adjustment for skin phototype is warranted in future studies. Because of the different skin phototype in controls there is a possibility of different ethnicities influencing the prevalence of atopy. There is no obvious mechanism to explain how asthma may lower the risk of melanoma. We suggest less exposure to the sun because of less outdoor activity or an altered immune system be looked into in future studies. Traditional risk factors for melanoma such as the skin phototype and number of nevi should be also taken into account when assessing alternative risk factors. We believe that our study is of value for future investigations, suggesting a methodological approach. For now, our data suggest that asthma may protect against cutaneous melanoma.

Conflict of interest The authors declare that they have no conflict of interest.

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