INVESTIGATIVE REPORT





# Inverse Association Between Atopy and Melanoma: A Case-control Study

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**Heightened cutaneous immune surveillance in atopic patients may inhibit development of melanoma. The aim of this study was to analyse the association between atopy and melanoma (development and outcome). A total of 188 cases of melanoma and 596 healthy controls were interviewed by telephone with a standardized questionnaire on atopic, demographic and melanoma characteristics. Cases were matched with controls on important confounders (age, sex, sunburn sensitivity, hair colour, number of moles, sunburn as juvenile, ever sunbed use, familial melanoma). Melanoma outcome data (disease relapse and death) within cases were retrieved. Analysis showed a general inverse association between atopy and melanoma development, but this was statistically significant only for a history of personal atopy (odds ratio 0.53, 95% confidence interval: 0.30–0.96, *p*-value = 0.04). Among melanoma patients, atopy did not affect survival or progression. In conclusion, this study suggests an inverse association between a history of atopy and melanoma development, but not with disease progression.**

*Key words:* atopy; atopic dermatitis; case-control study; epidemiology; melanoma; risk factors.

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Melanoma is the most frequent lethal form of cutaneous malignancy among Caucasians. An increase in mortality rates and incidence rates of melanoma has been detected (1), whereby a further increase in incidence rates of melanoma in the coming years is forecasted (2). Melanoma accounts for approximately 75% of all skin cancer deaths, which translates into the loss of thousands of lives. In 2008, 45,000 deaths due to melanoma were reported worldwide (3). Although there are several novel treatment options for advanced melanoma currently under investigation, mortality rates remain high. It has been hypothesized that a possible negative link between atopy and melanoma might exist due to the hyperactive immune system in atopic patients, which might prevent the development of malignancy through increased immune surveillance (4, 5). Moreover, the fact that melanoma is an immunogenic tumour might render this disease susceptible to the heightened immune surveillance in atopic patients (6). In addition, it has been shown that fewer naevi are present in patients with atopic dermatitis (AD), which implies that AD might protect against melanoma, since a high naevi count is a well-known risk factor for melanoma (7). However, atopy is an inflammatory disease, and inflammation has been linked with tumour development and has been postulated as one of the hallmarks of cancer. It has been hypothesized that inflammation can contribute to genetic instability and might even sustain a pro-oncogenic environment (4, 8).

To date, studies that have been conducted on the association between atopy and melanoma are scarce and contradictory. Three studies in large cohorts of subjects with AD have reported lower incidence ratios of melanoma cases in AD vs. non-AD populations (4, 9, 10), while a recent study found a significant positive association between AD and melanoma (11). These studies examined the incidence of melanoma in AD vs. non-AD subjects, but did not take other melanoma risk factors into account. Three other studies comparing the incidence of AD in a melanoma case vs. a healthy control population, demonstrated a significant negative (12) and non-significant positive association (13) between melanoma and AD, but these studies also did not correct for melanoma risk factors, except for a recent Dutch study that corrected for phototype (14). To the best of our knowledge, none of the studies conducted on atopy and melanoma investigated the association between atopy and melanoma survival or progression.

Therefore, we sought to examine the association of atopy-related variables and melanoma development and progression in a case-control population, using a validated questionnaire for AD diagnosis, controlled for the major confounders of melanoma.

## METHODS

### *Data collection*

Cases and controls were recruited from March 2004 to January 2008. Local ethics committees gave approval for the study (S number: 24960). A cohort of consecutive cutaneous patients with melanoma treated at the Department of Dermatology in University Hospitals Leuven and Antwerp University Hospital in Belgium were included after obtaining informed consent. All participants

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were informed about the aim (further insight in the cause of skin cancer and prevention of skin cancer) and content of the study (answering a questionnaire). They were also informed about the possible risks, the advantages of the study, the protection of their privacy, the right to information, and their right to withdraw from the study at any time. Two hundred and one consecutive melanoma cases were approached for the study. For each case, at least 2 controls were selected from the same street (or residence area) using the telephone book. Both groups were interviewed via a telephone call with a standardized questionnaire for the demographic data (age, sex and year of birth) and melanoma risk factors. The following major melanoma risk factors were registered: sunburn sensitivity (ability to burn after sun exposure in the beginning of the summer and after 1 h without sun protection), ability to tan (the ability to develop a tanned skin at the end of the summer after chronic sun exposure), natural hair colour, eye colour, number of moles, sunburn as juvenile, sunburn in the last 5 years, ever sunbed use, and presence of melanoma in first-degree family members were noted. Potential participants were given a schematic diagram along with the introduction letter for the study to instruct them how to assess their number of moles. For the ascertainment of AD, a questionnaire, namely the UK Working Party's diagnostic criteria for AD was used (15) (**Table I**), which has been validated in several studies with a sensitivity of 80% and a specificity of 97% (16). Atopic dermatitis was defined as having an itchy skin plus at least 3 of the following criteria: itchy condition present before the age of 2 years, eczema on the elbows or knees, ankles, neck, around the eyes or ears, a history of asthma or hay fever and/or dry skin in the last year. The same questionnaire and 2 additional questions were used to define other atopy-related variables, namely personal atopy, respiratory atopy, active atopy and familial atopy (Table I). Personal atopy was defined as either having had AD or respiratory atopy. Respiratory atopy was defined as having had asthma or hay fever. Active atopy was defined as eczema (red, irritated, itchy rash) on the knees or elbow folds at the time of the interview. Familial atopy was positive when any of the siblings, children and/or parents ever had hay fever, eczema and/or asthma.

For the survival analyses, histopathological data and data on relapse date, date of last follow-up and date of death were collected from hospital records.

### *Statistical methods*

The analyses consisted of 2 parts. First, we analyzed the possible correlation between atopy and presence of melanoma through comparison of the melanoma cases with the controls. Secondly, which concerns only the melanoma cases, the correlation between atopy and outcome (progression-free survival (PFS) and overall survival (OS)) was evaluated. Descriptive statistics, such as Fisher's exact and Mann-Whitney *U* tests, were used to evaluate distribution differences in characteristics between cases and controls with regard to demographic (age, sex) and major melanoma risk factors. A 1:1 matching was performed between cases and controls, matching for age, sex, and on all confounders found to be statistically significantly different between cases and controls in the descriptive analyses, more specifically sunburn sensitivity, tanning ability, natural hair colour, eye colour, number of moles, sunburn as juvenile, sunburn in the last 5 years, ever sunbed use, and presence of melanoma in first-degree family. Exact matches on the statistically significant confounders were made, except for age, where a maximal difference of 5 years has been allowed. Cases and controls within pairs were compared on atopy-related variables using exact McNemar's tests. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Given that fewer naevi were seen in patients with AD, and that naevi count was the strongest predictor for melanoma risk amongst the potential confounders (i.e. highest area under the curve (AUC) in univariable analyses; results not shown), a sub-analysis was performed within the group with no/few naevi count. For the outcome analysis within the melanoma cases, histopathological data on relapse date, date of last follow-up and date of death were collected. Patients were followed from the time of diagnosis. The cut-off date for follow-up was 31 December 2014. Survival period was calculated from the time of diagnosis until the last follow-up visit if the patient was still alive, or until date of death. Any cause of death is considered an event for the OS and death due to melanoma for melanoma-related death (MRD). Progression-free period was calculated from time of diagnosis until date of progression or any cause of death or last follow-up. Cox proportional hazards models were used to analyse the association of atopy with OS, MRD and PFS. Due to the low number of events, corrections for the confounder's age and staging were performed separately (referred to as bivariable models).

Significance level was set at $p=0.05$. All tests were 2-sided. Analyses were performed in SAS (version 9.2 of the SAS System for Windows. Copyright 2002 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks of SAS Institute Inc., Cary, NC, USA).

**Table I. Questions used for the definition of the atopy-related variables and their definitions**

| |
|---|
| *UK Working Party's diagnostic criteria*[a] |
| 1. Have you ever had an itchy skin condition? |
| 4. Have you ever had asthma [wheezing] or hay fever (sneezing, runny nose, itchy eyes in the summer)? |
| 2. If yes, was this present before the age of two years? |
| 3. Have you ever had eczema on the elbows or knees, ankles, neck, around the eyes or ears? |
| 4. Have you ever had asthma [wheezing] or hay fever (sneezing, runny nose, itchy eyes in the summer)? |
| 5. Have you had dry skin in the last 12 months? |
| *Definitions* |
| AD: question number 1=yes plus at least 3 other questions were answered yes |
| Personal atopy: if AD is present or question 4 was answered yes |
| Respiratory atopy: if question 4 was answered yes |
| *Extra questions on* |
| Active AD: Do you currently have eczema (red, irritated, itchy rash) on the knee or elbow folds? |
| Familial atopy: Have any of your siblings, children and/or parents ever had hay fever, eczema and/or asthma? |

[a]Adapted from Williams et al., 1994 (16).
AD: atopic dermatitis.

## RESULTS

Out of the 1,058 healthy controls approached, there were 237 refusals and 225 individuals could not be reached for the actual interview. A total of 596 controls were therefore included. Of the 201 cases contacted, there was 1 refusal, and 5 could not be contacted. Seven cases were excluded because the diagnosis of melanoma could not be confirmed on revision, leading to a final total of 188 cases.

Baseline characteristics found to be significantly associated with presence of melanoma in the univariate analyses were: age, sunburn sensitivity, hair colour, number of moles, sunburn as juvenile, sunbed use, and familial melanoma (**Table II**).

Matching cases with controls for age, sex, and the aforementioned 7 confounders resulted in a final total of 116 pairs. For all atopy-related variables, a negative association was found with the melanoma risk, i.e. the

**Table II. Baseline characteristics of the study population**[a]

| | Controls | Cases | *p*-value |
|---|---|---|---|
| Total, *n* | 596 | 188 | |
| Age, years, mean | 57.4 | 52.2 | < 0.001 |
| Sex, *n* | | | |
| Male | 224 | 69 | 0.863 |
| Female | 372 | 119 | |
| Sunburn sensitivity, *n* | | | |
| Yes | 440 | 163 | < 0.001 |
| No | 156 | 25 | |
| Tanning ability, *n* | | | |
| Brown/very brown | 548 | 170 | 0.547 |
| Never/very mild | 48 | 18 | |
| Hair colour, *n* | | | |
| Light | 262 | 111 | < 0.001 |
| Dark | 332 | 77 | |
| Eye colour, *n* | | | |
| Light | 438 | 143 | 0.700 |
| Dark | 151 | 45 | |
| Moles, *n* | | | |
| No/few | 498 | 107 | < 0.001 |
| Multiple/many | 81 | 78 | |
| Sunburn as juvenile, *n* | | | |
| No | 354 | 83 | < 0.001 |
| Yes | 224 | 99 | |
| Sunburn last 5 years, *n* | | | |
| No | 507 | 158 | 0.812 |
| Yes | 85 | 28 | |
| Ever sunbed use, *n* | | | |
| No | 315 | 69 | < 0.001 |
| Yes | 280 | 117 | |
| Familial melanoma (first-degree), *n* | | | |
| No | 564 | 163 | < 0.001 |
| Yes | 4 | 23 | |

[a]Results of univariate analysis of the differences in baseline characteristics between cases and controls.

prevalence was lower for the cases compared with the controls, resulting in ORs lower than 1 (**Table III**). However, only for personal atopy was this negative relation also significant (OR 0.53; 95% CI 0.30–0.96; *p*-value 0.04).

In the univariate analysis of the major confounders for melanoma risk, high naevus count was found to be the most important. Therefore, a sub-analysis in the group with no/few moles was conducted. This subgroup analysis on 79 pairs confirmed a relevant difference between cases and controls in personal atopy (29% vs. 13%, $p=0.03$) and respiratory atopy (27% vs. 13%, $p=0.06$) (detailed data not shown).

Cox analysis within the group of melanoma cases did not reveal a significant association between all atopy-related variables and PFS. The bivariable analysis, whereby a correction for staging or for age was conducted, did not alter the conclusions (**Table IV**). Also, for OS and melanoma-related death, no evidence was found for an association between atopy variables and outcome (data not shown).

**Table III. Association of atopy-related variables and melanoma development**

| | Controls *n* (%) | Cases *n* (%) | $p^a$ | OR[b] (95% CI) | $p^b$ |
|---|---|---|---|---|---|
| Atopic dermatitis | 11 (9.5) | 5 (4.3) | 0.21 | | |
| Yes | | | | 0.46 (0.16; 1.31) | 0.14 |
| No | | | | Ref. | |
| Personal atopy | 35 (30.2) | 20 (17.2) | 0.04 | | |
| Yes | | | | 0.53 (0.30; 0.96) | 0.04 |
| No | | | | Ref. | |
| Respiratory atopy | 32 (27.6) | 19 (16.4) | 0.07 | | |
| Yes | | | | 0.55 (0.30; 1.02) | 0.06 |
| No | | | | Ref. | |
| Active atopy | 5 (4.3) | 2 (1.7) | 0.45 | | |
| Yes | | | | 0.40 (0.08; 2.06) | 0.27 |
| No | | | | Ref. | |
| Familial atopy | 58 (50.0) | 52 (44.8) | 0.52 | | |
| Yes | | | | 0.82 (0.49; 1.36) | 0.44 |
| No | | | | Ref. | |

[a]McNemar's test results. [b]Results of the conditional logistic regression models. Odds ratio (OR) refers to the odds for being a case. CI: confidence interval.

## DISCUSSION

In this clinically well characterized case-control population, we found a significant negative association between personal atopy and melanoma development, while no significant associations were found between atopy and melanoma outcome.

A strength of this paper is the investigation of the relationship between atopy and melanoma development in a clinically well-characterized case-control population. A huge effort had been made to minimize selection bias of controls by choosing healthy, unrelated controls. Another strength of this paper is the use of an extensive questionnaire with which all major melanoma risk factors were meticulously registered, both in the melanoma population and control population. The study by Hajdarbegovic et al. (14) was the only previous study on melanoma and atopy that took account of phototype as confounder. Although phototype affects melanoma

**Table IV. Results of Cox regression analyses for the association between atopy-related variables and progression-free survival**[a]

| | Subjects (events) *n* (*n*) | Univariable results HR (95% CI) | *p*-value | Bivariable results corrected for staging HR (95% CI) | *p*-value corrected for staging | Bivariable results corrected for age HR (95% CI) | *p*-value corrected for age |
|---|---|---|---|---|---|---|---|
| Atopic dermatitis | 166 (28) | 1.49 (0.35; 6.30) | 0.61 | 3.02 (0.69; 13.34) | 0.20 | 2.01 (0.46; 8.80) | 0.39 |
| Personal atopy | 170 (29) | 1.02 (0.41; 2.50) | 0.97 | 1.05 (0.41; 2.69) | 0.91 | 1.28 (0.51; 3.23) | 0.61 |
| Respiratory atopy | 173 (30) | 1.09 (0.45; 2.68) | 0.84 | 1.10 (0.43; 2.80) | 0.84 | 1.37 (0.55; 3.41) | 0.52 |
| Active atopy | 173 (30) | 0.00 (0.00; ND) | 0.11 | 0.00 (0.00; ND) | 0.21 | 0.00 (0.00; ND) | 0.17 |
| Familial atopy | 173 (30) | 0.00 (0.00; ND) | 0.11 | 0.00 (0.00; ND) | 0.21 | 0.61 (0.28; 1.37) | 0.22 |

[a]Results of univariable and bivariable Cox regressions analyses, performed on the set of 173 melanoma cases with a median follow-up of 7 years. In the bivariable m odel, staging or age was added as a confounder. Since Wald tests are not valid in case there are no events for a specific level of the predictor, all reported *p*-values are obtained with likelihood-ratio tests (with 1 and 3 degrees of freedom for the effects of atopy and staging, respectively).
HR: Hazard ratio; ND: not defined; CI: confidence interval.

risk, it is not the only confounder, as demonstrated in this study.

When matched for important melanoma confounders (sunburn sensitivity, hair colour, number of moles, sunburn as juvenile, ever sunbed use, familial melanoma), age and sex, negative associations with melanoma development were observed for all 5 variables referring to atopy. This observed inverse association between atopy and melanoma is in line with previous literature which also found a lower risk of melanoma in atopics (4, 9, 10, 12, 17). In our study the correlation was only significant for personal atopy and we have to acknowledge that a strong claim about this correlation is not possible in the absence of a correction for multiple testing. Note that the power to detect differences between cases and controls depends on the prevalence, which differs strongly between the atopy-related variables. For example, in the matched analysis less than 5% of the controls have active atopy. To detect a significant reduction among the cases for this variable, a much larger study is required. Larger studies would help to further determine the nature of the link between melanoma and atopy. Another possible limitation is response bias. Although the response rate in the case group is high, that of the controls is not. It is probable that those who were contacted and had AD are more prone to cooperate if they think that there could be some personal benefit to be gained. It is also possible that recall bias might play a role in both groups. Recall bias might be present, since atopy tends to be more prominent at a young age. However, the case-control setting and random selection of controls should attenuate this bias. Also, the use of a validated questionnaire for AD diagnosis, whereby a combination of factors are taken into account before a positive diagnosis is made, might also reduce recall bias. The association between AD and melanoma OS, melanoma-related death, and recurrence-free survival were investigated, but this yielded no significant associations. It could be that the higher immunosurveillance associated with atopy may protect against development of melanoma, but is not enough to protect against progression. In addition, lack of any association should be regarded with caution, since there were relatively few events in our study population.

In summary, this study suggests an inverse correlation between personal atopy and melanoma development when matched for important confounders. In addition, no evidence has been found for an association between atopy and melanoma survival or progression.

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## REFERENCES

1. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 2012; 23: 524–530.
2. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989–2005. J Invest Dermatol 2010; 130: 1807–1812.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 27: 2893–2917.
4. Synnerstad I, Fredrikson M, Ternesten-Bratel A, Rosdahl I. Low risk of melanoma in patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2008; 22: 1423–1428.
5. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res 1970; 13: 1–27.
6. Strauss DC, Thomas JM. Transmission of donor melanoma by organ transplantation. Lancet Oncol 2010; 11: 790–796.
7. Synnerstad I, Nilsson L, Fredrikson M, Rosdahl I. Fewer melanocytic nevi found in children with active atopic dermatitis than in children without dermatitis. Arch Dermatol 2004; 140: 1471–1475.
8. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009; 30: 1073–1081.
9. Hagstromer L, Ye W, Nyren O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. Arch Dermatol 2005; 141: 1123–1127.
10. Olesen AB, Engholm G, Storm HH, Thestrup-Pedersen K. The risk of cancer among patients previously hospitalized for atopic dermatitis. J Invest Dermatol 2005; 125: 445–449.
11. Arana A, Wentworth CE, Fernandez-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the UK. Br J Dermatol 2010; 163: 1036–1043.
12. Kolmel KF, Compagnone D. Melanoma and atopy. Dtsch Med Wochenschr 1988; 113: 169–171.
13. Beral V, Evans S, Shaw H, Milton G. Cutaneous factors related to the risk of malignant melanoma. Br J Dermatol 1983; 109: 165–172.
14. Hajdarbegovic E, Atiq N, van der Leest R, Thio B, Nijsten T. Atopic dermatitis is not a protective factor for melanoma but asthma may be. Int J Clin Oncol 2014; 19: 708–711.
15. Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med 2005; 352: 2314–2324.
16. Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. UK Diagnostic Criteria for Atopic Dermatitis Working Party. Br J Dermatol 1996; 135: 12–17.
17. Skaaby T, Husemoen LL, Roswall N, Thuesen BH, Linneberg A. Atopy and development of cancer: a population-based prospective study. JACI: In Practice 2014; 2: 779–785.