



Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: [www.jdsjournal.com](http://www.jdsjournal.com)



## Atopic dermatitis, naevi count and skin cancer risk: A meta-analysis

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### ARTICLE INFO

#### Article history:

Received 8 June 2016

Received in revised form 12 July 2016

Accepted 15 July 2016

#### Keywords:

Atopic dermatitis

Naevi count

Cutaneous melanoma

Keratinocyte skin cancer

Meta-analysis

### ABSTRACT

**Background:** The risk of skin malignancy among atopic dermatitis (AD) patients is not well established. **Objective:** We reviewed the epidemiological evidence on the association between AD, naevi count, and the risk of cutaneous melanoma and keratinocyte skin cancer (KSC).

**Methods:** We included all studies that compared the naevi count and the risk of skin cancer (melanoma and/or KSC) between AD patients and unaffected individuals. We calculated summary relative risks (SRRs) and 95% confidence intervals (CI) through random effects models; explored correlates of between-studies heterogeneity using sub-group and sensitivity analysis; and assessed publication bias using a funnel-plot-based approach.

**Results:** The number of common naevi larger  $\geq 2$  mm on the whole body was consistently lower among AD patients vs. unaffected individuals when measured by trained health professionals. The risk of melanoma was not increased among AD patients (SRR = 0.77, 95%CI 0.44–1.35,  $I^2 = 85\%$ ). We found a significantly increased risk of basal cell cancer (BCC) (SRR = 1.34, 95%CI 1.03–1.75,  $I^2 = 24.0\%$ ) but not for squamous cell cancer (SRR = 1.91, 95% CI 0.74–4.91,  $I^2 = 0.0\%$ ); however, only a few papers adjusted for phenotypic characteristics and/or sunlight exposure. We found no evidence of publication bias.

**Conclusions:** AD patients may be at increased BCC risk; however, methodological limitations prevented from drawing definitive conclusions. Despite the lack of strong scientific evidence, AD patients should avoid excessive sun exposure, regularly perform skin self examination, and consult a doctor in case of a suspicious skin lesion.

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### 1. Introduction

Atopic dermatitis (AD) (also known as atopic eczema) is a type of chronic relapsing inflammation of the skin characterized by severe itching, rash and frequent secondary bacterial infections (most notably *Staphylococcus aureus*) induced by the scratching of the eczematous lesions [1]. Prevalence of atopic dermatitis appears to have stabilized after decades of steady increase in wealthier

nations (where it may affect as high as 20% of children and 3% of adults), but is still increasing in several low-income countries [2,3]. Because of its elevated prevalence, severely negative impact on patients' well-being and quality of life, and chronic course with relapses and remissions, atopic dermatitis has substantial social burden and associated healthcare costs [4–6]. In particular, patients with moderate-to-severe AD may require systemic immunomodulating treatments to adequately control symptoms [7].

Atopic dermatitis has a complex pathogenesis [8]. Genetic defects and environmental factors (including detergents, water hardness and pH, personal care products, traffic-related air pollutants, and others) may lead to a disturbance of the epithelial barrier and predispose to the sensitization to a number of allergens, including house dust mites, pollen and food allergens, which is the proximate cause of atopic dermatitis flares [9,10]. The Th2-polarization of newborns and infants' immune system (favoured by a reduced microbial exposure in early life because

**Abbreviations:** AD, atopic dermatitis; CI, confidence intervals; ICD, international classification of diseases; KSC, keratinocyte skin cancer; RR, relative risk; SRR, summary relative risk; UVB, ultraviolet B.

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<http://dx.doi.org/10.1016/j.jdermsci.2016.07.009>

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of excessive household hygiene, small family size, lack of pets at home, and postnatal antibiotic exposure) favours the sensitization to allergens and facilitates the onset of atopic dermatitis as well as allergic rhinitis and asthma (the so-called “atopic triad”) [9–11]. An important role of leukocytes, natural killer cells and platelets in the pathogenesis of atopic dermatitis has been hypothesized as well [12,13].

The initial observation of an inverse association between AD and body naevi count in paediatric populations [14] gave rise to the hypothesis that the risk of melanoma may be reduced among AD patients. The topic is of considerable importance since a better understanding of the role of the immune system in melanoma development might help develop more effective therapies for advanced melanoma [15]. This hypothesis was tested in several studies over the years, with conflicting results [16–18]. Likewise, the several studies investigating the relationship between atopic dermatitis and keratinocyte skin cancer (KSC) risk provided inconsistent results [16,17,19]. To help clarify this issue, we conducted a review of the literature and meta-analysis of all published papers focusing on the association between atopic dermatitis, body naevi count, and the risk of cutaneous melanoma and keratinocyte skin cancer.

## 2. Materials and methods

### 2.1. Data sources and search strategy

We planned, conducted, and reported this systematic literature search and review following MOOSE guidelines regarding meta-analysis of observational studies [20]. We reviewed published reports using validated search strategies [21,22] from the following database: PubMed, Ovid MEDLINE, Google Scholar, and the ISI Web of Science/Science Citation Index Expanded. The literature search was conducted (and lastly updated on April 30th, 2016) by using a combination of a MESH term denoting the exposure (atopic dermatitis or eczema) and a MESH term denoting an outcome of interest (melanoma, skin cancer, or naevi/moles), i.e. by typing the following search string: (“atopic dermatitis” OR “atopic eczema” OR “eczema”) AND (“melanoma” OR “skin cancer” OR “naevi” OR “nevi” OR “moles”). Two authors (SC and SG) first screened titles and abstracts; those considered as potentially eligible for inclusion were obtained and read in full-text. Additional studies were collected by perusing the reference lists of the retrieved articles, including previously published reviews and meta-analyses.

### 2.2. Inclusion criteria and data extraction

Studies focusing on atopic dermatitis and naevi count should report the mean (or median) naevi count (either total body or on the arm) among AD patients and healthy controls, along with the result (exact p-value) of a statistical test for the comparison of means (or medians). Studies on the association between atopic dermatitis and skin cancer risk (melanoma and/or KSC) were included if they provided the minimum information necessary to obtain a relative risk (RR) estimate (i.e. odds ratio, incidence rate ratio, or hazard ratio) and a measure of statistical uncertainty (i.e. 95% confidence intervals [95%CI], standard errors, variance, confidence intervals or exact P-value of the significance of the estimates). We only included independent studies in order to avoid giving double weight to a single study; in case of multiple reports of the same study, we considered the estimates from the most recent publication. Only human studies were considered as potentially eligible for inclusion; no language or time restrictions were applied.

The following information from each included paper was also extracted and coded: authors, year of publication, study period,

type of study design, country of the study, number and sources of cases and controls, main characteristics of study populations (including age and gender distribution), use of matching in study design, definition of exposure (including the International Classification of Diseases [ICD] code when available) and adjustments used for statistical analyses. Data were extracted and cross-checked independently by two investigators (SG and SC); any disagreement was resolved by consensus.

### 2.3. Statistical analysis

Studies on the relationship between atopic dermatitis and naevi count were reviewed narratively. For studies on the relationship between AD and skin cancer risk, all measures of relative risk and the corresponding measure of statistical uncertainty, adjusted for the maximum number of confounding variables available, were translated into log relative risk, and corresponding variance, with the formula proposed by Greenland [23].

We fitted random effects models and obtained summary relative risks (SRR) from likelihood estimates using the PROC MIXED procedure of SAS software version 8.02 (SAS Institute Inc, Cary, NC, USA) [20]. Homogeneity of effects across studies was assessed using the Chi-square statistic and quantified by  $I^2$ , which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance [24,25]. Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the  $p=0.10$  level of association. Between-study heterogeneity was investigated by sub-group analyses and meta-regressions. We performed a sensitivity analysis to evaluate whether results were influenced by a single study. A funnel-plot-based approach was used for assessing publication bias by evaluating regression of  $\ln(RR)$  on the sample size, weighted by the inverse of the variance [26].

## 3. Results

The literature search produced 77 potentially relevant papers (Fig. 1). After applying inclusion and exclusion criteria, eighteen papers were included in the meta-analysis.

### 3.1. Atopic dermatitis and total body nevus count

Five papers reported on the association between atopic dermatitis and naevi count (Table 1) [14,27,28,29,30].

In three studies, the diagnosis of AD was made by a health professional at the moment of naevi count. The number of common naevi larger  $\geq 2$  mm on the whole body was found to be significantly lower among those suffering from AD, both among children (two studies, 1064 participants overall, median age 7 or 9 years [26,28]) and among adults (430 participants, median age 41 years [14]).

In two other studies that surveyed paediatric populations 1925 children aged 6 years in Uter et al. [27], 269 children aged 3 years in Dellavalle et al. [30], the diagnosis of AD ever since birth was reported by participants' parents. In the former study, no significant difference was found in the number of common naevi larger  $\geq 2$  mm among AD vs. non-AD children. In the latter study, the number of common naevi of any size on the whole body was found to be significantly higher among AD vs. non-AD children.

### 3.2. Atopic dermatitis and cutaneous melanoma risk

We reported in Table 2 the main features of the eight independent studies that investigated the association between AD and melanoma risk.

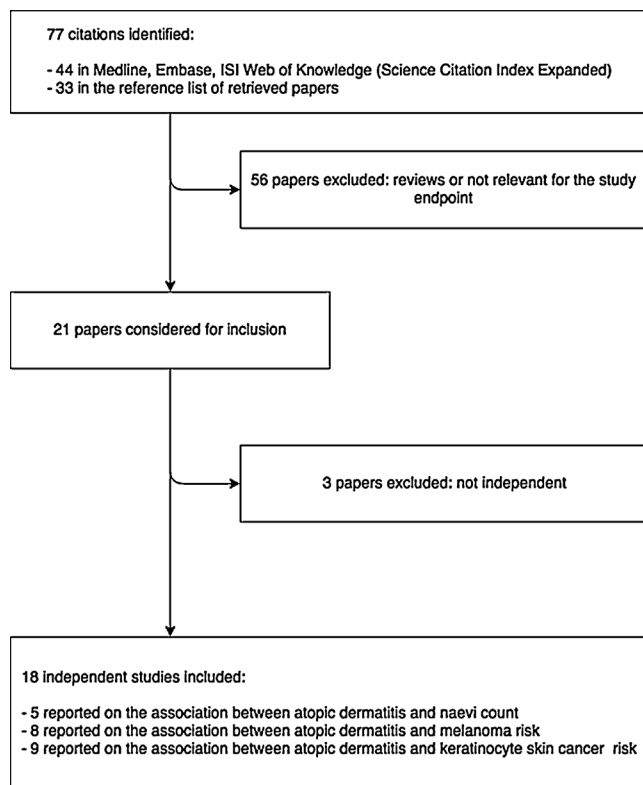


**Fig. 1.** Flow-chart of the selection process for the studies included in the meta-analysis of the association between atopic dermatitis and naevi count and risk of melanoma and keratinocyte skin cancer.

In four of these studies, large cohorts of AD patients (cohort size ranging between 15,666 and 66,258) were assembled and followed-up for a median of 5.3–15.4 years, and their age-, gender and calendar time-specific melanoma incidence was compared with that of the general population [16,17,31,32]. In all these studies, a diagnosis of AD (ICD-9 code 691) made by a physician during a hospitalization or an outpatient clinic visit was a criterion

for inclusion in the cohort, and no adjustment was made by phenotypic characteristics or patterns of exposure to UVR. The median age at recruitment ranged between six [17] and twenty-six years [16]. The remaining four studies had a case-control design, with melanoma cases diagnosed at a median age of 49–57 years and the exposure defined as a self-reported history of AD (past medical diagnosis [33,34] or symptoms consistent with AD [35]; no details were given in the study by Bhattacharya et al. [18]). None of the case-control studies provided estimates adjusted by phenotypic characteristics; an adjustment by exposure to sunlight (namely, sports and/or outdoor activities) was only made in the paper by El-Zein et al.

The four cohort studies contributed 60 melanoma cases developed among 147,517 AD patients, while the four case-control studies enrolled over 600 melanoma cases. The SRR was 0.77 (95% CI 0.44–1.35, Fig. 2), with high between-studies heterogeneity ( $I^2=85\%$ ) and no evidence of publication bias. We investigated between-study heterogeneity and the influence of possible sources of bias by meta-regression and subgroup analysis, which did not reveal any factor significantly related with variability of risk estimates; in sensitivity analysis, the exclusion of no single paper led to a substantial reduction of the between-studies heterogeneity. There was no evidence of publication bias affecting the results.

### 3.3. Atopic dermatitis and keratinocyte skin cancer risk

The four cohort studies mentioned in the previous section also investigated whether the risk of KSC among AD patients deviated from that in the general population (Table 3) [16,17,31,32]. Four case-control studies reported on the association between AD and KSC risk: Cheng et al. included 375 early-onset BCC and 254 SCC and provided estimates adjusted by skin reaction to sunlight and (for SCC only) by the number of lifetime painful sunburns [36]; Ming et al. included 1533 KSCs but failed to adjust by both phenotypic characteristics and patterns of sun exposure [19]; Milán et al. enrolled 333 twin pairs discordant for BCC (of which 149 male and 184 female pairs), with no adjustment by patterns of sun exposure [37]; and Hajdarbegovic et al. [38] reported separate age- and gender-adjusted estimates for the association between a AD and the risk of BCC and SCC (based on 352 and 78 cases,

**Table 1**

Main features and results of studies that examined the association between atopic dermatitis and naevi count.

| First author, year | Country | Study type                                                                              | Sample size | % males | Median age | Naevi count                           | Atopic dermatitis diagnosis                                                                 | % with atopic dermatitis | Results                                                                                                                            |
|--------------------|---------|-----------------------------------------------------------------------------------------|-------------|---------|------------|---------------------------------------|---------------------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Kallas, 2006       | Estonia | Cross-sectional study                                                                   | 549         | 51      | 9          | Common naevi, $\geq 2$ mm, body count | At naevi count, diagnosed by a health professional                                          | 5.6%                     | Median count lower among AD (20) vs. non-AD (27) ( $p < 0.05$ )                                                                    |
| Synnerstad, 2004   | Sweden  | Cross-sectional study                                                                   | 515         | 53      | 7          | Common naevi, $\geq 2$ mm, body count | At naevi count, diagnosed by a health professional<br>Ever since birth, reported by parents | 21.4%<br>24.1%           | Median count lower among AD (4) vs. non-AD (9) ( $p < 0.01$ )<br>Median count lower among AD (6) vs. non-AD (9) ( $p < 0.05$ )     |
| Uter, 2005         | Germany | Cross-sectional study                                                                   | 1925        | NA      | 6          | Common naevi, $\geq 2$ mm, body count | Ever since birth, reported by parents                                                       | 11.4%                    | No significant difference                                                                                                          |
| Dellavalle, 2004   | USA     | Case-control study nested within a trial of additional sun protection vs. standard care | 269         | NA      | 3          | Common naevi, any size, body count    | Ever since birth, reported by parents                                                       | 16.4%                    | Median count higher among AD (7.5) vs. non-AD (5) ( $p < 0.01$ )                                                                   |
| Broberg, 2000      | Sweden  | Cross-sectional study                                                                   | 430         | 53      | 41         | Common naevi, $\geq 2$ mm, body count | At naevi count, diagnosed by a health professional                                          | 11.9%                    | Median count lower among AD (5) vs. non-AD (53) ( $p < 0.0001$ )<br>Mean count lower among AD (9) vs. non-AD (67) ( $p < 0.0001$ ) |

NA: not available.

**Table 2**  
Main features and results of studies that examined the association between atopic dermatitis and melanoma risk.

| First author, year  | Country     | Study design          | No. melanoma | Cohort size/no. controls | Median age <sup>a</sup> | RR   | 95% CI    | Adjusting variables |        |                        |                           |
|---------------------|-------------|-----------------------|--------------|--------------------------|-------------------------|------|-----------|---------------------|--------|------------------------|---------------------------|
|                     |             |                       |              |                          |                         |      |           | Age                 | Gender | Phenotype <sup>b</sup> | Sun exposure <sup>c</sup> |
| Hagströmer, 2005    | Sweden      | Cohort of AD patients | 10           | 15,666                   | 16                      | 0.6  | 0.3–1.2   | ✓                   | ✓      |                        |                           |
| Arana, 2010         | UK          | Cohort of AD patients | 36           | 66,258                   | 26                      | 1.74 | 1.25–1.41 | ✓                   | ✓      |                        |                           |
| Hwang, 2012         | Taiwan      | Cohort of AD patients | 2            | 34,263                   | 24                      | 2.35 | 0.26–8.47 | ✓                   | ✓      |                        |                           |
| Jensen, 2012        | Denmark     | Cohort of AD patients | 12           | 31,330                   | 6                       | 0.59 | 0.30–1.02 | ✓                   | ✓      |                        |                           |
| El-Zein, 2010       | Canada      | Case-control study    | 94           | 512                      | 53                      | 0.64 | 0.20–2.20 | ✓                   | ✓      |                        | ✓                         |
| Kölmel, 1988        | Germany     | Case-control study    | 331          | 380                      | 49                      | 0.24 | 0.04–0.87 |                     |        |                        |                           |
| Hajdarbegovic, 2014 | Netherlands | Case-control study    | 184          | 169                      | 57                      | 1.05 | 0.50–2.23 |                     |        |                        |                           |
| Bhattacharya, 2016  | US          | Case-control study    | unknown      | unknown                  | 61                      | 0.35 | 0.16–0.73 | ✓                   |        |                        |                           |

AD: atopic dermatitis.

RR: relative risk. CI: confidence intervals.

<sup>a</sup> Median age at recruitment for cohort study, and median age at melanoma diagnosis for case-control studies.

<sup>b</sup> Any of skin colour, hair colour, eye colour, naevi count or phototype.

<sup>c</sup> Any of intermittent or chronic exposure to sunlight, history of sunburns, and outdoor activities.

respectively). Finally, Dyer et al. investigated the association between self-reported history of AD and the risk of developing a BCC on the face and ears among patients previously diagnosed with at least two KSCs; reported estimates were adjusted by sun sensitivity and occupational sun exposure [39].

Overall, 270 KSC cases were diagnosed in the four cohorts of AD patients; 2925 KSC cases were included in the three case-control

studies; and 498 s- or higher-order BCC cases were diagnosed among the 1131 KSC patients enrolled in the study by Dyer et al. The SRR for the risk of KSC among AD patients was 1.25 (95%CI 0.94–1.58,  $I^2 = 85\%$ , Fig. 2) with no evidence of publication bias. In subgroup analysis, the SRR was 1.34 (95%CI 1.03–1.75,  $I^2 = 24\%$ ) for BCC, and 1.91 (95%CI 0.74–4.91,  $I^2 = 0\%$ ) for SCC (Fig. 2). The exclusion of the study by Dyer et al. [39] (which differed from the

### Cutaneous melanoma

Kölmel, 1988  
Hagströmer, 2005  
Arana, 2010  
El-Zein, 2010  
Hwang, 2012  
Jensen, 2012  
Hajdarbegovic, 2014  
Bhattacharya, 2016  
Summary risk estimate=0.77 (95%CI: 0.44, 1.35)

### Keratinocyte skin cancer

Ming, 2004  
Hagströmer, 2005  
Arana, 2010  
Hwang, 2012  
Summary risk estimate=1.25 (95%CI: 0.94, 1.58)

### Basal cell carcinoma

Milán, 2003, Men  
Milán, 2003, Women  
Dyer, 2012  
Jensen, 2012  
Cheng, 2015  
Hajdarbegovic, 2016  
Summary risk estimate=1.34 (95%CI: 1.03, 1.75)

### Squamous cell carcinoma

Jensen, 2012  
Cheng, 2015  
Hajdarbegovic, 2016  
Summary risk estimate=1.91 (95%CI: 0.74, 4.91)

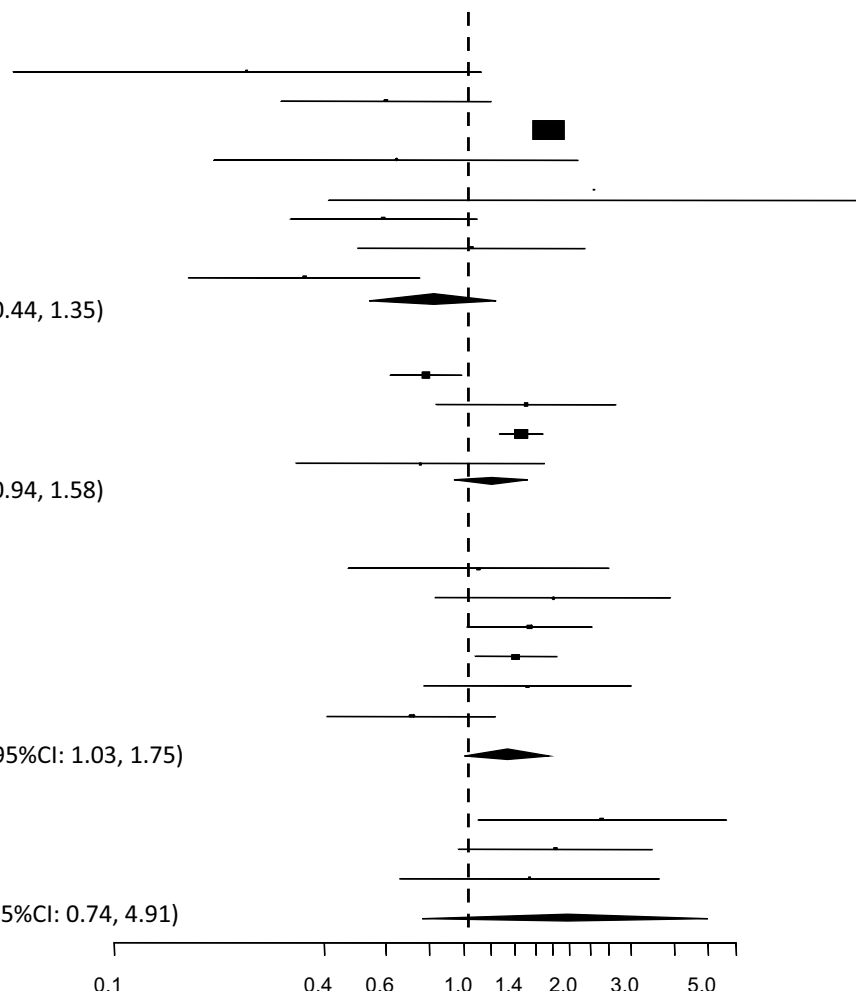


**Fig. 2.** Forest plot for the association between atopic dermatitis and the risk of melanoma and keratinocyte skin cancer.

**Table 3**

Main features and results of studies that examined the association between atopic dermatitis and keratinocyte skin cancer risk.

| First author, year  | Country     | Study design                        | Skin cancer type | No. KSC cases | Cohort size/no. controls | Median age <sup>a</sup> | RR   | 95% CI    | Adjusting variables |        |                        |                           |
|---------------------|-------------|-------------------------------------|------------------|---------------|--------------------------|-------------------------|------|-----------|---------------------|--------|------------------------|---------------------------|
|                     |             |                                     |                  |               |                          |                         |      |           | Age                 | Gender | Phenotype <sup>b</sup> | Sun exposure <sup>c</sup> |
| Hagströmer, 2005    | Sweden      | Cohort of AD patients               | KSC              | 12            | 15,666                   | 16                      | 1.5  | 0.8–2.6   | ✓                   | ✓      |                        |                           |
| Arana, 2010         | UK          | Cohort of AD patients               | KSC              | 187           | 66,258                   | 26                      | 1.46 | 1.27–1.69 | ✓                   | ✓      |                        |                           |
| Hwang, 2012         | Taiwan      | Cohort of AD patients               | KSC              | 7             | 34,263                   | 24                      | 0.75 | 0.30–1.54 | ✓                   | ✓      |                        |                           |
| Jensen, 2012        | Denmark     | Cohort of AD patients               | BCC              | 57            | 31,330                   | 6                       | 1.41 | 1.07–1.83 | ✓                   | ✓      |                        |                           |
|                     |             |                                     | SCC              | 7             |                          |                         | 2.48 | 1.00–5.11 |                     |        |                        |                           |
| Dyer, 2012          | USA         | Cohort of BCC patients <sup>d</sup> | BCC              | 498           | 1131                     | 72                      | 1.54 | 1.03–2.32 | ✓                   |        | ✓                      | ✓                         |
| Milán, 2003         | Finland     | Case-control study <sup>e</sup>     | BCC              | 149           | 149                      | 61                      | 1.10 | 0.47–2.59 | ✓                   | ✓      | ✓                      |                           |
|                     |             |                                     |                  | 184           | 184                      |                         | 1.80 | 0.83–3.90 | ✓                   | ✓      | ✓                      |                           |
| Ming, 2004          | USA         | Case-control study                  | KSC              | 1533          | 1378                     | 66                      | 0.78 | 0.61–0.98 | ✓                   | ✓      |                        |                           |
| Cheng, 2015         | USA         | Case-control study                  | BCC              | 375           | 251                      | 40                      | 1.52 | 0.77–3.01 | ✓                   | ✓      | ✓                      |                           |
|                     |             |                                     | SCC              | 254           | 432                      | 61                      | 1.83 | 0.97–3.45 | ✓                   | ✓      | ✓                      | ✓                         |
| Hajdarbegovic, 2016 | Netherlands | Case-control study                  | BCC              | 352           | 4023                     | 68                      | 0.71 | 0.41–1.24 | ✓                   | ✓      |                        |                           |
|                     |             |                                     | SCC              | 78            | 4297                     | 68                      | 1.54 | 0.66–3.62 | ✓                   | ✓      |                        | ✓                         |

AD: atopic dermatitis. KSC: keratinocyte skin cancer. BCC: basal cell cancer. SCC: squamous cell cancer.

RR: relative risk. CI: confidence intervals.

<sup>a</sup> Median age at recruitment for cohort study, and median age at melanoma diagnosis for case-control studies.<sup>b</sup> Any of skin colour, hair colour, eye colour, naevi count or phototype.<sup>c</sup> Any of intermittent or chronic exposure to sunlight, history of sunburns, and outdoor activities.<sup>d</sup> The reported RR is for the chance of being diagnosed with a second BCC among patients with a first BCC.<sup>e</sup> This is a case-control study of twin pairs discordant for BCC. RRs were separately reported for males and females patients.

others in providing an estimate for the risk of a second- or higher-order BCC among KSC patients) only marginally affected the overall SRR (1.22, 95%CI 0.95–1.69,  $I^2 = 65\%$ ). Finally, the sensitivity analysis revealed that nearly all of the between-studies heterogeneity was due to the study by Ming et al. [19], whose exclusion led to a significantly increased risk of KSC among AD patients (SRR 1.43, 95%CI 1.25–1.62) with low between-study heterogeneity ( $I^2 = 7\%$ ).

#### 4. Discussion

We reviewed the epidemiological evidence on the association between atopic dermatitis and either body naevi count or skin cancer risk (melanoma and KSC). We found fairly convincing evidence in favour of the hypothesis that AD patients have a lower naevi count compared to unaffected subjects. The only study showing a result in the opposite direction [30] was poorly comparable with the others as it considered naevi of any size instead of those larger than  $\geq 2$  mm; furthermore, the diagnosis of AD was reported by children's parents instead of being made by a health professional. A reduced early-life exposure to sunlight is a possible explanation for the observed association, as it is causally linked to both atopic dermatitis [40,41] and a lower naevi count among children [42,43]. The ultraviolet B (UVB) radiation-induced modulation of Th1 and Th2 immune response has been proposed to explain the former relationship [44,45] while mutations at the BRAF gene are thought to mediate the association between early-life exposure to UVB radiation and the number of acquired melanocytic nevi in childhood [46]. In addition, cytokines released in the skin of AD patients (like interleukin-1 $\alpha$ , interleukin-6 and tumour necrosis factor- $\alpha$ ) may have paracrine effects on nearby cells and inhibit melanocyte proliferation and nevus formation [47,48].

Epidemiological data on the relationship between AD and melanoma risk are rather conflicting. Most likely, the main reason for this is the heterogeneity across published papers in terms of study design and study subjects. Studies assembling a cohort of AD patients from hospital discharge records and following them up by linking with cancer and mortality registries are immune from recall bias and may estimate the latency between AD diagnosis and skin cancer occurrence, but fail in adjusting for potential confounders like phenotypic factors and patterns of exposure to

UVB, as this information is usually not available in the registries upon which these studies are based. On the other side, case-control studies have the potential to make these adjustments (although most of those published so far did not, see Table 2), but are prone to exposure misclassification (including recall bias) as the diagnosis of atopic dermatitis may be quite distant in time and is usually self-reported. An additional source of inconsistency across studies can be found in the difference in median age of subjects that were included (Table 2). These multiple sources of bias make it difficult to draw firm conclusions on the association between atopic dermatitis and melanoma risk.

Most studies agree in showing that the KSC risk is increased among AD patients, although only a few papers presented risk estimates that were adjusted for phenotypic characteristics and/or exposure to sunlight. Atopic dermatitis is highly associated with an inherited defect of filaggrin, a key protein in the formation and functioning of the skin barrier [49]. This genetic defect is more frequent among fair skinned people of Northern European ancestry, who are the most at risk population for both AD and skin cancer. The loss of filaggrin function results in downstream depletion of urocanic acid, which is the most important filter of ultraviolet light in the upper epidermis. The penetration of a higher proportion of incident ultraviolet radiation (also favoured by a thinner-than-normal corneum layer among AD patients [50]) might explain the observed increased KSC risk among AD patients. However, filaggrin loss-of-function mutations have been reported to be associated with both an increase and a decrease in KSC incidence by different authors [51,52]; in addition, it remains unclear why the risk of melanoma is not increased as well among these patients. In contrast to the other studies, Ming et al. found a reduced risk of KSC among AD patients [19]. Reasons for this discrepancy may be the reliance on KSC self-reporting as a possible inclusion criterion for cases; the use of patients with benign dermatological conditions (like warts, seborrheic keratosis, acne rosacea, and others, some of which are associated with sun exposure [53,54]) among controls; the assessment of AD symptoms via mail survey; and the lack of adjustment for phenotypic characteristics and exposure to sunlight. By excluding this study, the evidence in favour of an association between atopic dermatitis and KSC risk became convincing, also given the low between-estimates heterogeneity and the lack of publication bias.

Phenotype and exposure to UVB radiation are the major risk factors for both melanoma and KSC; therefore the failure to adjust for them is a severe limitation of any study aiming to investigate the aetiology of skin cancer. This limitation is even more serious here, since exposure to sunlight can alleviate the symptoms of atopic dermatitis [55–57], and it might be hypothesized that subjects with AD expose themselves to sunlight more than healthy people, although this has never been investigated in a dedicated survey as far as we know. A further limitation is the frequent lack of information about topical and/or systemic treatments administered prior to recruitment (including drug type, dosage and duration of use, and incidence of adverse events during phototherapy). Most systemic immunomodulatory agents used in the treatment of AD (including cyclosporine A, methotrexate, mycophenolate, and others [7]) may have a potential carcinogenic effect. Paradoxically, the calcineurin inhibitors tacrolimus and pimecrolimus (approved for treatment of AD in 2000–2001 [58] and considered as carcinogenic by the US Food and Drug Administration [59]) appear to reduce the risk of melanoma [60] and KSC [61,62] compared to untreated AD patients. Finally, subjects with AD may be more likely to undergo skin examination and receive a diagnosis of skin cancer: the resulting surveillance bias would attenuate or reverse an inverse association or inflate a positive one.

In conclusion, the unsatisfactory internal validity and non-comparability of studies published so far prevent from giving a clear-cut answer to the question of whether subjects with AD are at increased or reduced risk of skin cancer compared to the general population. One could advance the hypothesis that the risk of skin cancer is indeed reduced among AD subjects during childhood and youth, as a consequence of their relatively low exposure to sunlight in the early years or life, but that this inverse association would disappear or even turn into a positive one during subsequent years, due to their propensity to expose themselves to sunlight to mitigate their symptoms. It should be emphasized, however, that the former is presented here purely as a working hypothesis to be tested in a suitably designed epidemiological study, and not as a conclusion based on the studies published so far. Despite the lack of strong scientific evidence, we recommend that subjects receiving a diagnosis of atopic dermatitis (or their parents, in case of children) are given advice by dermatologists and paediatricians to avoid an excessive exposure to sunlight, and instructed on the importance to check their skin regularly and consult a doctor in case of a suspicious lesion, whether pigmented or not.

#### Authors' contributions

SC and SG conceived the study, conducted the literature search and extracted the data. SG performed the statistical analyses. SC drafted the first version of the manuscript. All the authors participated to the writing of the manuscript and critically reviewed and approved its final version.

#### Source of funding

None.

#### Competing interests

All authors declare they have no conflicts of interest to disclose.

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