

Atopic dermatitis is not associated with actinic keratosis: cross-sectional results from the Rotterdam study

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Summary

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Accepted for publication

14 January 2016

Funding sources

The Rotterdam study is supported by the Erasmus MC University Medical Centre and Erasmus University Rotterdam; the Dutch Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the municipality of Rotterdam. None played a role in design, analysis or reporting of this study.

Conflicts of interest

None declared.

E.H. and H.B. contributed equally to this manuscript.

DOI 10.1111/bjd.14423

Background Epidermal barrier impairment and an altered immune system in atopic dermatitis (AD) may predispose to ultraviolet-induced DNA damage.

Objectives To study the association between AD and actinic keratosis (AK) in a population-based cross-sectional study.

Methods AD was defined by modified criteria of the U.K. working party's diagnostic criteria. AKs were diagnosed by physicians during a full-body skin examination, and keratinocyte cancers were identified via linkage to the national pathology database. The results were analysed in adjusted multivariable and multinomial models.

Results A lower proportion of subjects with AD had AKs than those without AD: 16% vs. 24%, $P = 0.002$; unadjusted odds ratio (OR) 0.60, 95% confidence interval (CI) 0.42–0.83; adjusted OR 0.74, 95% CI 0.51–1.05; fully adjusted OR 0.69, 95% CI 0.47–1.07. In a multinomial model patients with AD were less likely to have ≥ 10 AKs (adjusted OR 0.28, 95% CI 0.09–0.90). No effect of AD on basal cell carcinoma or squamous cell carcinoma was found: adjusted OR 0.71, 95% CI 0.41–1.24 and adjusted OR 1.54, 95% CI 0.66–3.62, respectively.

Conclusions AD in community-dwelling patients is not associated with AK.

What's already known about this topic?

- Patients with severe atopic dermatitis (AD) treated with ultraviolet therapy and immunosuppressants are at an increased risk of keratinocyte malignancies.

What does this study add?

- Community-dwelling, average patients with AD do not have more actinic keratoses or keratinocyte cancers than those without AD.
- There is no support for extra actinic keratosis and keratinocyte cancer screening in patients with mild-to-moderate AD.

Atopic dermatitis (AD) is one of the most prevalent inflammatory skin conditions, affecting up to 30% of infants and up to 10% of adults. Its incidence has tripled in the past three decades.^{1–4} AD results from an impaired epidermal barrier,

due mostly to mutations in the filaggrin gene, combined with an overactive, T helper 2-polarized immune system.² It has been shown that the defective barrier may predispose patients with AD to more ultraviolet (UV) radiation-induced DNA

damage and subsequently increase the risk of keratinocyte cancers (KCs).⁵ However, there is also ample evidence that increased epithelial turnover and enhanced immunosurveillance actually protect against carcinogenesis in atopic skin.^{6,7}

KCs are common and their incidence is still increasing, which is most likely due to changes in UV exposure patterns.⁵ Basal cell carcinoma (BCC) is the most common cancer in people of European ancestry. Squamous cell carcinoma (SCC) occurs at a comparable rate with melanoma, especially in elderly individuals and those chronically exposed to the sun.^{8,9} Actinic keratosis (AK) is a keratinocyte premalignancy and is also highly prevalent (25% of Dutch inhabitants aged > 50 years) and is associated with high levels of cumulative UV exposure.^{10,11}

In several mouse studies, altered filaggrin expression and metabolism have been demonstrated to lead to an increased susceptibility to UVB-induced DNA damage.^{4,5,12–14} In humans the results are inconsistent and studies lack a clear definition of exposure. Filaggrin loss-of-function mutations were not associated with incident skin cancer in a Danish cohort of 13 376 genotyped individuals.¹⁵ Three retrospective registry-based cohort studies observed a 1.5–2.5-fold increased risk of developing KC in patients with AD, but these studies suffered from substantial residual confounding.^{16–18} In contrast, four small retrospective studies suggested no association between AD and KC,^{19–22} and one mail survey including 254 patients with AD suggested that AD had a protective effect on the development of KC.²³ None of these observational studies reported the association between AD and AK.

The objective of the current study was to investigate whether subjects with AD have more AKs than individuals without AD in a population-based Dutch cohort (the Rotterdam Study; RS).²⁴

Patients and methods

Study design and study population

The RS is an ongoing, prospective, Dutch population-based cohort study that has followed the inhabitants of the Ommoord district of Rotterdam, the Netherlands since 1990.²⁴

Currently there are 14 926 participants in the RS, which reflects the population of the Netherlands in terms of comorbidities and healthcare consumption. The population of the RS is regularly subjected to medical tests by various methods such as magnetic resonance imaging, electrocardiograms, pulmonary function testing and blood chemistry analysis.

Dermatological screening was introduced in August 2010. Since then, full-body skin examination (FBSE), with the exception of the skin covered by socks and underwear, has been conducted by four dermatology-trained physicians focusing on the most common skin diseases such as skin (pre-) malignancies, AD, hand eczema, psoriasis and varicose veins. This was a predefined set of findings and diagnoses. All participants of the RS undergo FBSE consecutively without a particular order. Participants who had undergone FBSE were included

in the present study. All measurements were performed once on each subject and no subjects refused FBSE. All were aged > 50 years and 95% were white.

The RS is approved by the medical ethics committee of the Erasmus University Medical Centre and the Netherlands Ministry of Health. All patients participating in the study gave written informed consent. This study is a cross-sectional study drawn from the RS.

Exposure: atopic dermatitis

The participants were interviewed at home, and FBSE was performed by trained physicians in a medical research facility in the centre of the district. No validated diagnostic criteria exist for adults with AD. However, in our practice, adults are diagnosed with AD on a daily basis. Therefore the commonly used U.K. working party's criteria, designed for a paediatric population, needed adjusting before they could be applied to our elderly population.²⁵ These guidelines comprise one major criterion plus three or more minor criteria. 'An itchy skin condition' is the must-have major criterion and the minor criteria are 'history of involvement of the skin creases', 'a personal history of asthma or hay fever', 'a history of generally dry skin in the last year', 'visible flexural eczema' and 'onset under 2 years of age'.

Because of the possible confusion of sun-damaged skin and hyperkeratosis of AKs with xerosis, and because of the high prevalence of dry skin in the elderly (56% of patients in the RS), the item 'history of generally dry skin' was excluded from our AD definition.²⁶ The personal history of other atopic diseases was extended with 'house dust mite allergy', because it is strongly related to atopic diseases.²⁷ Furthermore, sites of visible eczema were adapted. In adults, AD also occurs on the hands and the trunk.²⁸ We therefore included these localizations. Finally, the age of onset was extended to 12 years, because most patients develop AD before this age.²⁵ AD could contribute to the development of AKs through either the defect in the epidermal barrier or chronic inflammation in the skin. In order to be able to differentiate between these two hypotheses we performed analyses on AD criteria separately. In the case of the barrier model, one would expect all patients with AD to have an increased risk, while for the chronic inflammation model, patients with current (long-standing) AD would be more at risk.

Outcome: actinic keratosis

As previously reported in a prevalence study within the RS, AKs were diagnosed by trained physicians and were defined as a rough (keratotic) lesion with adherent scaling and erythema, not fitting other diagnoses.¹¹ The cumulative number of observed AKs was divided into four categories: zero, one to three, four to nine or ≥ 10 AKs. Limiting the reporting of AK to categories instead of a continuous variable prevents inter-rater variability to some degree and makes for a more clinical

cally relevant outcome corresponding to no, mild, moderate or severe AK.

Outcome: keratinocyte cancer

As described previously, the BCCs and SCCs were histologically confirmed by linking the RS participants to PALGA, a network of histopathology and cytopathology that administers the information of all biopsies and excisions from 1991 onward on a national level.¹¹ If at the time of the skin examination suspicious lesions were observed, they were biopsied, treated and included if pathologically confirmed as BCC or SCC.

Covariates

Previously identified risk factors for AK such as sex, age and pigmentation status were integrated in our analyses.¹¹ Pigmentation status was defined as a combination of three variables: hair colour at a young age, eye colour and skin colour. The variable 'hair colour' contained four categories (fair/blond, dark blond/brown, red and black); 'eye colour' had three categories (blue, intermediate, brown) and 'skin colour' had six options (albino, white, white to olive, light brown, brown, dark brown to black). The sum of the variables was recoded into three categories of light, medium or dark pigmentation status. Male baldness at the time of the skin examination was also recorded as a binary variable.

Other possible risk factors for AKs were available from interview data: living in a sunny country for > 1 year, the use of immunosuppressive medication, smoking, wearing sunglasses and hats for protection, and the number of lifetime sunburns. The first three questions had binary responses and the last two were categorized as never/almost never, often/not always and always, and the absolute number of sunburns. These variables are not known for an association with AD, but because of their importance as a traditional risk factor for AKs, they were taken into account and were used in the fully adjusted model.²⁷ Finally, we included possible confounders only when the effect was > 10% for the association between AD and AK in the main adjusted model (i.e. bivariate approach for selection of confounders).²⁹

Statistical analysis

The null hypothesis was that AD is not associated with AK in a population-based sample. The sample size for this study was calculated *a priori* and was based on a power of 80% and an altered risk of one-third [odds ratio (OR) of ≤ 0.66 or ≥ 1.33], based on an estimated AD prevalence of 10%. The calculated sample size (number of cases) for these ORs lies between 829 and 1253. The study was powered for a univariate analysis for the association between AK and AD, as SCC and BCC are not prevalent enough to provide > 829 cases. The primary analyses were performed by univariate and multivariate binary logistic regression looking at the association between AD and each of AK, SCC and BCC separately. In a

multinomial logistic regression model, the number of AKs was also analysed by categories, namely 1–3, 4–9 and > 10 AKs, to assess whether the number of AKs changed the effect in relation to AD. Sensitivity analysis was performed to investigate whether having active dermatitis or a past history of it, or history of atopy was driving a potential association, and whether altering the definition of exposure would alter the OR of the association. Individuals with missing variables relevant for the analyses were excluded. P-values < 0.05 were considered significant. All data were analysed using SPSS 21.0 (IBM, Armonk, NY, U.S.A.), except for the sample-size calculation, using PS Power and Sample Size Calculation version 3.0 (Department of Biostatistics, Vanderbilt University, Nashville, TN, U.S.A.).

Results

Patient characteristics

An FBSE and home interview were carried out for a total of 4375 participants. The proportion of women in the cohort was 56% and the mean age was 67.6 years (range 53–100) (Table 1). Of the 4375 participants, 24% had at least one AK, of whom 56.9% had one to three AKs, 22.8% had four to nine and 20.4% had > 10. The mean age of subjects with AKs was significantly higher than those without AKs: 73.0 vs. 65.9 years ($P < 0.01$).

Atopic dermatitis and actinic keratosis

Of the 4375 screened participants, 6.3% met the AD criteria. A significantly lower proportion of people with AD had AK compared with those without AD (16% vs. 24%, $P = 0.002$; unadjusted OR 0.60, 95% CI 0.42–0.83) (Table 2). Of all the available potential confounders, only age and sex changed the OR between AD and AK by $\geq 10\%$ and therefore were included in the main multivariate model. After adjusting for age and sex, the association between AD and AK was not significant (adjusted OR 0.74, 95% CI 0.51–1.05; Table 2). A comparable OR was found in the fully adjusted model: 0.69 (95% CI 0.47–1.07).

In the multinomial model taking the AK categories into account, one to three AKs and four to nine AKs showed no significant association with AD in the unadjusted, age- and sex-adjusted, and fully adjusted analyses (Table 2). In contrast to these low-number AK categories, patients with AD were approximately 72% less likely to have ≥ 10 AKs than those without AD (adjusted OR 0.28, 95% CI 0.09–0.90). However, this association did not remain significant in the fully adjusted model. The decreasing OR followed a statistically significant trend ($P < 0.001$) (Table 2).

In order to determine which of the AD criteria were driving the association (barrier defect or chronic inflammation), we analysed the criteria separately. From the total group of 260 persons diagnosed with AD, 92 had active dermatitis, 209 had flexural involvement, 169 had a history of atopy and 119

were diagnosed with eczema before the age of 12 years. The ORs for these criteria are shown in Table 3. Two minor criteria – active dermatitis and a history of atopy – had significant effects on the adjusted OR for the association of AD and AK: OR 0.57, 95% CI 0.42–0.77 and OR 0.75, 95% CI 0.60–0.92, respectively. Exclusion of hand dermatitis from the analysis did not alter the OR essentially; however, the CI became

insignificant due to loss of power: OR 0.62, 95% CI 0.25–1.55 and adjusted OR 0.70, 95% CI 0.27–1.84.

Atopic dermatitis and keratinocyte cancers

Of the 4375 people in the RS, 352 (8%) had one or more BCCs, of whom 16 had AD and 336 did not have AD ($P = 0.10$). In binary logistic regression having AD did not increase the likelihood of having a BCC with and without adjustment for age and sex (OR 0.64, 95% CI 0.37–1.11 and adjusted OR 0.71, 95% CI 0.41–1.24). Seventy-eight people had one or more SCCs. Six of them had AD and 72 did not meet the criteria for AD ($P = 0.50$). AD did not change the likelihood of having an SCC, with an unadjusted OR 1.33 (95% CI 0.57–3.08) and adjusted OR 1.54 (95% CI 0.66–3.62).

Discussion

Our findings suggest that within a population-based sample, patients with AD do not have more AKs than the rest of the population. Moreover, this study indicates that in individuals with AD the odds of having > 10 AKs are significantly lower. A gradient of decreasing ORs with increasing number of AKs was discernible, suggesting a biological effect. We did not find a significant association between KCs (either BCC or SCC) and AD. However, this study was not powered for these subanalyses and for the association between AD and BCC or SCC. Nonetheless, the results of our study suggest that average, community-dwelling patients with AD are not at an increased risk of AK and KCs.

In the past, two hypotheses have been used to explain the associations between AD and KC. One dictates that the overactive, atopic immune system in AD brings about increased immunosurveillance of neoplastic cells, while the other implies that the impaired epidermal barrier of AD actually predisposes to more UV-induced damage and subsequent KC.³ When analysing the AD criteria separately it appears that the minor criterion 'active dermatitis' is the strongest driver of the negative association, suggesting that patients with long-standing and/or active AD are more protected. AKs are usually accompanied by erythema and inflammation, which can be

Table 1 Frequencies and characteristics of the study population

Characteristic	Cases of AK (n = 1050)	Controls with no AK (n = 3325)	P-value
Atopic dermatitis criteria			0.002
No	1006 (95.8)	3107 (93.4)	
Yes	42 (4.0)	218 (6.6)	
Missing data	2 (0.2)	0	
Sex			< 0.001
Female	444 (42.3)	1988 (59.8)	
Male	606 (57.7)	1337 (40.2)	
Age (years)			< 0.001
Mean	73.0	65.9	
< 70	379 (36.1)	2373 (71.4)	
70–79.99	483 (46.0)	764 (23.0)	
≥ 80	188 (17.9)	188 (5.7)	
Pigmentation status (eye, hair and skin colour)			< 0.001
Dark	55 (5.2)	450 (13.5)	
Medium	667 (63.5)	2190 (65.9)	
Light	260 (24.8)	528 (15.9)	
Missing data	68 (6.5)	157 (4.7)	
Tendency to develop sunburn			< 0.001
Low	521 (49.6)	2168 (65.2)	
High	366 (34.9)	947 (28.5)	
Missing data	163 (15.5)	210 (6.3)	
History of living in a sunny country > 1 year			0.003
No	820 (78.1)	2783 (83.7)	
Yes	73 (7.0)	367 (11.0)	
Missing data	157 (15.0)	175 (5.3)	
Sun-protective behaviour			< 0.001
Never/almost never	255 (24.3)	1151 (34.6)	
Often/not always	298 (28.4)	937 (28.2)	
Always	340 (32.4)	1062 (31.9)	
Missing data	157 (15.0)	175 (5.3)	

Values are n (%) unless stated otherwise.

Table 2 Binary logistic regression of the association between atopic dermatitis and actinic keratosis (AK), unadjusted and adjusted models (n = 4113)

Method	Number of AKs	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a	Fully adjusted OR (95% CI) ^b
Binary logistic regression	≥ 1	0.60 (0.42–0.83)	0.74 (0.51–1.05)	0.69 (0.47–1.07)
Multinomial logistic regression ^c	1–3	0.75 (0.51–1.12)	0.89 (0.60–1.33)	1.12 (0.64–1.96)
	4–9	0.56 (0.28–1.11)	0.75 (0.37–1.50)	0.75 (0.27–2.08)
	≥ 10	0.20 (0.07–0.64)	0.28 (0.09–0.90)	0.19 (0.03–1.43)

OR, odds ratio; CI, confidence interval. ^aAdjusted for sex and age. ^bAdjusted for sex, age, pigmentation status, history of living in a sunny country, sun-protective behaviour, male baldness, number of sunburns, smoking and use of immunosuppressive medication. ^cReference category zero AKs; $P < 0.001$ for trend in decreasing ORs across AK categories.

Table 3 Binary logistic regression models (unadjusted and adjusted) for the association between actinic keratosis and separate atopic dermatitis (AD) criteria

Variable	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
AD criteria (all)	42	218	0.60 (0.42–0.83)	0.74 (0.51–1.05)
Hand dermatitis excluded	34	170	0.62 (0.25–1.55)	0.70 (0.27–1.84)
Active dermatitis	60	292	0.63 (0.47–0.84)	0.57 (0.42–0.77)
Atopy in history	142	608	0.62 (0.51–0.76)	0.75 (0.60–0.92)
Eczema diagnosed at < 12 years	49	221	0.73 (0.53–1.00)	0.91 (0.65–1.27)
Flexural itch history	101	407	0.84 (0.66–1.06)	0.98 (0.76–1.26)

OR, odds ratio; CI, confidence interval. ^aAdjusted for sex and age.

visualized by histopathology. This inflammatory response can lead to spontaneous remission of immunogenic AKs. Eczematous skin may mount this inflammatory response more easily.⁷

An alternative explanation for the protective effect we have found may be the locally increased turnover of keratinocytes or altered signalling between keratinocytes and immune cells.^{6,30} A cohort study of 57 815 patients who had been tested for total serum IgE and Phadiatop revealed no effect of serological atopy on the incidence of various cancers including KCs.³¹ This suggests no general protective effect of systemic atopy. It is also possible that a difference in behaviour between patients with AD and controls could explain the difference. For example, patients with AD may be more aware of their skin and sun damage and may be more adherent to sun-protective behaviours. There is a possibility of detection bias if patients with AD present to physicians more often and have their AKs treated. Furthermore, patients with AD may be more skilled in the correct and frequent application of sunscreens or may avoid the sun in general because of embarrassment with skin lesions.

This is the first study to examine the association between AD and AK. The strengths of this study are the large number of patients, the fact that the presence of AK was diagnosed by trained physicians and that the number of AKs was established in detail. Furthermore, we took into account several confounders, which enhances the validity of the study. There are also some limitations to this study. This was a cross-sectional study, and the outcome (AK) was determined by a single measurement without longitudinal data. AK and AD have very differing ages of peak prevalence. In fact, the development of AD may be preceded by the development of AK by decades, which makes a longitudinal study impossible at this moment starting at age of onset of AD up to the age of 40 years when the first AKs appear. This necessitates retrospective ascertainment of exposure/AD to some degree.

There are no validated AD diagnostic criteria for adults. The use of the U.K. working party's modified criteria may have led to the inclusion of other forms of eczema. This would lead to a dilution of effect. The group that met the AD criteria comprised 6.9% of the total study population. This is comparable with the prevalence of AD in children from the 1940s and 1950s (childhood years in our study population), as described in the literature.³² Moreover, the exclusion of hand

dermatitis in our sensitivity analyses did not lead to different results. Unfortunately we could not assess the overlap in skin areas for eczematous skin and AKs. In this study we did not know which patients received treatment for severe AD, such as immunosuppressants and UVB therapy. These treatments contribute to the risk of cutaneous (pre)malignancies and may have led to uncontrolled confounding of AD on AK and KC risk, and could explain why some of the studies in AD cohorts have found an increased risk. However, our patients with AD are community dwelling, and the percentage of cases of severe AD treated by these modalities is expected to be low.

Several previous studies have also found an inverse relationship between AD and KC. One case-control study showed an adjusted OR of 0.78 (95% CI 0.61–0.98), but the authors used subjects with other cutaneous diseases as the control group, which might have influenced their results.²³ Ming *et al.* found similar results, but selected their controls out of a 'dermatitis' group.²³ Kaae *et al.* examined the filaggrin gene mutation status and found nonsignificant ORs < 1.00. They concluded that filaggrin mutation carrier status is not important for the association between AD and BCC.³³

However, the pathomechanism remains unclear. Future studies should focus on physician-made diagnosis of AD, as well as on the filaggrin gene status as exposures. It is also necessary to examine whether the sites of KCs and AKs overlap with the skin areas affected by AD.

In conclusion, patients with AD were not found to have more AKs or KCs. Moreover, individuals with AD seem to be less likely to develop multiple AKs.

References

- Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol* 2006; **118**:209–13.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**:1483–94.
- Hajdarbegovic E, Verkouteren J, Balak D. Non-melanoma skin cancer: the hygiene hypothesis. *Med Hypotheses* 2012; **79**:872–4.
- Mildner M, Jin J, Eckhart L *et al.* Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model. *J Invest Dermatol* 2010; **130**:2286–94.
- Denecker G, Hoste E, Gilbert B *et al.* Caspase-14 protects against epidermal UVB photodamage and water loss. *Nat Cell Biol* 2007; **9**:666–74.

- 6 Guinea-Viniegra J, Zenz R, Scheuch H *et al.* Differentiation-induced skin cancer suppression by FOS, p53, and TACE/ADAM17. *J Clin Invest* 2012; **122**:2898–910.
- 7 Strid J, Sobolev O, Zafirova B *et al.* The intraepithelial T cell response to NKG2D-ligands links lymphoid stress surveillance to atopy. *Science* 2011; **334**:1293–7.
- 8 Dupuy A, Dehen L, Bourrat E *et al.* Accuracy of standard dermoscopy for diagnosing scabies. *J Am Acad Dermatol* 2007; **56**:53–62.
- 9 Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *Lancet* 2010; **375**:673–85.
- 10 He W, Zhu F, Ma X *et al.* Actinic skin damage and mortality – the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *PLoS ONE* 2011; **6**:e19907.
- 11 Flohil SC, van der Leest RJ, Dowlatshahi EA *et al.* Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol* 2013; **133**:1971–8.
- 12 El-Khateeb EA, Ragab NF, Mohamed SA. Epidermal photoprotection: comparative study of narrowband ultraviolet B minimal erythema doses with and without stratum corneum stripping in normal and vitiligo skin. *Clin Exp Dermatol* 2011; **36**:393–8.
- 13 Hong SP, Kim MJ, Jung MY *et al.* Biopositive effects of low-dose UVB on epidermis: coordinate upregulation of antimicrobial peptides and permeability barrier reinforcement. *J Invest Dermatol* 2008; **128**:2880–7.
- 14 Barresi C, Stremnitzer C, Mlitz V *et al.* Increased sensitivity of histidinemic mice to UVB radiation suggests a crucial role of endogenous urocanic acid in photoprotection. *J Invest Dermatol* 2011; **131**:188–94.
- 15 Skaaby T, Husemoen LL, Thyssen JP *et al.* Filaggrin loss-of-function mutations and incident cancer: a population-based study. *Br J Dermatol* 2014; **171**:1407–14.
- 16 Dyer RK, Weinstock MA, Cohen TS *et al.* Predictors of basal cell carcinoma in high-risk patients in the VATTC (VA Topical Tretinoin Chemoprevention) trial. *J Invest Dermatol* 2012; **132**:2544–51.
- 17 Arana A, Wentworth CE, Fernández-Vidaurre C *et al.* Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol* 2010; **163**:1036–43.
- 18 Jensen AO, Svaerke C, Körmendiné Farkas D *et al.* Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977–2006). *Am J Clin Dermatol* 2012; **13**:29–36.
- 19 Hagstromer L, Ye W, Nyrén O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. *Arch Dermatol* 2005; **141**:1123–7.
- 20 Hwang CY, Chen YJ, Lin MW *et al.* Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan. *Int J Cancer* 2012; **130**:1160–7.
- 21 Milan T, Verkasalo PK, Kaprio J, Koskenvuo M. Lifestyle differences in twin pairs discordant for basal cell carcinoma of the skin. *Br J Dermatol* 2003; **149**:115–23.
- 22 Cheng J, Zens MS, Duell EJ *et al.* History of allergy and atopic dermatitis in relation to squamous cell and basal cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev* 2015; **24**:749–54.
- 23 Ming ME, Levy R, Hoffstad O *et al.* The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. *J Am Acad Dermatol* 2004; **50**:357–62.
- 24 Hofman A, Darwish Murad S, van Duijn CM *et al.* The Rotterdam Study: 2014 objectives and design update. *Eur J Epidemiol* 2013; **28**:889–926.
- 25 Bieber T, Bussmann C. Atopic dermatitis. In: *Dermatology* (Bolognia J, Jorizzo J, Schaffer J, eds), 3rd edn. Amsterdam: Elsevier Saunders, 2012; 203–16.
- 26 Paul C, Maumus-Robert S, Mazereeuw-Hautier J *et al.* Prevalence and risk factors for xerosis in the elderly: a cross-sectional epidemiological study in primary care. *Dermatology* 2011; **223**:260–5.
- 27 Jacquet A. Innate immune responses in house dust mite allergy. *ISRN Allergy* 2013; **2013**:735031.
- 28 Zeppa L, Bellini V, Lisi P. Atopic dermatitis in adults. *Dermatitis* 2011; **22**:40–6.
- 29 Wakkee M, Hollestein LM, Nijsten T. Multivariable analysis. *J Invest Dermatol* 2014; **134**:e20.
- 30 Cipolat S, Hoste E, Natsuga K *et al.* Epidermal barrier defects link atopic dermatitis with altered skin cancer susceptibility. *Elife* 2014; **3**:e01888.
- 31 Lindelof B, Granath F, Tengvall-Linder M, Ekblom A. Allergy and cancer. *Allergy* 2005; **60**:1116–20.
- 32 Taylor B, Wadsworth J, Wadsworth M, Peckmah C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. *Lancet* 1984; **2**:1255–7.
- 33 Kaae J, Thyssen JP, Johansen JD *et al.* Filaggrin gene mutations and risk of basal cell carcinoma. *Br J Dermatol* 2013; **169**:1162–4.