

# Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K.

A. Arana,\* C.E. Wentworth,† C. Fernández-Vidaurre,‡ R.G. Schlienger,§ E. Conde¶\*\* and F.M. Arellano\*†

\*Risk Management Resources, Pharmacovigilance Services SL, 50001 Zaragoza, Spain

†Risk Management Resources, LLC, Bridgewater, NJ, U.S.A.

‡Novartis Pharmaceuticals Corp., Global Clinical Epidemiology, East Hanover, NJ, U.S.A.

§Novartis Pharma AG, Global Clinical Epidemiology, Basel, Switzerland

¶Hematology Service, Hospital Marqués de Valdecilla, Santander, Spain

\*\*Faculty of Medicine, Universidad de Cantabria, Santander, Spain

## Summary

### Correspondence

Alejandro Arana.

E-mail: arana.riskmr@gmail.com

### Accepted for publication

1 June 2010

### Key words

atopic dermatitis, cancer, cohort studies, epidemiology, incidence, lymphoma

### Conflicts of interest

The study was funded by an unrestricted grant from Novartis. Risk Management Resources had the final decision contractually on the content of the manuscript as well as the journal of choice. R.G.S. and C.F.-V. are employees of Novartis.

DOI 10.1111/j.1365-2133.2010.09887.x

**Background** Atopic dermatitis (AD) affects approximately 20% of children and 1–3% of adults in developed countries.

**Objective** To study the incidence of cancer in patients with AD in the U.K. general population.

**Methods** We conducted a follow-up study in the U.K. using The Health Improvement Network (THIN) database. We calculated the incidence rate (IR) of the first occurrence of overall cancer, lymphoma, melanoma and nonmelanoma skin cancer (NMSC) in the general population, in patients with AD and in individuals without AD. In addition we calculated the IR ratio (IRR) of overall cancer and subtypes of cancer in patients with AD vs. those without.

**Results** The study population included 4 518 131 patients [2 336 230 (51.7%) female]. There were 129 972 subjects [68 688 (52.8%) female] with a diagnosis of cancer (excluding NMSC). The IR (per 10 000 person-years) of cancer (excluding NMSC) was 42.41 [95% confidence interval (CI) 42.18–42.64]; of lymphoma 1.70 (95% CI 1.65–1.74); of skin melanoma 1.71 (95% CI 1.67–1.76) and of NMSC 11.76 (95% CI 11.64–11.88). The age- and sex-adjusted IRR for cancer (excluding NMSC) was 1.49 (95% CI 1.39–1.61); for lymphoma 2.21 (95% CI 1.65–2.98); for melanoma 1.74 (95% CI 1.25–2.41); and for NMSC 1.46 (95% CI 1.27–1.69).

**Conclusions** Our results indicate an increased incidence of cancer overall as well as of specific cancer subtypes, including lymphoma, in patients with AD. Further studies are needed to disentangle the effects of treatment for AD from AD itself.

The prevalence of atopic dermatitis (AD) in Western countries has increased over the past 30 years.<sup>1</sup> AD affects approximately 20% of children and 1–3% of adults in developed countries.<sup>2</sup> The disease can decrease patients' quality of life considerably, especially in severe cases. Patients may suffer from itch, loss of sleep, scratch trauma and skin infections. AD may continue for prolonged periods of time or may be of a relapsing, remitting nature.

Several studies have examined the relationship between 'atopic conditions' and cancer, yielding very different results.<sup>3–10</sup> There are two major hypotheses linking 'atopic conditions' and cancer. According to one, the presence of the

allergy will act as a stimulant of the immune system that will inhibit the development of cancer.<sup>7</sup> The second theory suggests that chronic stimulation of the immune system by an antigen will induce the development of random pro-oncogenic mutations and therefore result in an increase in cancer risk.<sup>7</sup> However, these apparently contradictory theories may be reconcilable and may depend on both the specific atopic condition and the particular cancer.

This observational study describes the occurrence of cancer in patients considered to be representative of the general U.K. population and the relationship between several types of cancer and AD.

## Methods

### Source population and data

We conducted a retrospective cohort study in The Health Improvement Network (THIN) database, which is representative of the general U.K. population. THIN is a validated electronic medical records database which contains records from general practices.<sup>11</sup> Currently, the THIN dataset contains data from 314 medical practices with a total of over 5.5 million patients of whom more than 4 million are actively registered with the practices and can be prospectively followed; most have recorded several years of data on their system. The records are made anonymous at the collection stage; therefore, identifying information is not available to THIN.

Conduct of the study was approved by the South East Multi-center Research Ethics Committee.

### Study population

The study population consisted of patients of all ages who had been enrolled for least 6 months with a THIN-registered practice, during the period 1 January 1992 to 23 March 2006.

### Exclusion criteria

No exclusion criteria other than a previous history of the specific cancer of interest were applied when describing the incidence rate (IR) of first occurrence of overall cancer [when we refer to overall cancer it implies all cancer types except nonmelanoma skin cancer (NMSC), unless otherwise specified], lymphoma, NMSC and melanoma. Four cohorts were built, one for each individual outcome studied.

### Cohort follow-up

This was from study entry (1 January 1992 or 6 months after enrolment date) to the study end (earliest of: case definition criteria, death or 23 March 2006).

### Case identification and characterization

Cases of cancer were identified by the presence of a Read code for the tumour under study (overall cancer, lymphoma, NMSC and melanoma) after the cohort entry date in the medical records of patients included in the cohort.

### Atopic dermatitis identification

Patients with AD were identified either by the presence of at least two correlative codes of AD, or by the presence of AD codes entered by a specialist. We compared the ascertainment of AD diagnoses yielded by this method with that obtained by the manual review of free text from a random sample of 1000 patients with one Read code for AD and a random sample of 1000 patients without Read codes for AD. The sensitivity of

this algorithm was low (42%), but the specificity was close to 100%.

### Statistical analysis

We calculated the IR of the first occurrence of cancer overall, and of lymphoma, melanoma or NMSC with 95% confidence interval (CI) according to a Poisson distribution.<sup>12</sup>

Mantel-Haenszel age- and sex-adjusted IR ratios (IRR) were calculated to compare the risk of cancer and subtypes of cancer in patients with AD vs. subjects without AD.

## Results

The initial study population consisted of 4 518 131 patients (2 336 230 female and 2 181 901 male) of whom 62 123 were excluded due to a history of cancer prior to cohort entry. Therefore, we calculated the incidence of first occurrence of cancer among 4 456 008 [2 297 213 (51.6%) female and 2 158 795 (48.4%) male] individuals who had not previously been diagnosed with cancer (Table 1).

The mean age (SD) in the overall study cohort was 39.8 (24.5) years for female subjects and 38.1 (22.9) years for male subjects. There were 66 258 patients with AD (1.5%). The mean age (SD) in the AD subcohort was 27.5 (23.4) years for female patients and 23.3 (23.7) years for male patients. The remaining 4 389 750 subjects without AD were on average between 10 and 15 years older than patients belonging to the AD subcohort (Table 1 and Fig. 1). The percentage of individuals younger than 20 years of age was higher among patients with AD (54.8%) than in subjects without AD (22.6%), while there were more patients older than 20 years among the subjects without AD than in patients with AD.

On average, the overall cohort was followed up for 6.78 years, yielding a total of 30 647 768 patient-years. The mean follow-up time was 3.16 years for patients with AD and 6.81 years for patients without AD.

There were 129 972 subjects with a diagnosis of cancer, of whom 68 688 (52.8%) were female. The crude IR of overall cancer was 42.41 (95% CI 42.18–42.64) per 10 000 person-years. The IR increased with age (Table 2), and overall was higher in female patients (crude IR 44.55; 95% CI 44.21–44.88) than in male patients (crude IR 40.24; 95% CI 39.93–40.56). The crude IR of overall cancer (excluding NMSC) in patients with AD was 33.24 (95% CI 30.83–35.80), which was lower than in subjects without AD (crude IR 42.44; 95% CI 42.21–42.67). For each age group, the IR of cancer in patients with AD was higher than in those without AD (Table 2, Fig. 2). The age- and sex-adjusted IRR for overall cancer comparing patients with AD with those without AD was 1.49 (95% CI 1.39–1.61).

We identified 5324 subjects with a diagnosis of lymphoma, of whom 2501 (47.0%) were female. The crude overall IR was 1.70 (95% CI 1.65–1.74) per 10 000 person-years and increased with age (Table 3). The crude IR of lymphoma in

Table 1 Age and sex distribution of the cohorts

| Age group (years) | Overall     |      |             |      | Patients with AD |      |             |      | Patients without AD |      |             |      |
|-------------------|-------------|------|-------------|------|------------------|------|-------------|------|---------------------|------|-------------|------|
|                   | Males       |      | Females     |      | Males            |      | Females     |      | Males               |      | Females     |      |
|                   | n           | %    | n           | %    | n                | %    | n           | %    | n                   | %    | n           | %    |
| ≤ 5               | 173 573     | 8.0  | 164 760     | 7.2  | 8822             | 29.1 | 7026        | 19.6 | 164 751             | 7.7  | 157 734     | 7.0  |
| 6–9               | 97 201      | 4.5  | 93 100      | 4.1  | 4763             | 15.7 | 4385        | 12.2 | 92 438              | 4.3  | 88 715      | 3.9  |
| 10–14             | 117 795     | 5.5  | 112 287     | 4.9  | 3194             | 10.5 | 3456        | 9.6  | 114 601             | 5.4  | 108 831     | 4.8  |
| 15–19             | 129 029     | 6.0  | 142 027     | 6.2  | 1978             | 6.5  | 2706        | 7.5  | 127 051             | 6.0  | 139 321     | 6.2  |
| 20–29             | 352 076     | 16.3 | 437 553     | 19.0 | 2528             | 8.3  | 4838        | 13.5 | 349 548             | 16.4 | 432 715     | 19.1 |
| 30–39             | 365 838     | 16.9 | 355 636     | 15.5 | 2148             | 7.1  | 4209        | 11.7 | 363 690             | 17.1 | 351 427     | 15.5 |
| 40–49             | 281 284     | 13.0 | 258 944     | 11.3 | 1758             | 5.8  | 2769        | 7.7  | 279 526             | 13.1 | 256 175     | 11.3 |
| 50–59             | 224 209     | 10.4 | 213 786     | 9.3  | 1602             | 5.3  | 2111        | 5.9  | 222 607             | 10.5 | 211 675     | 9.4  |
| 60–69             | 176 235     | 8.2  | 169 177     | 7.4  | 1429             | 4.7  | 1720        | 4.8  | 174 806             | 8.2  | 167 457     | 7.4  |
| 70–79             | 140 685     | 6.5  | 156 937     | 6.8  | 1275             | 4.2  | 1469        | 4.1  | 139 410             | 6.5  | 155 468     | 6.9  |
| 80–89             | 83 645      | 3.9  | 140 632     | 6.1  | 729              | 2.4  | 990         | 2.8  | 82 916              | 3.9  | 139 642     | 6.2  |
| 90+               | 17 225      | 0.8  | 52 374      | 2.3  | 109              | 0.4  | 244         | 0.7  | 17 116              | 0.8  | 52 130      | 2.3  |
| Total             | 2 158 795   | 100  | 2 297 213   | 100  | 30 335           | 100  | 35 923      | 100  | 2 128 460           | 100  | 2 261 290   | 100  |
| Age (years)       |             |      |             |      |                  |      |             |      |                     |      |             |      |
| Mean (SD)         | 38.1 (22.9) |      | 39.8 (24.5) |      | 23.3 (23.7)      |      | 27.5 (23.4) |      | 38.3 (22.8)         |      | 40.0 (24.5) |      |
| Median            | 35.7        |      | 35.4        |      | 12.6             |      | 20.7        |      | 35.7                |      | 35.6        |      |
| IQR 25–75         | 20.7, 54.7  |      | 21.7, 57.7  |      | 5.6, 36.7        |      | 7.4, 40.7   |      | 21.3, 54.7          |      | 21.7, 57.7  |      |

AD, atopic dermatitis; IQR 25–75, interquartile range 25% and 75%.

patients with AD was 2.05 (95% CI 1.49–2.75), and greater than in individuals without AD (crude IR 1.69; 95% CI 1.65–1.74). When stratified by age, the IR of lymphoma was higher in patients with AD compared with those without AD in all age strata above 10 years of age, except in ages 20–30 years (Table 3; Fig. 3). The age- and sex-adjusted IRR was 2.21 (95% CI 1.65–2.98).

A total of 5375 subjects had a diagnosis of melanoma of the skin, of whom 3154 (58.7%) were female. The crude overall IR for melanoma was 1.71 (95% CI 1.67–1.76) per 10 000 person-years and increased with age (Table 4). The crude IR of melanoma in patients with AD was 1.68 (95% CI 1.17–2.32), and was comparable to that found in subjects without AD (IR 1.71; 95% CI 1.67–1.76). Stratification by age showed that in all age strata  $\geq 15$  years, the IR of melanoma

was higher in patients with AD compared with individuals without AD (Table 4; Fig. 4). The age- and sex-adjusted IRR was 1.74 (95% CI 1.25–2.41).

We found 36 584 subjects with a diagnosis of NMSC, of whom 18 573 (50.8%) were female. The crude overall IR of NMSC was 11.76 (95% CI 11.64–11.88) per 10 000 person-years and increased with age (Table 5). The crude IR of NMSC in patients with AD was 8.77 (95% CI 7.56–10.12), and was lower than in subjects without AD (IR 11.78; 95% CI 11.66–11.90). The IR of NMSC in individual age strata were generally higher in patients with AD compared with those without (Table 5; Fig. 5). The age- and sex-adjusted IRR showed an increased risk of NMSC in patients with AD compared with those without an AD diagnosis (IRR 1.46; 95% CI 1.27–1.69). We performed a sensitivity analysis excluding cases of carcinoma in situ (CIS; Bowen disease, Queyrat erythroplasia and others). The results were not influenced by the exclusion of CIS (data not shown).

## Discussion

In general, the IR of cancer in THIN was comparable with that in the U.K. population. The IR of first occurrence of overall cancer was 42.41 per 10 000 person-years in THIN, compared with 45.7 in female and 47.1 in male subjects in the general population from the U.K.<sup>13</sup> The methods for calculating IR however were not identical. We calculated the IR of the first occurring cancer whereas the comparison data were on cancer (excluding NMSC) but any cancer, not only the first occur-

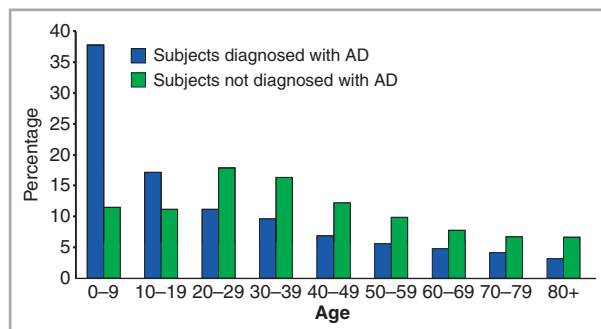


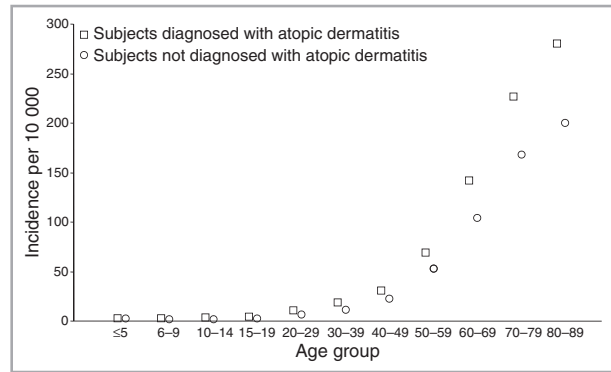
Fig 1. Age distribution of subjects with and without atopic dermatitis (AD).

**Table 2** Incidence of first cancer (excluding nonmelanoma skin cancer) in the general U.K. population (incidence rates as cases per 10 000 persons-years)

| Overall           |                 |               | Patients with AD     |               |                 |               | Patients without AD  |               |                 |               |                      |               |           |           |
|-------------------|-----------------|---------------|----------------------|---------------|-----------------|---------------|----------------------|---------------|-----------------|---------------|----------------------|---------------|-----------|-----------|
| Age group (years) | Number of cases | Patient-years | Incidence per 10 000 | 95% CI        | Number of cases | Patient-years | Incidence per 10 000 | 95% CI        | Number of cases | Patient-years | Incidence per 10 000 | 95% CI        | Crude IRR | 95% CI    |
| ≤ 5               | 396             | 1 807 757     | 2.19                 | 1.98–2.41     | 13              | 47 422        | 2.74                 | 1.46–4.69     | 383             | 1 769 325     | 2.16                 | 1.95–2.39     | 1.27      | 0.67–2.19 |
| 6–9               | 303             | 1 924 703     | 1.57                 | 1.40–1.76     | 10              | 40 882        | 2.45                 | 1.17–4.50     | 293             | 1 884 712     | 1.55                 | 1.38–1.74     | 1.57      | 0.75–2.94 |
| 10–14             | 321             | 1 817 195     | 1.77                 | 1.58–1.97     | 5               | 21 829        | 2.29                 | 0.74–5.35     | 316             | 1 795 853     | 1.76                 | 1.57–1.97     | 1.30      | 0.42–3.07 |
| 15–19             | 452             | 1 654 431     | 2.73                 | 2.49–2.99     | 10              | 13 766        | 7.26                 | 3.48–13.36    | 442             | 1 641 239     | 2.69                 | 2.45–2.96     | 2.70      | 1.28–5.01 |
| 20–29             | 2722            | 4 130 476     | 6.59                 | 6.35–6.84     | 23              | 20 686        | 11.12                | 7.05–16.68    | 2699            | 4 114 024     | 6.56                 | 6.32–6.81     | 1.69      | 1.07–2.55 |
| 30–39             | 5588            | 4 929 260     | 11.34                | 11.04–11.64   | 39              | 19 849        | 19.65                | 13.98–26.85   | 5549            | 4 912 115     | 11.30                | 11.00–11.60   | 1.74      | 1.24–2.38 |
| 40–49             | 10 073          | 4 424 059     | 22.77                | 22.33–23.22   | 46              | 14 181        | 32.44                | 23.76–43.24   | 10 027          | 4 411 316     | 22.73                | 22.29–23.18   | 1.43      | 1.04–1.90 |
| 50–59             | 19 887          | 3 744 498     | 53.11                | 52.38–53.85   | 79              | 11 234        | 70.32                | 55.71–87.57   | 19 808          | 3 734 289     | 53.04                | 52.31–53.79   | 1.33      | 1.05–1.65 |
| 60–69             | 30 233          | 2 890 602     | 104.59               | 103.42–105.77 | 158             | 9262          | 170.59               | 145.21–199.07 | 30 075          | 2 882 041     | 104.35               | 103.18–105.53 | 1.63      | 1.39–1.91 |
| 70–79             | 36 102          | 2 139 943     | 168.71               | 166.97–170.45 | 183             | 7254          | 252.26               | 217.41–291.02 | 35 919          | 2 133 225     | 168.38               | 166.66–170.11 | 1.50      | 1.29–1.73 |
| 80–89             | 23 895          | 1 184 844     | 201.67               | 199.13–204.24 | 134             | 4196          | 319.32               | 268.24–377.11 | 23 761          | 1 181 024     | 201.19               | 198.67–203.74 | 1.59      | 1.33–1.88 |
| Total             | 129 972         | 30 647 768    | 42.41                | 42.18–42.64   | 700             | 210 563       | 33.24                | 30.83–35.80   | 129 272         | 30 459 164    | 42.44                | 42.21–42.67   | 0.78      | 0.73–0.84 |

AD, atopic dermatitis; CI, confidence interval; IRR, incidence rate ratio of patients with AD vs. patients without AD.

AD, atopic dermatitis; CI, confidence interval; IRR, incidence rate ratio of patients with AD vs. patients without AD.

**Fig 2.** Incidence rates of overall cancer in patients with and without atopic dermatitis.

rence, as derived from the International Agency for Research on Cancer (IARC).<sup>13</sup> The IR of lymphoma was 1.7 per 10 000 person-years in THIN compared with 1.7 in female and 1.9 in male subjects in the U.K. general population.<sup>13</sup> The IR of melanoma was 1.71 per 10 000 person-years compared with 1.3 in female and 1.0 in male subjects.<sup>13</sup> The IR of NMSC was 11.76 per 10 000 person-years in THIN. NMSC is not reported in cancer registries included in IARC.<sup>13,14</sup> THIN is considered to be representative of the U.K. general population and our results confirm this for cancer. The small differences seen in overall cancer could be attributed to the fact that in our study only first occurrence of cancer was taken into account compared with any occurrence in the IARC publication,<sup>13</sup> or to small differences in age distributions. However, in the case of melanoma, we should take into account a possible degree of under-reporting in the standard cancer registries<sup>15</sup> that feed data into the IARC.

In general, the IR of cancer found in this study was higher in patients with AD when individual age strata were compared, but lower or similar when the overall crude rate was compared. This is explained by the difference in the age distribution of the populations. The mean age of subjects with AD was almost 15 years lower than in the population without AD; this is not surprising as AD is more prevalent in childhood and adolescence. As the cancer incidence increases with age, the younger AD population will correspondingly have a lower IR of the disease, which at least partly explains the differences in follow-up between patients with and without AD. Standardization by age corrects for the age differences in the cohorts and the association with AD becomes apparent. Sex had no substantial effect.

In a review of published epidemiological studies on AD and cancer risk, Wang and Diepgen<sup>10</sup> revealed that a history of AD may be associated with a decreased risk of pancreatic cancer, brain tumours and childhood leukaemia. Hagströmer *et al.*<sup>16</sup> found an increased risk of developing any cancer in a register-based retrospective cohort study in Sweden, especially for lymphoma [standardized incidence ratio (SIR) 2.0; 95% CI 1.4–2.9]. Olesen *et al.*,<sup>17</sup> in a follow-up study in Denmark, found that hospitalized adult patients with AD had an

Table 3 Incidence of lymphoma in the general U.K. population (incidence rates as cases per 10 000 persons-years)

| Age group (years) | Overall         |               |                      |           | Patients with AD |               |                      |            | Patients without AD |               |                      |           |
|-------------------|-----------------|---------------|----------------------|-----------|------------------|---------------|----------------------|------------|---------------------|---------------|----------------------|-----------|
|                   | Number of cases | Patient-years | Incidence per 10 000 | 95% CI    | Number of cases  | Patient-years | Incidence per 10 000 | 95% CI     | Number of cases     | Patient-years | Incidence per 10 000 | 95% CI    |
| ≤2                | 7               | 673 341       | 0.10                 | 0.05–0.20 | 0                | 12 539        | 0                    | 0–2.94     | 7                   | 660 801       | 0.11                 | 0.04–0.22 |
| 3–5               | 12              | 1 145 083     | 0.10                 | 0.06–0.18 | 0                | 35 624        | 0                    | 0–1.04     | 12                  | 1 109 459     | 0.11                 | 0.06–0.19 |
| 6–9               | 18              | 1 927 712     | 0.09                 | 0.06–0.14 | 0                | 40 924        | 0                    | 0–0.90     | 18                  | 1 886 788     | 0.10                 | 0.06–0.15 |
| 10–19             | 125             | 3 477 570     | 0.36                 | 0.30–0.43 | 3                | 35 323        | 0.85                 | 0.18–2.48  | 122                 | 3 442 247     | 0.35                 | 0.29–0.42 |
| 20–29             | 244             | 4 147 911     | 0.59                 | 0.52–0.67 | 0                | 20 780        | 0.00                 | 0–1.78     | 244                 | 4 127 131     | 0.59                 | 0.52–0.67 |
| 30–39             | 384             | 4 970 366     | 0.77                 | 0.70–0.85 | 5                | 20 115        | 2.49                 | 0.81–5.80  | 379                 | 4 950 251     | 0.77                 | 0.69–0.85 |
| 40–49             | 526             | 4 493 934     | 1.17                 | 1.07–1.27 | 2                | 14 564        | 1.37                 | 0.17–4.96  | 524                 | 4 479 370     | 1.17                 | 1.07–1.27 |
| 50–59             | 876             | 3 860 017     | 2.27                 | 2.12–2.42 | 4                | 11 774        | 3.40                 | 0.93–8.70  | 872                 | 3 848 243     | 2.27                 | 2.12–2.42 |
| 60–89             | 3132            | 6 684 307     | 4.69                 | 4.53–4.86 | 30               | 23 266        | 12.89                | 8.70–18.40 | 3102                | 6 661 040     | 4.66                 | 4.50–4.82 |
| Total             | 5324            | 31 380 241    | 1.70                 | 1.65–1.74 | 44               | 214 909       | 2.05                 | 1.49–2.75  | 5280                | 31 165 332    | 1.69                 | 1.65–1.74 |
|                   |                 |               |                      |           |                  |               |                      |            |                     |               |                      | 0.88–1.62 |

AD, atopic dermatitis; CI, confidence interval; IRR, incidence rate ratio of patients with AD vs. patients without AD.

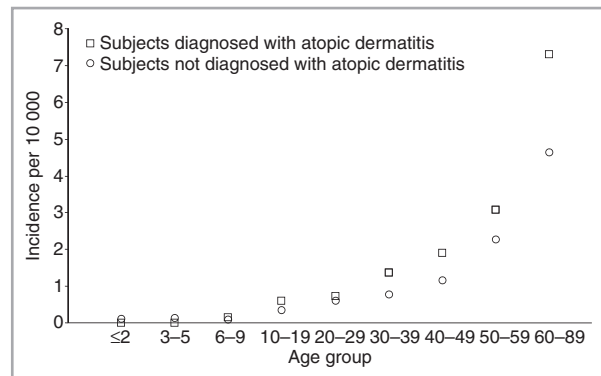


Fig 3. Incidence rates of lymphoma in patients with and without atopic dermatitis.

increased risk of cancer. Our study supports previous findings of an increased overall cancer risk, as we observed an almost 50% increase in the risk of cancer in the AD cohort compared with subjects without AD (age- and sex-adjusted IRR 1.49; 95% CI 1.39–1.61).

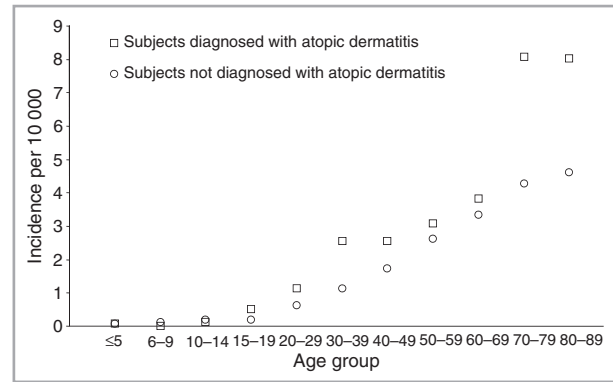
A twofold increase in the risk of lymphoma was observed in subjects with AD compared with subjects without AD (age- and sex-adjusted IRR 2.21; 95% CI 1.65–2.98). If there were no other confounding factors to explain the association obtained, it would corroborate findings from some previous studies that reported an association of AD and an increased risk of lymphoma.<sup>8,18–20</sup> Söderberg *et al.*<sup>8</sup> found an association between 'eczema' during childhood and non-Hodgkin lymphoma (NHL) in adulthood yielding a relative risk (RR) of 2.3 (95% CI 1.0–5.3). Zhang *et al.*<sup>18</sup> found an increased odds ratio (OR) of T-cell NHL among patients with eczema (OR 2.5; 95% CI 1.1–5.7). Doody *et al.*<sup>19</sup> also found that eczema may be associated with NHL in a case-control study in the U.S.A. (OR 1.9; 95% CI 0.6–5.8), and finally, Cartwright *et al.*<sup>20</sup> observed an increase in the risk of NHL among patients with confirmed eczema dermatitis in a hospital-based case-control study in the U.K. (OR 1.6; 95% CI 1.1–2.4). On the other hand, two studies in the general population of the U.S.A. and France failed to detect an increase in the risk of NHL among patients with eczema: Bernstein and Ronald<sup>21</sup> in the U.S.A. found an OR of 0.6 (95% CI 0.4–1.0) and Fabbro-Peray *et al.*<sup>22</sup> in France an OR of 0.5 (95% CI 0.3–0.7). Both studies share a sensitive definition of eczema, which comprised any type of eczema including self-reported eczema. In our study, the definition of AD was specific rather than sensitive, and true differences in the incidence of lymphoma were more likely to become apparent.

For NMSC we also found an increased risk in patients with AD (age- and sex-adjusted IRR 1.46; 95% CI 1.27–1.69). In the Swedish study by Hagströmer *et al.*<sup>16</sup> the risk for NMSC seemed to be increased in patients with AD (SIR 1.5; 95% CI 0.8–2.6). Olesen *et al.*<sup>17</sup> found that half the excess cases of cancer found were keratinocyte carcinomas, which could be a

**Table 4** Incidence of melanoma skin cancer in the general U.K. population (incidence rates as cases per 10 000 persons-years)

| Age group (years) | Overall         |               |                      |           | Patients with AD |               |                      |            | Patients without AD |               |                      |           |
|-------------------|-----------------|---------------|----------------------|-----------|------------------|---------------|----------------------|------------|---------------------|---------------|----------------------|-----------|
|                   | Number of cases | Patient-years | Incidence per 10 000 | 95% CI    | Number of cases  | Patient-years | Incidence per 10 000 | 95% CI     | Number of cases     | Patient-years | Incidence per 10 000 | 95% CI    |
| ≤5                | 12              | 1 817 731     | 0.07                 | 0.03–0.11 | 0                | 47 448        | 0                    | 0–0.78     | 12                  | 1 770 283     | 0.07                 | 0.04–0.12 |
| 6–9               | 19              | 1 927 738     | 0.10                 | 0.06–0.15 | 0                | 40 973        | 0                    | 0–0.90     | 19                  | 1 886 814     | 0.10                 | 0.06–0.16 |
| 10–14             | 33              | 1 820 285     | 0.18                 | 0.13–0.25 | 0                | 21 856        | 0                    | 0–1.69     | 33                  | 1 798 428     | 0.18                 | 0.13–0.26 |
| 15–19             | 34              | 1 657 851     | 0.21                 | 0.14–0.29 | 1                | 13 793        | 0.72                 | 0.02–4.04  | 33                  | 1 644 058     | 0.20                 | 0.14–0.28 |
| 20–29             | 263             | 4 148 733     | 0.63                 | 0.56–0.72 | 2                | 20 775        | 0.96                 | 0.12–3.48  | 261                 | 4 127 958     | 0.63                 | 0.56–0.71 |
| 30–39             | 583             | 4 970 624     | 1.17                 | 1.08–1.27 | 6                | 20 116        | 2.98                 | 1.10–6.49  | 577                 | 4 950 508     | 1.17                 | 1.07–1.27 |
| 40–49             | 777             | 4 492 824     | 1.73                 | 1.61–1.86 | 4                | 14 536        | 2.75                 | 0.75–7.05  | 773                 | 4 478 288     | 1.73                 | 1.61–1.85 |
| 50–59             | 1015            | 3 857 958     | 2.63                 | 2.47–2.80 | 4                | 11 773        | 3.40                 | 0.93–8.70  | 1011                | 3 846 185     | 2.63                 | 2.47–2.80 |
| 60–69             | 1021            | 3 046 443     | 3.35                 | 3.15–3.56 | 4                | 10 062        | 3.98                 | 1.08–10.18 | 1017                | 3 036 381     | 3.35                 | 3.15–3.56 |
| 70–79             | 1009            | 2 321 538     | 4.35                 | 4.08–4.62 | 10               | 8302          | 12.04                | 5.78–22.14 | 999                 | 2 313 236     | 4.32                 | 4.06–4.60 |
| 80–89             | 609             | 1 311 890     | 4.64                 | 4.28–5.03 | 5                | 5152          | 9.71                 | 3.15–22.63 | 604                 | 1 306 738     | 4.62                 | 4.26–5.01 |
| Total             | 5375            | 31 373 614    | 1.71                 | 1.67–1.76 | 36               | 214 737       | 1.68                 | 1.17–2.32  | 5339                | 31 158 877    | 1.71                 | 1.67–1.76 |
|                   |                 |               |                      |           |                  |               |                      |            |                     |               | 0.98                 | 0.68–1.36 |

AD, atopic dermatitis; CI, confidence interval; IRR, incidence rate ratio of patients with AD vs. patients without AD.

**Fig 4.** Incidence rates of melanoma in patients with and without atopic dermatitis.

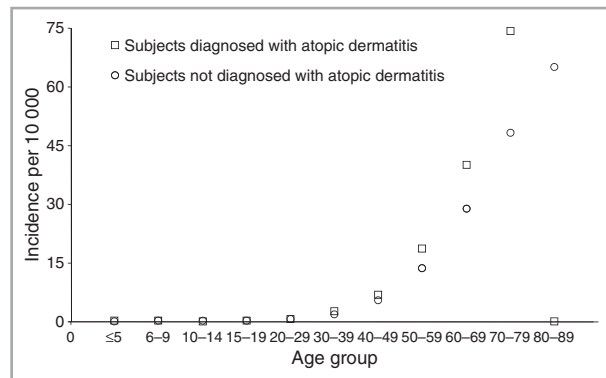
result of a detection bias or due to the carcinogenic potentials of some of the treatments of severe AD. The Finnish Adult Twin Cohort study showed that female subjects with a history of AD tended to be more likely to develop basal cell carcinoma (OR 1.8; 95% CI 0.8–3.9), but this was not seen in male individuals (OR 1.1; 95% CI 0.5–2.6).<sup>23</sup> Other authors have reported no association between NMSC and AD.<sup>9,24,25</sup> However, these were automated database studies and NMSC is known to be frequently under-reported<sup>26</sup> in many databases. Given that patients with AD are more likely to seek medical attention and have their skin examined more frequently, it is possible that NMSC cases would be preferentially diagnosed in the AD group.<sup>17</sup> The mean follow-up time in patients with AD was 3.16 years, and it is possible that in some cases the symptoms of an incipient skin cancer led to the diagnosis of AD, and eventually to the detection of NMSC. This potential bias and the detected association require further confirmation in other studies of the possible association between AD and NMSC found in this study.

The higher incidence of melanoma observed in the AD cohort (age- and sex-adjusted IRR 1.74; 95% CI 1.25–2.41) was surprising given that AD has been associated with a decrease in the number of melanocytic naevi,<sup>27,28</sup> although the studies were based on small sample sizes. In addition, other studies have not reported an increased risk of malignant melanoma (SIR 0.6; 95% CI 0.3–1.2).<sup>16</sup> Likewise, in a hospital-based case-control study on melanoma and atopy<sup>29</sup> it was reported that three subjects had pure eczema among 331 melanoma cases vs. 11 with eczema (seven pure eczema, three with eczema and rhinitis, and one with eczema, rhinitis and asthma) among 380 controls. The possible under-reporting of NMSC common to databases does not extrapolate to melanoma and the diagnosis of melanoma in THIN is sufficiently accurate for research.<sup>30</sup> However, our analysis only controlled for sex and age. It is possible that other determinants of melanoma (e.g. skin type, eye/hair colour, history of sunburn, family history of melanoma, geographical region or socioeconomic status, which are either recorded incompletely or not at all in THIN) were present more frequently in the AD subgroup. Another possible expla-

**Table 5** Incidence of nonmelanoma skin cancer in the general U.K. population (incidence rates as cases per 10 000 persons-years)

| Age group (years) | Overall         |               |                      |             | Patients with AD |               |                      |              | Patients without AD |               |                      |             |
|-------------------|-----------------|---------------|----------------------|-------------|------------------|---------------|----------------------|--------------|---------------------|---------------|----------------------|-------------|
|                   | Number of cases | Patient-years | Incidence per 10 000 | 95% CI      | Number of cases  | Patient-years | Incidence per 10 000 | 95% CI       | Number of cases     | Patient-years | Incidence per 10 000 | 95% CI      |
| ≤5                | 17              | 1 817 714     | 0.09                 | 0.05–0.15   | 0                | 47 448        | 0                    | 0.0–0.78     | 17                  | 1 770 266     | 0.10                 | 0.06–0.15   |
| 6–9               | 33              | 1 927 673     | 0.17                 | 0.12–0.24   | 1                | 40 914        | 0.24                 | 0.01–1.36    | 32                  | 1 886 759     | 0.17                 | 0.12–0.24   |
| 10–14             | 25              | 1 820 217     | 0.14                 | 0.09–0.20   | 0                | 21 849        | 0.00                 | 0.0–1.69     | 25                  | 1 798 368     | 0.14                 | 0.09–0.21   |
| 15–19             | 25              | 1 657 804     | 0.15                 | 0.10–0.22   | 0                | 13 791        | 0.00                 | 0.0–2.67     | 25                  | 1 644 013     | 0.15                 | 0.10–0.22   |
| 20–29             | 227             | 4 148 767     | 0.55                 | 0.48–0.62   | 1                | 20 785        | 0.48                 | 0.01–2.68    | 226                 | 4 127 981     | 0.55                 | 0.48–0.62   |
| 30–39             | 884             | 4 969 895     | 1.78                 | 1.66–1.90   | 4                | 20 139        | 1.99                 | 0.54–5.08    | 880                 | 4 949 756     | 1.78                 | 1.66–1.90   |
| 40–49             | 2477            | 4 484 613     | 5.52                 | 5.31–5.75   | 10               | 14 516        | 6.89                 | 3.30–12.67   | 2467                | 4 470 097     | 5.52                 | 5.30–5.74   |
| 50–59             | 5235            | 3 830 823     | 13.67                | 13.30–14.04 | 20               | 11 642        | 17.18                | 10.50–26.52  | 5215                | 3 819 181     | 13.65                | 13.28–14.03 |
| 60–69             | 8676            | 2 991 541     | 29.00                | 28.40–29.62 | 45               | 9760          | 46.11                | 33.65–61.65  | 8631                | 2 981 781     | 28.95                | 28.34–29.56 |
| 70–79             | 10 896          | 2 237 427     | 48.70                | 47.79–49.62 | 61               | 7826          | 77.95                | 59.67–100.01 | 10 835              | 2 229 601     | 48.60                | 47.69–49.52 |
| 80–89             | 8089            | 1 225 873     | 65.99                | 64.56–67.44 | 45               | 4600          | 97.82                | 71.44–130.68 | 8044                | 1 221 272     | 65.87                | 64.44–67.32 |
| Total             | 36 584          | 31 112 346    | 11.76                | 11.64–11.88 | 187              | 213 270       | 8.77                 | 7.56–10.12   | 36 397              | 30 899 076    | 11.78                | 11.66–11.90 |

AD, atopic dermatitis; CI, confidence interval; IRR, incidence rate ratio of patients with AD vs. patients without AD.

**Fig 5.** Incidence rates of nonmelanoma skin cancer in patients with and without atopic dermatitis.

nation for this association is the surveillance bias mentioned above (patients with AD having their skin examined more frequently than patients without AD and therefore having a higher chance of being diagnosed with melanoma). Alternatively it could be that AD indeed increases the risk of melanoma. This possible association between AD and melanoma should be explored in further analytical studies with full control of risk factors for melanoma, and validation of the diagnosis of melanoma.

Like any other study this one has its limitations. Patients with AD were identified either by the presence of at least two correlative codes of AD, or by the presence of AD codes entered by a specialist. The specificity of this diagnostic method was close to 100%, and we feel confident that the incidences of cancer reported for the AD cohort would represent that of patients with AD. The sensitivity of this algorithm was low (42%) and the relative risks comparing the AD cohort with the non-AD cohort will be slightly closer to the null value as the non-AD population will contain a small proportion, approximately 2% of true AD patients not identified as AD by the algorithm. [If the 66 258 patients with AD identified represent 42% of the total patients with AD, then the total number of patients with AD is  $66\,258 \times (100/42) = 157\,757$ . Of those, 66 258 have been identified with AD in the study, and  $157\,757 - 66\,258 = 91\,499$  were considered non-AD patients. These 91 499 patients represent 2% of 4 389 750 total non-AD patients studied.] We have not addressed the effect of severity of AD in this study. This is partly due to the fact that there is not a specific Read code in THIN that classifies AD according to disease severity. Although proxies have been used in other studies to identify patients with possibly severe underlying AD (e.g. to classify patients referred to a dermatologist as those with severe AD, or those with at least four physician visits for AD per year),<sup>31,32</sup> we did not rely on them for this descriptive study. Also, the study did not have any information on the duration of AD diagnoses. We did not validate the cases of cancer, although a recent study yielded very high positive predictive values, at least for lymphoma.<sup>32</sup>

Although in a study like this, residual confounding cannot be excluded with certainty, in conclusion, we found an increased risk of overall cancer in patients with AD compared with patients without AD. There was a clear increase in the risk of lymphoma in patients with AD. The increased risk of melanoma and NMSC that we found needs confirmation from other studies that allow controlling for risk factors other than age and sex and ensure complete ascertainment of cases. Further studies are needed to disentangle the effects of treatment for AD from AD itself.

### What's already known about this topic?

- Atopic dermatitis is associated with an increased risk of lymphoma.

### What does this study add?

- This study reports the incidence rate of cancer (general and some specific cancers) in patients with atopic dermatitis and the general population.

## References

- Fleming S, Bodner C, Devereaux G *et al.* An application of the United Kingdom working party diagnostic criteria for atopic dermatitis in Scottish infants. *J Invest Dermatol* 2001; **117**:1526–30.
- Williams H, Robertson C, Stewart A *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol* 1999; **103**:125–38.
- McWhorter WP. Allergy and risk of cancer. A prospective study using NHANES I followup data. *Cancer* 1988; **62**:451–5.
- Sverson RK, Davis S, Thomas DB *et al.* Acute myelocytic leukemia and prior allergies. *J Clin Epidemiol* 1989; **42**:995–1001.
- Eriksson NE, Holmén A, Högsted A *et al.* A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995; **50**:718–22.
- Talbot-Smith A, Fritschi L, Divitini ML *et al.* Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. *Am J Epidemiol* 2003; **157**:606–12.
- Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. *Am J Epidemiol* 2003; **158**:316–27.
- Söderberg KC, Hagmar L, Schwartzbaum J, Feychting M. Allergic conditions and risk of hematological malignancies in adults: a cohort study. *BMC Public Health* 2004; **4**:51.
- Ming ME, Levy R, Hoffstad MA *et al.* The lack of relationship between atopic dermatitis and nonmelanoma skin cancers. *J Am Acad Dermatol* 2004; **50**:357–62.
- Wang H, Diepgen PL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006; **154**:205–10.
- Lewis JD, Schinnar R, Bilker QB *et al.* Validation studies of the health improvement network (THIN) database for pharmaco-epidemiology research. *Pharmacoepidemiol Drug Saf* 2007; **16**:393–401.
- Rothman KJ. *Epidemiology, an Introduction*. New York: Oxford University Press, 2002.
- Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide*. IARC Cancer Base no. 5, version 2.0. Lyon: IARC Press, 2004.
- Hall HI, Jamison P, Fulton JP *et al.* Reporting of cutaneous melanoma to cancer registries in the United States. *J Am Acad Dermatol* 2003; **49**:624–30.
- Koh HK, Clapp RW, Barnett JM *et al.* Systemic underreporting of cutaneous malignant melanoma in Massachusetts. Possible implications for national incidence figures. *J Am Acad Dermatol* 1991; **24**:545–50.
- Hagströmer L, Ye W, Nyrén O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. *Arch Dermatol* 2005; **141**:1123–7.
- 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**:445–9.
- Zhang Y, Holford TR, Leaderer B *et al.* Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 2004; **15**:419–28.
- Doody MM, Linet MS, Glass AG *et al.* Leukemia, lymphoma, and multiple myeloma following selected medical conditions. *Cancer Causes Control* 1992; **3**:449–56.
- Cartwright RA, McKinney PA, O'Brien C *et al.* Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res* 1988; **12**:81–8.
- Bernstein L, Ronald RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. *Cancer Res* 1992; **52**:S5510–15.
- Fabbro-Peray P, Daures JP, Rossi JF. Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control* 2001; **12**:201–12.
- 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.
- Naylor M, Elmets C, Jaracz E, Rico JM. Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus. *J Dermatolog Treat* 2005; **16**:149–53.
- Margolis DJ, Hoffstad O, Bilker W. Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults. *Dermatology* 2007; **214**:289–95.
- Schrijvers CTM, Stronks K, van de Mheen DH *et al.* Validation of cancer prevalence data from a postal survey by comparison with cancer registry records. *Am J Epidemiol* 1994; **139**:408–14.
- Broberg A, Augustsson A. Atopic dermatitis and melanocytic naevi. *Br J Dermatol* 2000; **142**:306–9.
- Synnerstad I, Nilsson L, Fredrikson F, Rosdahl I. Fewer melanocytic nevi found in children with active atopic dermatitis than in children without dermatitis. *Arch Dermatol* 2004; **140**:1471–5.
- Kölmel KF, Compagnone D. Melanom und Atopie. *Dtsch Med Wochenschr* 1988; **113**:169–71.
- Meal A, Leonardi-Bee J, Smith C *et al.* Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care* 2008; **16**:49–52.
- Arellano FM, Wentworth CEW, Arana A *et al.* Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; **127**:808–16.
- Arellano FM, Arana A, Wentworth CEW *et al.* Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. *J Allergy Clin Immunol* 2009; **123**:1111–16.