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The potential for malignancy from atopic disorders and allergic inflammation: A systematic review and meta-analysis

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Abstract

Objective: While chronic inflammation is a well-established risk factor for malignancy, studies evaluating the relationship between allergic inflammation and cancer have revealed conflicting results. Here, we aimed to assess the association between allergic inflammation in the lung (asthma), skin (eczema) or esophagus (eosinophilic esophagitis; EoE) and cancer at the organ site.

Design: We conducted a systematic review of the literature to identify observational studies (case-control, cohort, and cross-sectional) evaluating the association between asthma and lung cancer, eczema and skin cancer, or EoE and esophageal cancer. Random-effects meta-analysis was performed to define pooled estimates of effects.

Data sources: PubMED, EMBASE, and Web of Science

Eligibility criteria for selection: Included studies evaluated the incidence of cancer.

Results: Thirty-two studies met the inclusion criteria, 27 in the lung, 4 in the skin, and 1 in the esophagus. Metanalysis of the 3 studies with prospective data collection of asthma diagnosis revealed a positive association with incident lung cancer (OR 1.27, 95% CI 1.09–1.44); however,

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this result was not consistently supported by the larger dataset of retrospective studies (OR 1.37, 95%CI 0.90–1.83). Overall, studies in the lung displayed significant heterogeneity (I^2 98%, p<0.0001), but no significant effect-modification on the association between asthma and lung cancer was identified for the variables of sex, smoking, or study design. Meta-analysis could not be applied to the 4 papers reviewed in the skin, but 3 suggested an association between eczema and non-melanoma skin cancer, while the remaining study failed to identify an association between melanoma and eczema. A single study meeting inclusion criteria showed no association between EoE and esophageal malignancy.

Conclusions: The current data cannot exclude the possibility of an association between atopy and malignancy the lung, skin and esophagus. The relationship between allergy and cancer should be explored further in prospective studies that any association identified between these conditions has the potential for significant public health implications

Systematic review registration: PROSPERO registration CRD42018092447

INTRODUCTION

Allergic disease is increasing in incidence world-wide and may manifest in different organs, including the lung, skin, and gastrointestinal tract[1,2]. Asthma, eczema, and eosinophilic esophagitis (EoE) cause chronic allergic inflammation of the lungs, skin, and esophagus, respectively. Allergic inflammation differs from autoimmune and infectious inflammation in that it tends to be driven by a T-helper 2 predominant inflammatory response (with interleukin 4, 5, 13) and an eosinophil and mast cell predominance. While clinicians strive to identify and mitigate antigen exposures, and provide therapeutic interventions where necessary, the efficacy of such approaches are variable. As a result, atopic patients often experience long-standing inflammation. These challenges underscore the importance of understanding the natural history of allergic diseases and how they may influence tissue biology.

Chronic inflammation is a well-established risk factor for malignancy across tissue types. Mechanisms through which a persistent inflammatory microenvironment facilitates tumorigenesis include increased cell turnover, free radical production, diminished DNA repair capacity and stromal activation[3]. In the gastrointestinal tract alone, ulcerative colitis has been associated with colon cancer, pancreatitis with pancreatic cancer, and gastroesophageal reflux disease with esophageal adenocarcinoma[4,5]. Despite this paradigm of chronic inflammation as a tumor promoter, various studies have demonstrated a negative association between allergic inflammation and cancer risk, with enhanced immunosurveillance and activation of cellular protective mechanisms (e.g. apoptosis, senescence) suggested as proposed mechanisms through which malignant transformation is limited in atopic tissues[6,7]. Additionally, allergic inflammation may be eosinophil-predominant, compared to other forms of chronic inflammation which are either mixed or neutrophil-predominant. The risk of allergic inflammation on cancer risk is not well established.

To assess the relationship between atopy and incidence of cancer specifically in the tissue in which allergic inflammation occurs, we performed a systematic review of literature

analyzing history of allergic conditions affecting the lung (asthma), skin (eczema) or esophagus (eosinophilic esophagitis; EoE) and incidence of malignancy in those organs. While few data exist regarding the risk of skin cancer and esophageal cancer in patients with eczema and EoE, respectively, there is a breadth of literature regarding the association between asthma and lung cancer. We, therefore, performed meta-analysis of relevant publications, overall and also individually in retrospective and prospective studies, to synthesize the evidence for a relationship between asthma and lung cancer.

METHODS

Design

We conducted a systematic review of the literature to assess whether organ specific atopy is associated with malignancy (PROSPERO registration CRD42018092447). The data have been reported according to the PRISMA guidelines for systematic review and meta-analyses (Supplemental Figure S1).

Literature Search

PubMED, EMBASE, and Web of Science databases were systematically searched with the assistance of a library scientist using key words and MeSH terms for each organ (e.g. eosinophilic esophagitis AND esophageal cancer). Included studies were English language, case-control, cohort, and cross-sectional design studies. The final literature search was performed on 26 January 2018.

Study Selection

Primary exposures for each key question were the allergic conditions asthma, atopic dermatitis, and EoE. Primary outcomes were incident lung cancer, skin cancer, and esophageal cancer, respectively. Diagnoses were accepted as presented in the original studies. Studies focused on populations at elevated cancer risk from non-tobacco toxin exposure (e.g. asbestos, coal) were excluded. Studies that failed to separate the allergic condition exposure in question from other comorbidities were excluded (e.g. co-association of asthma and hay fever with lung cancer). Studies that evaluated only cancer mortality (without separating cancer incidence) were excluded.

Two authors (ABM, KW) independently reviewed all abstracts to determine whether the study met study inclusion criteria. Differences were resolved by discussion and any disagreement was resolved by consulting additional reviewers (ESD, ETJ), who made the final decision. Full texts of all studies selected were obtained for data extraction.

Data Extraction

Two authors (ABM, KW) independently extracted data from full text articles. Details of the studies were documented in a standardized table, including the following data elements: first author, year, study design, sample size(s), measure obtained (e.g. odds ratio, hazard ration, relative risk), effect estimates, and potential for bias, including possible confounding factors.

Risk of Bias Assessment

Quality assessment of all eligible articles was done by two authors (ABM, KW), with any differences discussed and resolved with a third author (MD). Study quality was assessed using the NIH National Heart, Lung, and Blood Institute Quality Assessment Tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Case control and cohort modules were utilized where appropriate.

Statistical Analyses

For comparisons where two or more studies reported a similar outcome and an odds ratio could be calculated from each, we estimated a pooled odds ratio using random-effects meta-analysis, according to the inverse-variance weighted method[8]. For studies that only reported a standardized incidence ratio (SIR), we used the SIR to impute numbers of subjects with and without the outcome in question from a comparison group of equal size, allowing combination with other studies in a pooled odds ratio. The main analyses pooled adjusted odds ratios from each study, when these were provided. We also performed sensitivity analyses pooling the raw numbers from each study. The meta-analysis only examined odds ratios, either reported or calculated, but did not pool odds ratios with other measures (such as hazard or risk ratio). Primary analyses considered only those study estimates that accounted for latency of lung cancer diagnosis (excluding asthma diagnoses reported within 1–5 years of cancer diagnosis), to reduce protopathic bias due to misattribution of early pulmonary symptoms, A sensitivity analysis included all estimates extracted irrespective of whether the cancer diagnosis was made within 1–5 years of the diagnosis of the allergic disease. We assessed between-study heterogeneity visually using forest plots and quantitatively with the I-squared (I^2) statistic, which is the percentage of total variance from between-study rather than within-study variance[9]. For each pooled effect, we estimated 95% confidence and predictive intervals, representing the confidence interval for the mean of the random-effects distribution and the range within which 95% of future study effects are predicted to fall, respectively[10]. To explore causes of heterogeneity, we performed subgroup analyses according to study characteristics including sex, smoking status, study design, risk of bias, and year of publication, when there were at least two studies in each subgroup. Specifically, we separated studies with data collected prospectively versus retrospectively when this affected the summary estimate. For asthma, where there were >10 studies assessing asthma in relation to lung cancer, funnel plots were examined visually for asymmetry suggestive of small-study effects (such as publication bias), supplemented with quantification by the Egger test[11]. If publication bias was detected, the “trim-and-fill” method was used to determine a random-effects summary estimate adjusted for publication bias[12]. All analyses were performed in STATA 14.2 (StataCorp, College Station, TX), with a significance threshold of a 2-sided $p<0.05$.

RESULTS

Literature Search Results

Our initial literature search identified 3929 records. After excluding duplicates and studies that did not meet the defined inclusion criteria, 92 articles were subjected to full-text review,

identifying 32 relevant studies: 27 in the lung, 4 in the skin, and 1 in the esophagus (Figure 1; Table 1–2).

Asthma and incidence of lung cancer

Twenty-seven studies of 939,248 unique asthmatic subjects examined the association of asthma with lung cancer incidence, and were pooled using random-effects meta-analysis (Table 1). The majority of the studies (22) were case-control studies, and only 3 studies collected data prospectively[13–15]. Asthma was associated with increased odds of incident lung cancer, but this was not statistically significant overall (OR 1.34, 95%CI 0.93–1.76, Figure 2) or in the subgroup of studies with retrospective data collection of asthma diagnosis (OR 1.37, 95%CI 0.90–1.83). The pooled estimate from the 3 prospective studies was significant due to less heterogeneity resulting in narrower confidence intervals, though with similar magnitude (OR 1.27, 95% CI 1.09–1.44). Heterogeneity resulted in a 95% predictive interval spanning the null in all analyses however. Indeed, 15 of the 26 studies had confidence intervals either spanning the null[13,14,16–26,26] or with a significant inverse association[27]. When restricting the analysis to studies that reported adjusted odds ratios (AORs), the magnitude of the association attenuated slightly and results were less heterogeneous (OR 1.19, 95% CI 0.99–1.38, I^2 47%, Supplemental Figure S2). The associations were very similar for a variety of sensitivity analyses, including analyses pooling raw numbers of patients rather than aORs (OR 1.38, 95% CI 1.09–1.74, Supplemental Figure S3) as well as analyses emphasizing non-latency-adjusted estimates along with either pooling AORs (OR 1.20, 95% CI 1.04–1.35) or pooling raw numbers of participants (OR 1.40, 95% CI 1.10–1.77) (Supplemental Figures S4, S5). In fact, accounting for latency did not significantly affect overall estimates (p=0.91, Supplemental Figure S4).

In subgroup analyses by patient characteristics, we emphasized meta-analytic estimates derived from raw numbers rather than adjusted odds ratios, since the reported aORs often adjusted for these factors already, by design. No significant effect-modification was found for the effects of sex or smoking on the association between asthma and lung cancer in the main analyses (Figures 3, 4, with sensitivity analyses using pooled aORs in Supplemental Figures S6, S7). For sex, this was true whether stratifying by studies that reported estimates by subgroups (Figure 3), or evaluating the effect of the percentage of male subjects in each study by metaregression (p=0.46). There were a greater number of studies including just women, which led to a very small, but statistically significant association between asthma and lung cancer in pooled estimates for females only, which was not significant in subgroups of only males (Figure 3). The association between asthma and lung cancer was not significantly different by smoking status either, whether stratifying by current smoking status (Figure 4a) or history of ever smoking (Figure 4b), or by metaregression of percentage of never-smokers (p= 0.62). Due to the larger number of smokers, as well as greater cancer incidence in this population, the association between asthma and lung cancer was still observed in the smoking subgroup, but did not meet statistical significance in the subgroup of non-smokers (Figure 4).

The magnitude of the odds ratios was consistent across other sensitivity analyses of study characteristics as well. An analysis removing the four studies where control group numbers were imputed from SIRs [14,28–30] reduced the overall power of the analysis without any change in the magnitude of the effect size (OR 1.32, 95% CI 0.85–1.79). Meta-regression did not reveal any statistically significant effect modification by study design (retrospectively vs prospectively collected data, p= 0.68) or year of publication (p=0.65). Of the 26 studies included in any analysis, 10 were at low risk of bias, 9 at medium, and 7 at high risk of bias (Supplemental Table 1). There was a trend toward lower pooled aORs with decreasing risk of bias, but this was not statistically significant (p=0.10). A sensitivity analysis excluding those studies at high risk of bias somewhat attenuated the magnitude of the estimate, and with less heterogeneity, but with some loss in the precision of the estimate given the reduced sample (OR 1.17, 95% CI 0.99–1.36, Supplemental Figure S8). There was statistically significant funnel plot asymmetry for the entire group of studies in the main analysis (Egger's test p<0.001, Supplemental Figure S9), but (atypically) with smaller studies showing smaller magnitudes of an association between asthma and lung cancer. This suggests the possibility that publication bias or other small-study effects could have biased the results toward the null. The pooled random-effects odds ratio adjusted for publication bias by the trim-and-fill method was 1.39 (95% CI 1.09–1.77, vs OR 1.34 for main effect, above), suggesting the contribution of small study effects was minor.

Eczema and incidence of skin cancer

In the skin, we identified 4 studies evaluating the relationship between eczema and cancer (Table 2). Three of these studies[31–33] reported a positive association between eczema and skin cancer. Olesen et al. identified 16 skin cancers in a cohort study of 2030 adults from Denmark in which the expected incidence was 6.6 (SMR 2.4, 95% CI 1.4–3.9)[31]. Cancers in this cohort were equally distributed between both males and females as well as squamous cell carcinomas (SCC) and basal cell carcinomas (BCC). Increased risk for skin cancer was statistically significant with follow up of 5–9 years, but failed to show statistical significance for cancers diagnosed in the population with >10 years of follow up. In an additional study, Dyer et al. reported a non-statistically significant positive association between history of eczema alone and BCC risk (HRR 1.38, 95% CI; 0.95–2.03; p=0.095)[32]. However, history of eczema was identified as an independent risk factor for developing BCC upon incorporation into a multivariate model adjusting for factors including age, 5-year history of skin cancer, and family history of skin cancer (HRR 1.52, 95% CI 1.01–2.09; p=0.037)[32]. A positive association between eczema and either SCC (OR 1.83, 95% CI 0.97–3.45) or early-onset BCC (OR 1.52, 95% CI 0.77–3.01) was identified by Cheng et al[33]; however, these associations did not reach statistical significance. Upon stratification by sex, men with a history of eczema displayed an increased risk of SCC (OR 3.5, 95% CI 1.33–11.15). By contrast, in women, neither a history of eczema nor allergy was associated with SCC (eczema: OR 0.95, 95% CI 0.35–2.57; allergy: OR 0.59, 95% CI 0.29–1.19). Both men (OR 2.02, 95% CI 0.61–6.72) and women (OR 1.59, 95% CI 0.66–3.80) exhibited a positive, but non-statistically significant association between history of eczema and BCC. Finally, in a cohort consisting of 94 Canadian men, El-Zein found no significant association between history of eczema and melanoma (OR 0.64, 95% CI 0.2–2.2)[18]. Two out of the three studies reporting a positive association between eczema and skin cancer were judged to be at

medium risk of bias and one, Olesen et al., was found to be at a high risk of bias due to failure to evaluate the effect of time or possible confounders, including sun-exposure. Conversely, El-Zein et al. was found to be at medium risk of bias due to failure to assess latency effects.

EoE and risk of esophageal cancer

Our literature search of PubMed, WOS, and Embase revealed one paper that met our inclusion criteria in the esophagus, Syed et al. There were two case series, Lipka et al and Straumann et al, which followed EoE patients for an average of 13.6 and 7.2 years respectively[34,35]. Lipka et al. was a single-center, retrospective case series, reporting no identification of esophageal malignancy via endoscopy in 13 EoE patients followed up over a 13.6-year mean period (range 5–24 years). Additionally, while 50% of EoE patients exhibited Barrett's esophagus, the premalignant precursor to esophageal adenocarcinoma, dysplasia was not detected upon histological review. Straumann et al. prospectively followed 30 adults with EoE for 11.5 years and found that none of these patients developed malignancy.

The study by Syed et al. was a cross-sectional population-based study utilizing an administrative database[36] with over 340 hospitals and 22 major health care systems participating. With over 27 million patients, 0.02% had a diagnosis of EoE. None of these EoE patients had documentation of a diagnosis code for co-morbid esophageal cancer. A limitation of this study was that only 5 years of data were available for these patients, which may not be a long enough time of exposure for malignant transformation.

DISCUSSION

The current study provides a comprehensive evaluation of data regarding asthma, eczema, and EoE, and their association with cancer risk in the affected organ. In contrast to the skin and esophagus, where few studies have been conducted to assess associations between allergy and organ-specific malignancy, numerous case-control and cohort studies have evaluated the association between asthma and cancer in the lung. Meta-analysis of these data revealed an increase in lung cancer risk in asthma patients that was significant when examining 3 studies with prospective collection of asthma diagnosis, but that was not consistently supported when evaluating either retrospective studies alone or the collective dataset. While at these differences with regard to data significance may be a result of decreased heterogeneity in the limited dataset provided by the prospective studies, these findings support the need additional studies with prospective collection of allergy diagnoses to further investigate the relationship between atopy and cancer. Notably, the positive association between asthma and lung cancer risk remained consistent upon sub-analyses for effects of sex and smoking status. Geographic location and distribution of histologic lung cancer subtypes represent two potential sources of heterogeneity among these studies, and there were no studies with eosinophilic or neutrophilic asthma specifically assessed. A limitation of the body of evidence on atopic disease and organ-specific cancer is the potential for bias. In those studies using surveys to ascertain past medical histories from cases and controls,[13–16,18–23,25–27,37–43] there is a potential for recall bias. Additionally, the

temporality of atopic disease state and cancer is difficult to ascertain. Similarly, depending on duration of atopy and treatment efficacy, risk of cancer could differ. Risk of cancer in the setting of inflammatory diseases with cancer predisposition, including pancreatitis, ulcerative colitis and gastroesophageal reflux disease are dependent on disease duration. While not all studies evaluated for duration of illness prior to onset of malignancy, we did make note of this in our systematic review. In the case of asthma, other meta-analyses have shown that increased risk of lung cancer diagnosis in the 2 years following the diagnosis of asthma, and no increase in the population with >10 years of asthma[44]. This may signify ascertainment bias, where lung cancer cases are identified due to increased health care surveillance at the time of asthma diagnosis. Additionally, eosinophilic asthma has been recently identified as an important subtype with different treatment algorithms. The studies we identified did not stratify by peripheral eosinophil count or eosinophilic asthma status, and it would be interesting to determine this risk in this purely allergic subpopulation.

In evaluating the association between eczema and skin cancer, our literature review identified only 4 studies meeting our inclusion criteria, each reporting different combinations of skin cancer subtypes which precluded meta-analysis. Three of these studies identified increased skin cancer risk in eczema patients (two of which were not statistically significant) while the fourth failed to define any association between eczema and melanoma. In the study by Cheng et al., the positive association between eczema and skin cancer was present in both early-onset basal and invasive squamous cell carcinoma while sub-type specific effects were not explored in the two other studies identifying increased cancer risk in eczema patients[33]. The study by El-Zein et al. found no evidence of an association between eczema and melanoma, however, given that other skin cancer types were not evaluated, the potential remains that eczema may differentially influence specific histologic subtypes of skin cancer[18]. Of these 4 studies, only that performed by Olesen et al. included a primary diagnosis of eczema as an inclusion criterion. While this may alleviate concerns of recall bias, it also raises the potential for detection bias, as patients with eczema have an increased likelihood of undergoing clinical skin examinations during which cancer and pre-cancerous lesions may be detected. Importantly, as latency exclusion was not utilized in any of the 4 studies that met inclusion criteria in the skin, there exists the potential for misdiagnosis of eczema occurring close to the time cancer diagnosis. Failure to control for severity of atopic inflammation represented in these 4 studies represents an additional source of heterogeneity. While it is possible that control of atopic dermatitis inflammation could reduce subsequent cancer risk, as is the case for inflammatory conditions such as ulcerative colitis[45], careful consideration must be given with regard to the agents used to alleviate allergic responses as links between several therapies and increased malignancy rates have been identified. For example, calcenurin inhibitors which are used topically to treat eczema have been associated with increased cancer risk in various organs, including the skin[46–48]. Additionally, the FDA has raised concerns regarding increased cancer rates in patients treated the anti-IgE antibody omalizumab. Although several studies failed to validate such concerns[49,50], further investigations are warranted.

While the relationship between EoE and esophageal cancer is only beginning to be explored, such investigations may be particularly valuable for physicians who remain hesitant to treat asymptomatic EoE patients given the high burden of therapy for treatment of EoE[51,52] and

the fact that it is widely believed that EoE does not contribute to increased risk of malignant transformation. Supporting this notion, Lipka and Straumann et al. both failed to detect esophageal malignancy in small (n=30 and 13 respectively) EoE patient cohorts[34,35]. The large cross-sectional population-based study by Syed et al. revealed that in 5,370 EoE patients evaluated, not a single case of esophageal malignancy was documented over a 5-year period[36]. Limitations for these studies include inability to examine sex-specific effects, follow-up periods that are short with regard to cancer development, which occurs over decades, and lack of reporting on the histopathologic subtype of esophageal malignancy being detected. While malignancy was not detected in EoE patients in the three studies described herein, eosinophils have been detected in esophageal cancer lesions[53,54], and patients with esophageal cancer often present with symptoms that are prevalent in EoE, including dysphagia[55]. Given that EoE has only been characterized as distinct disease entity in the past two decades, it is possible that undiagnosed EoE cases may have influenced carcinogenesis in the esophagus. Several studies have reported esophageal granular cell tumors in EoE patients[56,57]; however, such reports were excluded from the current analysis as these lesions are generally benign and of neuroendocrine origin. Nevertheless, the relationship between EoE and granular cell tumors would merit future assessment to determine if there is a true association or if it is incidental.

The strengths of the current study included its rigorous systematic review methods conforming to current guidelines, and its large sample size with nearly 1 million cases of lung cancer evaluated, allowing for evaluation of both smoking and sex differences within the studies. There were limitations in our ability to fully understand allergic inflammation and cancer risk in the skin and esophagus due to lack of studies in this area. There is a great need to further understand the consequences of long-term eosinophilic inflammation in the esophagus. EoE diagnosis is often delayed[58] and treatment response rates are low, therefore many patients experience ongoing inflammation despite attempts at therapy[59]. Recently developed *in vitro* and *ex vivo* tissue engineering strategies, such as esophageal organoids, offer the unique ability to culture differentiated esophageal epithelia with eosinophils for prolonged periods[60,61]. These experiments may provide further better understanding of the mucosal stress responses and the evolution of carcinogenesis in the esophagus.

As allergic disorders increase in incidence, it is important that we consider the long-term effects of allergic inflammation. The current study indicates some weak associations between allergic inflammation (e.g. asthma and eczema) and carcinogenesis within the organ in which they occur; however, heterogeneity and potential for confounding in the available literature preclude firm conclusions on the presence of such associations. This review highlights the need for future prospective cohort studies, with careful consideration for duration of allergic disease, type of inflammation, medication usage, success of treatment and disease activity control, and well-defined outcomes related to malignancy to elucidate the clinical impact of the complex interplay between chronic inflammation and carcinogenesis. Such studies will provide population-based data that will inform our understanding of how allergic inflammation influences carcinogenesis and may have critical implications for cancer prevention and therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1. Eosinophilic Esophagitis and Esophageal Cancer
2. Eczema and Skin Cancer
3. Asthma and Lung Cancer

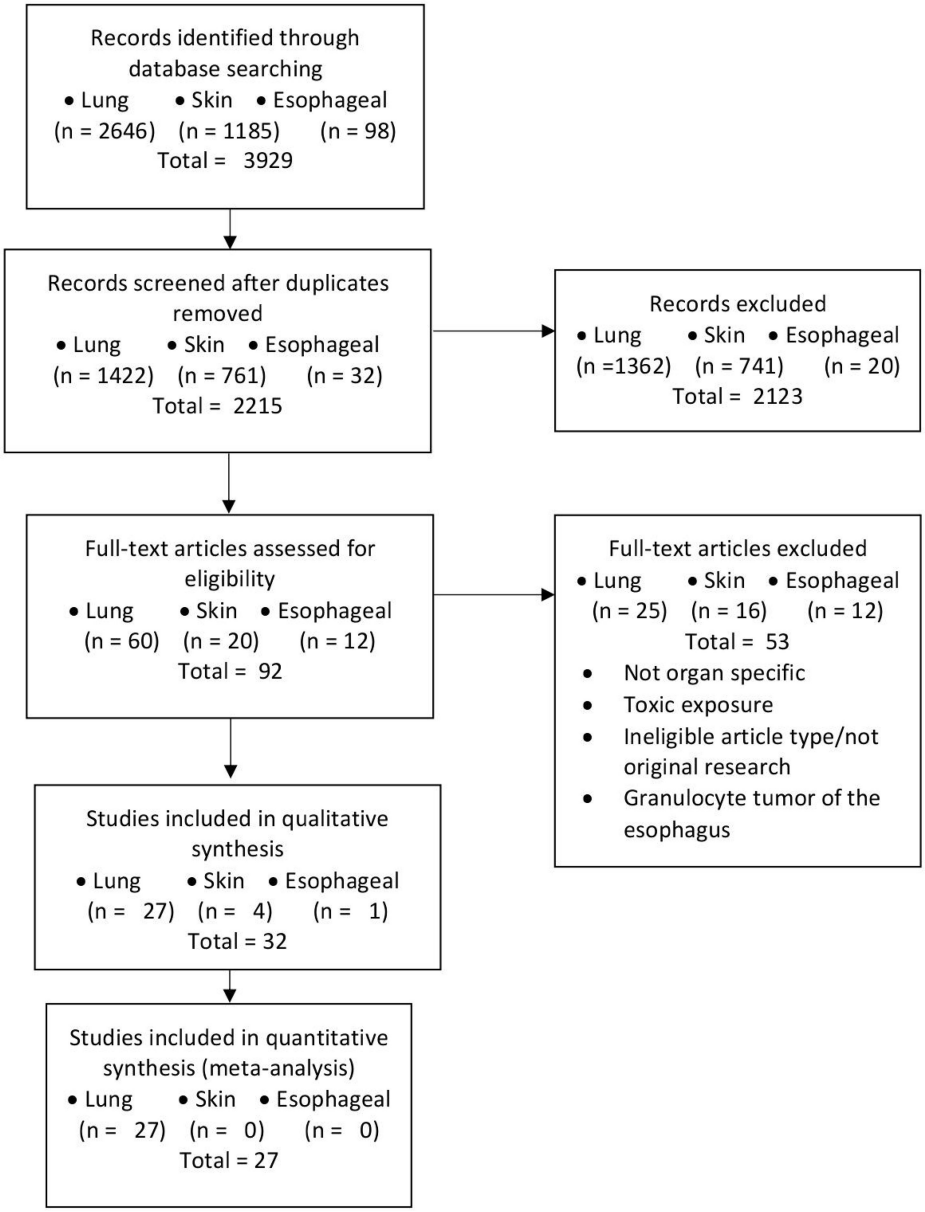

Figure 1:
Flow chart of searches performed.

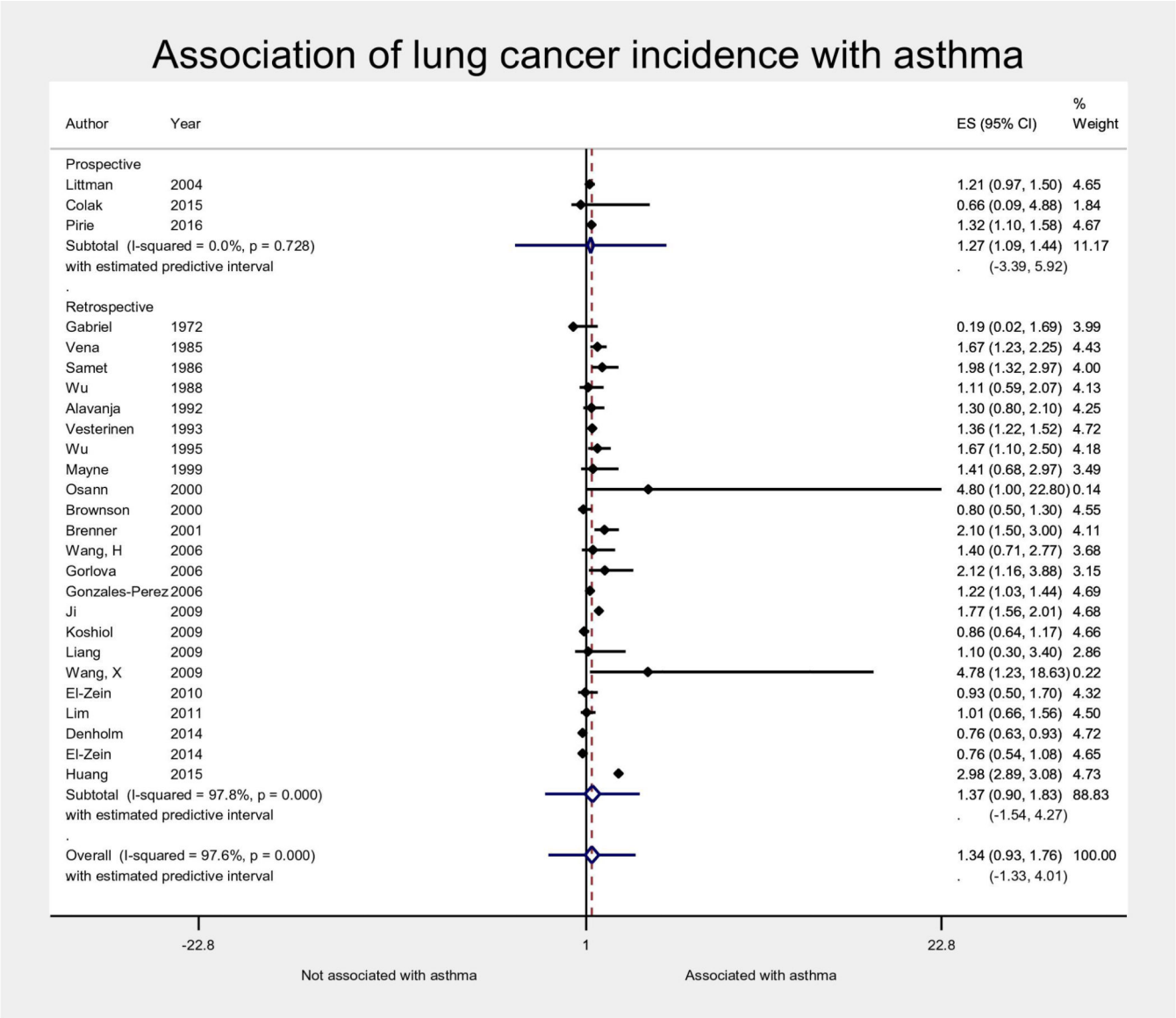

Figure 2:

Random-effects meta-analysis of association of lung cancer incidence and asthma, with 95% confidence interval (diamond) and estimated predictive interval (lines extending on either side of diamond). Forest plot is stratified by study design. Adjusted odds ratios were used if provided by original study, and otherwise calculated from raw numbers of the original study (and therefore crude, unadjusted). Estimates that accounted for latency between asthma and lung cancer diagnosis were selected when available. ES, estimate (here, adjusted odds ratio); CI, confidence interval.

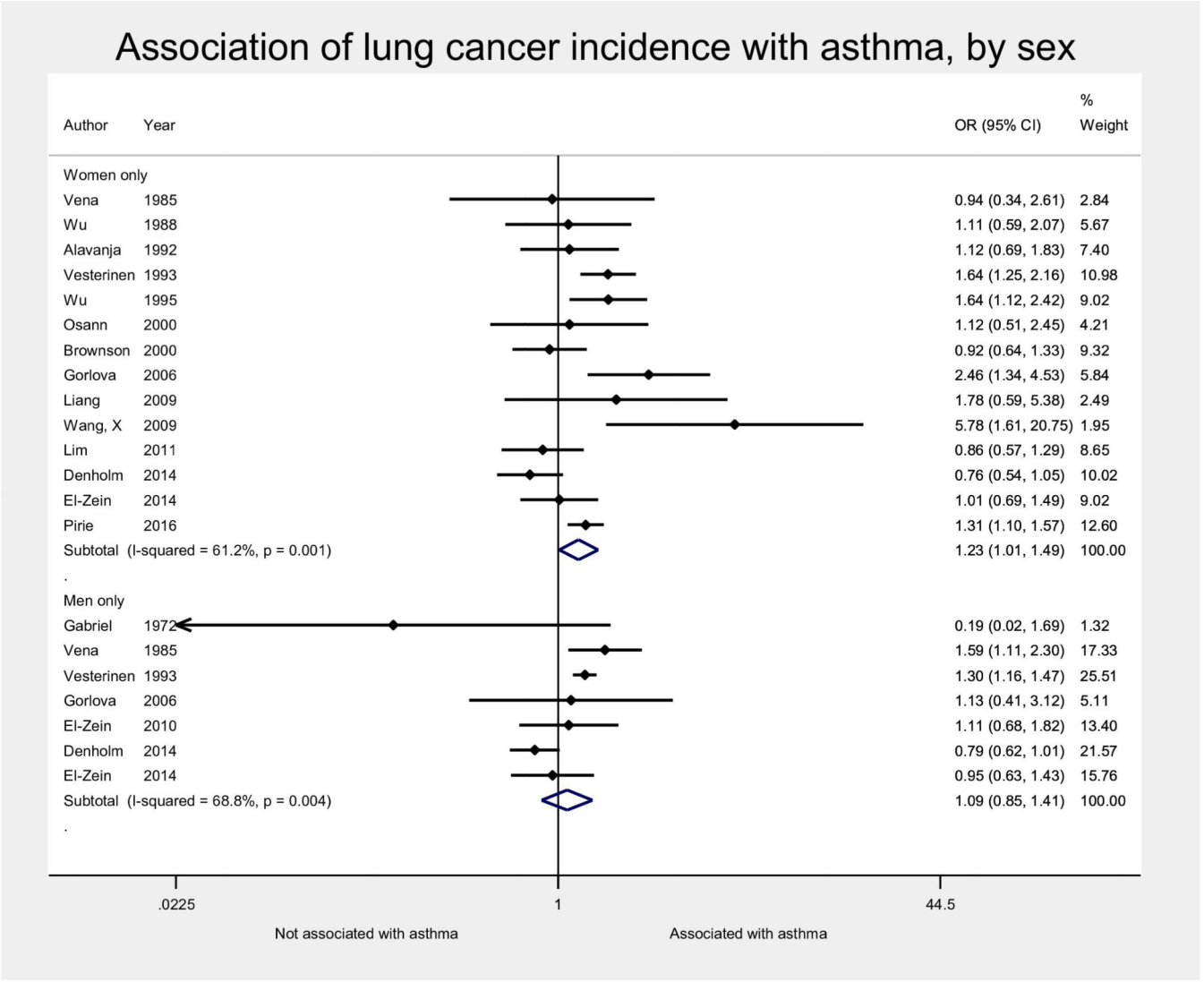

Figure 3:

Random-effects meta-analysis of association of lung cancer incidence and asthma, stratified by sex. The association of asthma with lung cancer was not significantly different by sex (p=0.46). Meta-analytic estimates calculated from raw numbers, given that most adjusted odds ratios already adjusted for sex. Estimates accounting for latency were used when provided. OR, odds ratio; CI, confidence interval.

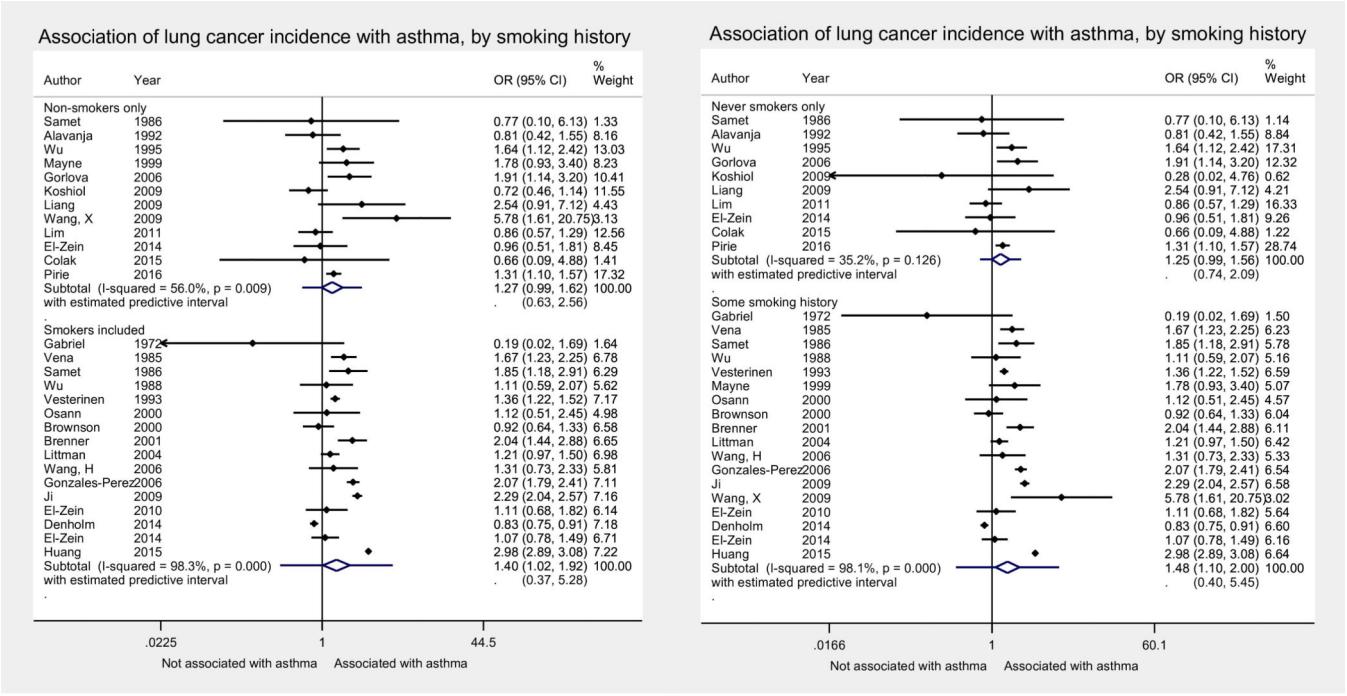

Figure 4:

Random-effects meta-analysis of association of lung cancer incidence and asthma, stratified by inclusion of any current smokers (***A***) or any ever-smokers (***B***). Meta-analytic estimates calculated from raw numbers, given that most adjusted odds ratios already adjusted for smoking. OR, odds ratio; CI, confidence interval.

Table 1:

Characteristics of published studies on asthma and lung cancer

Author	Year	Study Type	Sex (M, F)	Smoking (S, NS, B, U)	Covariates	Latency Considered (Yes/No)	Total	Quality assessment
Alavanja et al	1992	Population-Based Case Control	F	NS	age, education, marital status, drivers status, health care finance registration, smoking history	Yes	2020	Fair
Boffetta et al	2002	Prospective population-based cohort	M, F	U	duration of follow-up, calendar year at entry, age at entry, other diagnoses at index hospitalization, dept of index hospitalization, # of hospitalizations during 1st year of follow up, presence of emphysema, chronic bronchitis, histological type of lung cancer	Yes	92986/std. pop.	Fair
Brenner et al	2001	Population-Based Case Control	M, F	B	active smoking and socioeconomic status	Yes	2651	Good
Brownson et al	2000	Population-Based Case Control	F	B	pack-years of smoking	Yes	1376	Good
Colak et al	2015	Prospective Cohort	M,F	B	age; sex; BMI; allergy; familial predisposition for asthma; childhood asthma, hay fever, or eczema; use of asthma medication; occupational exposure to dust and/or fumes; daily exposure to passive smoking; leisure time physical activity; education; annual household income; and cumulative tobacco consumption, alcohol consumption, systolic and diastolic blood pressure, total cholesterol, LDL, HDL, triglycerides, use of cholesterol-lowering medication, and presence of diabetes	No	94079	Poor
Denholm et al	2014	large international case–control consortium	M,F	B	sex, age, center, ever-employed in a high-risk occupation, education, smoking status, cigarette pack-years, and time since quitting smoking.	Yes	27684	Good
El-Zein et al (and Ramanakumar et al)	2010	Population-Based Case Control	M	B	smoking, asbestos, ancestry, silica- all included in regression models	Yes	1267	Fair
El-Zein et al	2014	Case Control	M,F	B	adjusted for age, sex (except in sex-specific analyses), education, respondent status, ethnocultural origin, fruit and vegetable consumption, and smoking (represented by the comprehensive smoking index). lifetime occupational history; and history of 11 selected medical conditions among which were asthma, allergic eczema and hay fever.	Yes	2655	Good
Gabriel et al	1972	Case control	M	U	allergy: hay fever, eczema, urticaria, food reactions, smoking status	No	300	Poor
Gonzales-Perez et al	2006	Cohort study with nested case control	M,F	B	age, sex, calendar year, BMI, alcohol, smoking, prior comorbidities (cardiovascular disease, diabetes, osteoarthritis/rheumatoid arthritis), health services utilization, use of aspirin, NSAID, paracetamol	Yes	19658	Good
Gorlova et al	2006	Case control	M,F	NS	age, gender, ethnicity, income, years of education	Yes	522	Good
Huang et al (and Jian et al)	2015	Population based cohort	M,F	U	age, gender, low income, lung diseases, comorbidities, urbanization and geographic area	No	15219024	Poor
Ji et al	2009	Longitudinal cohort	M,F		5-year age (person-years calculated from the last hospitalization admission for asthma until diagnosis of cancer, death emigration of closing date), gender, period (5-year group), socioeconomic class, residential area	Yes	140425/std pop	Poor

Author	Year	Study Type	Sex (M, F)	Smoking (S, NS, B, U)	Covariates	Latency Considered (Yes/No)	Total	Quality assessment
Koshiol et al (total)	2009	Population-based case control	M,F	B	smoking, other previous lung diseases, and study design variables	Yes	3523	Good
Liang et al	2009	Case Control	F	NS	age, marital status, years of schooling, ethnicity, 5 years ago BMI, passive smoking exposure, coal fuel use, exposure to coal smoke and cooking fumes, history of mental trauma in last 20 years, lifetime exercise habits, family cancer history in 1st-degree relatives	Yes	505	Fair
Lim et al	2011	Case Control	F	B	age, history of cancer in first-degree relative, fruit and vegetable consumption, country of origin, dialect group, housing type, number of years in school, environmental tobacco exposure at home, environmental tobacco exposure at work and study	No	1808	Fair
Littman et al	2004	Prospective Cohort	M,F	S	sex, and exposure cohort (female; male, in smoker cohort; male, in asbestos-exposed worker cohort), study arm (intervention or placebo), education, BMI, years smoked and years smoked squared, average number of cigarettes smoked per day and average number of cigarettes smoked per day squared, and all other lung diseases, and stratified by smoking status (former or current).	No	17698	Poor
Mayne et al	1999	Population based case-control	M,F	NS	years of schooling, cigarettes per day, lifetime passive smoke exposure, frequency of consumption of fresh fruit and vegetables, whole milk and supplemental vitamin E	Yes	874	Good
Osann et al	2000	Case control	F	B	age, education, smoking	No	302	Fair
Pirie et al	2016	Cohort	F	NS	age, oral contraceptive use, region, deprivation quintile, height	Yes	1.2 million	Good
Samet et al	1986	Case control	M,F	B	tobacco use, residence history, occupational history, diet, passive exposure to tobacco smoke and certain occupational agents, history of respiratory diseases, personal history of physician-diagnosed chronic bronchitis, emphysema, asthma, tuberculosis, and other chest illnesses	No	1314	Poor
Vena et al	1985	Case control	M,F	B	age, smoking, lifetime history of asthma, hay fever, hives, eczema,	Yes	5225	Good
Vesterinen et al	1993	Cohort	M,F	U	age, sex	Yes	77952/std pop	Fair
Wang et al	2009	Population based control	F	B	age, employment, total dish-year, intake of yellow/orange/dark green veggies, intake of multivitamins	Yes	504	Fair
Wang et al	2006	Case control	M,F	B	age, education, BMI, family history of cancer (1st degree), smoking status, alcohol consumption	No	4467	Fair
Wu et al	1995	Case control	F	NS	Adjusted for age, area, ethnicity or adjusted for age, area, ethnicity, education, exposure to tobacco during early life	No	1665	Fair
Wu et al	1988	Case Control	F	B	Pack-years smoking, years since smoking stopped, depth of inhalation, adenocarcinoma	No	672	Poor

Table 2:

Characteristics of published studies on eczema and skin cancer

Author	Year	Study Type	Control	Case	Total	Cancer Type	Covariates	Latency Considered (Yes/No)	Sex (M, F)	Odds Ratio	Confidence Interval	Quality Assessment
Cheng et al	2015	Case control	BCC: 251 SCC: 432	BCC: 375 SCC: 254	1312	Early onset BCC and invasive SCC	age, sex, smoking status, corticosteriod use, immunosuppressant drug use, organ transplantation, ultraviolet radiation therapy, number of lifetime painful sunburns, skin reaction to first hour of summer sun, solar elastosis, actinic keratosis, family history of keratinocyte cancer,recreation outdoors time, mole/freckles history, alcohol consumed per month, coffee/tea consumption, tanning lamp use, history of UV radiation therapy, history of radiation therapy	yes	M,F	BCC: 1.52 SCC: 1.83	BCC: 0.77–3.01 SCC: 0.97–3.45	Fair
Dyer et al	2012	Cohort	1079	52	1131	BCC	sex, age, education, BCCs/SCCs in prior 5 years, family history of skin cancer, history of eczema, smoking status (current/former), sunburn history, Use of 5-FU, ACE/ARB, history of warts, sun sensitivity, latitude of residence history, total occupational decades outdoors in sun history, vacation history, total recreational months, ethnicity of grandparents, days spent outside, sunscreen use	yes	M,F	1.38	0.95–2.03	Fair
El-Zien	2010	Case control	512	94	606	Melanoma	ancestry, sports/outdoor activities	yes	M	0.64	0.2–2.2	Fair
Olesen et al (adults)	2005	Cohort	2014	16	2030	All keratinocyte cancers	N/A	yes	M,F	2.4	1.4–3.9	Poor