Exposure to Trace Elements and Risk of Skin Cancer: A Systematic Review of Epidemiologic Studies

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Abstract

Exposure to environmental trace elements has been studied in relation to many cancers. However, an association between exposure to trace elements and skin cancer remains less understood. Therefore, we conducted a systematic review of published epidemiologic literature examining the association between exposure to trace elements, and risk of melanoma and keratinocyte carcinoma in humans. We identified epidemiologic studies investigating exposure to arsenic, cadmium, chromium, copper, iron, selenium, and zinc and risk of skin cancer in humans. Among the minerals, arsenic, selenium, and zinc had more than five studies available. Exposure to arsenic was associated with increased risk of keratinocyte carcinoma, while too few studies existed on melanoma to draw conclusions. Exposure to selenium was associated with possible increased risk of keratinocyte carcinoma. Studies of zinc and skin cancer were case-control in design and were found to have inconsistent associations. The data on the association between cadmium, chromium, copper, and iron and risk of skin cancer remain too sparse to draw any conclusions. In summary, epidemiologic studies on exposure to trace elements and cutaneous malignancies are limited. Studies with larger sample sizes and prospective designs are warranted to improve our knowledge of trace elements and skin cancer.

Introduction

Keratinocyte carcinoma, including cutaneous basal (BCC) and squamous cell carcinoma (SCC), are the most commonly diagnosed cancers in the United States (1-3). BCCs account for nearly 80% of all keratinocyte carcinomas diagnosed annually (3-5). The remaining 20% of keratinocyte carcinoma cases are mostly SCC (3, 6, 7).

Melanoma is a malignant skin tumor that arises from melanocytes (8). Although melanoma accounts for less than 5% of all cutaneous malignancies, it is the most lethal, representing 75% of all deaths due to skin cancer (1, 9). Overall, melanoma and keratinocyte carcinomas represent a significant economic and disease burden that is projected to continue to increase in the coming years (10).

Trace elements include metals that are widely distributed in the natural environment, as well as in numerous industrial, domestic, and agricultural settings. Concerns regarding exposure to potential health hazards from these metals have prompted extensive research on the subject of metal carcinogenicity (11-13). Chromium, for example, has been associated with increased lung cancer incidence (13). Similarly, arsenic has been linked to increased mortality from bladder and kidney cancers (11). The subject of metal carcinogenicity is one of increasing importance, as it represents a potentially modifiable risk factor. Exposure to trace elements has been implicated in the pathogenesis of skin cancers (11, 14). However, with the exception of arsenic (11), the degree of association and potential underlying mechanisms are still poorly understood.

This review examines existing epidemiologic literature on trace elements and skin cancer risk. These elements include arsenic, cadmium, chromium, copper, iron, selenium, and zinc.

Materials and Methods

Search strategy

We sought to identify epidemiologic studies relevant to the research question: which environmental trace element exposures are associated with skin cancer? Searches were performed in PubMed, Web of Science, and Embase (1972–July 2018) with the terms "melanoma" OR "squamous cell carcinoma" OR "basal cell carcinoma" OR "keratinocyte carcinoma" OR "non-melanoma skin cancer" OR "skin cancer," AND with "metals" OR "trace...
metals’ OR ‘heavy metals’ OR ‘minerals’ OR ‘environmental exposure’ OR ‘occupational exposure.’ From this search, we were able to select metals with existing literature relating to skin cancer. A secondary search included the above terms with ‘arsenic’ OR ‘cadmium’ OR ‘chromium’ OR ‘copper’ OR ‘iron’ OR ‘selenium’ OR ‘zinc’ (presented in Tables 1–5). We also searched aluminum, beryllium, calcium, cobalt, lead, manganese, magnesium, mercury, and nickel given prior published possible associations with other cancers or role in normal skin development, homeostasis, and repair (12, 13, 15–19).

Study selection

Studies reviewed reported exposure to one of the above-mentioned minerals in relation to risk of skin cancer in adult populations. All selected articles were original research, peer-reviewed, published in English, and specifically evaluated exposure to metal directly. If the full text of articles were unavailable, they were acknowledged in the text, but excluded in the tables. Only human epidemiologic studies were included. For example, nickel was excluded from the review since we found only nonhuman studies investigating nickel exposure and skin cancer (20–22). Only studies that explicitly investigated exposure to the mineral itself were included. For example, mercury was excluded from this review because it only has been studied indirectly with regard to occupations with possible exposure and risk of melanoma (23, 24). Only minerals with literature suggesting a possible biological mechanism for risk of skin cancer were included. For example, lead was excluded given that there was no experimental data to suggest risk. Only one epidemiologic study was found about lead exposure and skin cancer, and it was a case–control study examining toenail lead levels and melanoma risk, which reported no association (25). We found no studies on exposure to aluminum, beryllium, calcium, cobalt, manganese, and magnesium and risk of skin cancer. Thus, we excluded these elements. The elements we ultimately evaluated were arsenic, cadmium, chromium, copper, iron, selenium, and zinc.

Nonepidemiologic studies, including nonhuman experiments, were discussed in the text to supplement discussion of cancer risk. We included randomized controlled trials (RCT), cohort, case-control, and cross-sectional studies. Ecologic studies were discussed in text, but excluded from tables given the diminished quality of design with risk of data inaccuracy and difficulty to control for potential confounders among other limitations (26). Furthermore, ecologic studies often investigated exposure to metals indirectly. However, some ecologic studies were described in the text to help evaluate the totality of evidence. Details about study design, study population, exposure source, exposure measures, and results were recorded.

Included studies are shown in Tables 1–4, and briefly discussed in the text. For arsenic, zinc, and selenium, which had more than 5 studies available, flowcharts of available studies were provided in Supplementary Material (Supplementary Figs. S1–S3). On the basis of quality of study design, more emphasis was placed on RCTs, followed by cohort studies, then case-control and cross-sectional studies, as the latter studies are increasingly more prone to bias (26). This was also the order of discussion of the studies in text, and the order of listed studies in Tables 1–4. When multiple publications were available from the same population, we used the most recent publications and excluded earlier ones (25, 27, 28).

Arsenic

Arsenic is a metalloid found ubiquitously in soil, rocks, and water. Human exposure occurs from ingestion of arsenic-contaminated water and foods including grain-based processed foods, dairy products, and fish (11, 29–32). Daily intake of arsenic from food and beverages is generally in the range of 20–300 μg/day (11). Water pollution by arsenic is a worldwide problem with over 226 million persons exposed (33, 34). Countries including Argentina, Bangladesh, Chile, India, Nepal, China, and Taiwan are reported to be among the most heavily affected by arsenic contamination (11, 35, 36).

Chronic exposure to arsenic has been associated with a variety of health problems including several types of cancer, neurologic disease, cardiovascular disease, and perinatal conditions (37–42). Arsenic is considered a group ‘A’ carcinogen by the US Environmental Protection Agency (EPA) and a group ‘I’ carcinogen by the International Agency for Research on Cancer (IARC) that can cause cutaneous SCC, BCC, kidney, bladder, and lung tumors (11, 43–45). The European Food Safety Authority (EFSA) determined that a dose between 0.3 and 8 μg/kg body weight/day is estimated to result in a 1% increased risk of keratinocyte carcinoma, lung, and bladder tumors (46).

Arsenic is also a cocarcinogen with ultraviolet radiation (UVR; refs. 47, 48), which can cause both keratinocyte and melanocyte damage (49–51). Compared with keratinocytes, melanocytes are more resistant to UVR-induced cytotoxicity. However, when keratinocytes or melanocytes are exposed to arsenite, which inhibits DNA repair through the enzyme PARP1, susceptibility to UVR damage becomes similarly enhanced in both cell types (52). The cocarcinogenic effects of arsenic and UVR could partly account for the epidemiologic findings suggesting an increased risk of melanoma and keratinocyte carcinoma upon exposure to arsenic.

Melanoma

There are few studies that evaluate the association between arsenic exposure and melanoma (Table 1A). To our knowledge, there are no RCTs that investigate arsenic exposure and risk of melanoma. A U.S. cohort study found no association between exposure to arsenic-containing pesticides and melanoma (Table 1A; ref. 53). Similarly, in a Danish cohort study, no association was found between exposure to arsenic in drinking water and risk for melanoma (Table 1A; ref. 54). A U.S. case–control study examined toenail arsenic exposure and melanoma using patients with colorectal cancer as controls, and found an increased risk of melanoma with increasing toenail arsenic concentrations (Table 1A; ref. 55). The association between arsenic exposure and melanoma risk needs to be evaluated in arsenic-endemic areas including Asian and Latin American countries (11, 56). The effect of arsenic exposure on melanoma risk may be modified by genetic or constitutional factors, such as skin color and sun sensitivity, as Asian and Hispanic populations are more resistant than Caucasian populations to melanoma (52, 57, 58).

Keratinocyte carcinoma

The link between arsenic exposure and keratinocyte carcinoma has been more extensively evaluated (11, 43–45), although, to our knowledge, there are no RCTs, and existing studies are largely ecologic in design. The characteristics of arsenic-associated skin tumors include SCC in situ, SCCs, and BCCs (59–61). The first evidence of arsenic’s carcinogenic effects was among patients
### Table 1. Epidemiologic studies of arsenic exposure and cutaneous melanoma (A) and keratinocyte carcinoma (B) listed by study design and year

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Demographics</th>
<th>Cases/controls or total participants</th>
<th>Exposures</th>
<th>Results (RR/OR/HR and 95% CI)</th>
<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Melanoma</strong></td>
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<tr>
<td>Dennis and colleagues, 2010 (53)</td>
<td>Agricultural Health Study</td>
<td>Sex: NS Mean age: 60; Cases: 48 Controls: 48 Country (region): US (Iowa, North Carolina) Ethnicity: NS</td>
<td>150 MM/24,704</td>
<td>Arsenic pesticide</td>
<td>OR = 1.3 (0.7-2.4) for never used vs. ever used</td>
<td>Age at enrollment, sex</td>
</tr>
<tr>
<td>Baastrup and colleagues, 2004 (55)</td>
<td>Prospective cohort study</td>
<td>Sex: 26,876M/29,502F Median age: 56 Country (region): Denmark (Copenhagen, Aarhus)</td>
<td>147 MM/56,378</td>
<td>Level of arsenic in the drinking water by time-weighted average exposure and by cumulated exposure</td>
<td>RR: 0.80 (0.59-1.08) for time-weighted average exposure of arsenic (per μg/L) RR: 0.96 (0.89-1.04) for cumulated arsenic exposure (per 5 mg)</td>
<td>Education, skin reaction to sun, sunburned during summer, area of enrollment</td>
</tr>
<tr>
<td>Case-control study</td>
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<tr>
<td>Beane Freeman and colleagues, 2004 (55)</td>
<td>Case control study (population-based)</td>
<td>Sex: M/F Cases: 205M/163F Controls: 240M/133F Median age: 60 Controls: 62 Country (region): US (Iowa) Ethnicity: Caucasian</td>
<td>326 MM/329 Controls diagnosed with colorectal cancer and frequency matched for sex and age</td>
<td>Toenail arsenic concentration</td>
<td>MM associated with highest quartile (≥0.084 μg/g) compared with lowest quartile ≤ 0.020 μg/g: OR = 2.1 (4.3-9.36) P_{trend} = 0.001</td>
<td>Age, sex, education</td>
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<td><strong>B. Keratinocyte carcinoma</strong></td>
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<tr>
<td>Hsueh and colleagues, 1997 (63)</td>
<td>Retrospective cohort study</td>
<td>Sex: 468M/613F Age: ≥50 Country: Taiwan</td>
<td>26KC/497</td>
<td>Cumulative arsenic exposure</td>
<td>Cumulative arsenic exposure (mg/L-yr) OR = 2.2 (0.95-3.0) for 1.00-1.45 2.61 (0.30-22.90) for 1.46-1.77 7.58 (0.95-60.3) for ≥17.7</td>
<td>Age, sex, education level</td>
</tr>
<tr>
<td>Baastrup and colleagues, 2008 (54)</td>
<td>Prospective cohort study</td>
<td>Sex: 26,876M/29,502F Median age: 56 Country (region): Denmark (Copenhagen, Aarhus)</td>
<td>1,010 KC/56,378</td>
<td>Level of arsenic in the drinking water by time-weighted average exposure and by cumulated exposure</td>
<td>RR: 0.99 (0.94-1.06) for time-weighted average exposure of arsenic (per μg/L) RR: 0.99 (0.97-1.01) for cumulated arsenic exposure (per 5 mg)</td>
<td>Adjusted: education, skin reaction to sun, sunburned during summer, occupation, area of enrollment</td>
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<tr>
<td>Case-control study</td>
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<tr>
<td>Yu and colleagues, 2000 (74)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: 28M/24F Mean age: 63 Country (region): Taiwan (Southwest region) Ethnicity: NS</td>
<td>2 BCC, 19 Bowen diseases (SCC in situ), 6 hyperkeratosis, hyperpigmentation Controls matched by age and sex</td>
<td>Urine levels of inorganic arsenic (InAs), methylarsionic acid (MMA) and dimethylarsinic acid (DMA)</td>
<td>Skin lesions associated with high % In As vs. low: OR = 3.50 (0.73-16.85) high % MMA vs. low: OR = 5.50 (1.22-24.81) Low % DMA vs. high: OR = 3.25 (1.06-9.97)</td>
<td>Sex, age, cigarette smoking, hepatitis B surface antigen, alcohol consumption, and regular tea intake</td>
</tr>
<tr>
<td>Karagas and colleagues, 2001 (76)</td>
<td>Case-control study (population-based)</td>
<td>Sex: BCC:182M/102F SCC: 38M/249F Controls: 315M/209F Age range: 25-74 Country (region): US, New Hampshire Ethnicity: NS</td>
<td>587 BCC, 284 SCC/524 Controls matched by age and sex</td>
<td>Toenail arsenic concentration</td>
<td>Above the 97th percentile (≥0.345 μg/g) compared with median ≤ 0.089 μg/g SCC OR = 2.07 (0.92-4.66) BCC OR = 1.44 (0.74-2.81)</td>
<td>Age and sex</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Epidemiologic studies of arsenic exposure and cutaneous melanoma (A) and keratinocyte carcinoma (B) listed by study design and year (Cont’d)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design (population-based)</th>
<th>Demographics</th>
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<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen and colleagues, 2003 (75)</td>
<td>Case-control study (hospital-based; 1996-1999)</td>
<td>Sex: Cases: 48M/28F Controls: 13M/93F Age range: &gt;30 Country (region): Taiwan (Southwest region) Ethnicity: NS</td>
<td>76KC/224</td>
<td>Percentage of urinary arsenic species, arsenic methylation ability, and cumulative arsenic exposure</td>
<td>Mean cumulative arsenic exposure (mg/L-year): Cases: 15.33 ± 18.8 Controls: 8.14 ± 15.48 P = 0.002</td>
<td>Age, sex, body-mass index (BMI), cigarette smoking, the use of hair dye, and education</td>
</tr>
<tr>
<td>Rosales-Castillo et al, 2004 (81)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: Cases: 71% male Controls: 21% male Age: mean 63 for cases and 47 for controls Country (region): Mexico Ethnicity: NS</td>
<td>42 KC/48</td>
<td>Historical arsenic exposure (arsenic concentration in the drinking water in the town of residency/years lived in the town/age)</td>
<td>Compared with low arsenic exposure and negative HPV seropositivity; OR=4.53 (0.63-32.76) for high arsenic exposure and negative HPV seropositivity OR=9.04 (1.48-55.41) for low arsenic exposure and positive HPV seropositivity OR=16.50 (2.97-91.75) for high arsenic exposure and positive HPV seropositivity</td>
<td>Age, gender, and sun exposure</td>
</tr>
<tr>
<td>Leonardi et al., 2012 (78)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: Cases: 237M/292F Control: 278M/262 F Age range: &gt;30 Country (region): Hungary, Romania, and Slovakia Ethnicity: NS</td>
<td>529 BCC/540</td>
<td>Lifetime average inorganic arsenic (iAs) concentration in residential drinking water, peak daily dose rate, cumulative iAs dose</td>
<td>OR=3.03 (1.70-5.41) for 19.5-187.3 vs. &lt;0.68 lifetime average iAs concentration (µg/L) P&lt;0.001  OR=2.50 (1.39-4.49) for 32.2-242.1 vs. &lt;0.73 peak daily iAs dose rate (µg/d) P&lt;0.001 OR=2.63 (1.45-4.78) for 0.55-4.46 vs. &lt;0.01 cumulative iAs dose (g) P&lt;0.001</td>
<td>County, age, sex, education, skin response to 1-hour midday sun, and skin complexion</td>
</tr>
<tr>
<td>Gilbert-Diamond and colleagues, 2013 (77)</td>
<td>Case-control study (population-based)</td>
<td>Sex: SCC: 284M/86F Control: 258M/78F Age range: 25-74 Country (region): US, New Hampshire Ethnicity: Caucasian</td>
<td>323 SCC/319 Controls matched by age, sex and state of residence</td>
<td>Urinary levels of iAs, MMA, and DMA, sum (∑As) of the species</td>
<td>For each ln-transformed µg/L increase: ln(iAs) OR = 1.37 (1.04-1.80) ln(MMA) OR = 1.34 (1.04-1.71) ln(DMA) OR = 1.34 (1.03-1.74)</td>
<td>Age, sex, BMI, education, smoking status, skin reaction to chronic sun exposure, and urinary creatinine concentration</td>
</tr>
<tr>
<td>Surdu and colleagues, 2013 (64)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: BCC: 231M/284F SCC: 38M/32F Controls: 272M/255F Age range 50-79 Countries (region): Hungary, Romania, Slovakia Ethnicity: NS</td>
<td>515 BCC, 70 SCC/527 controls matched to by county of residence, sex and 5-year-age group</td>
<td>Cumulative lifetime workplace dust/fume arsenic exposure (&gt;232.5 hr) &gt;7,232.5 hr vs. ≤105 hr KC: OR = 1.94 (0.76-4.95) BCC: OR = 1.90 (0.72-4.99) SCC: OR = 2.69 (0.50-14.59)</td>
<td>Sex, age, county of residence, family history of cancer, skin propensity to sunburns, and lifetime average arsenic concentration in drinking water</td>
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(Continued on the following page)
treated with arsenic-containing compounds for psoriasis, and then later in Germans exposed to arsenic-containing pesticides (44, 45). Eventually, several regions with high levels of arsenic-contaminated drinking water revealed a dose-related relationship between arsenic exposure and keratinocyte carcinoma (11). For example, in 1968, Tseng and colleagues conducted an ecologic analysis of arsenic-contaminated drinking water and keratinocyte carcinoma prevalence among 40,421 residents in 37 villages of Taiwan’s blackfoot disease endemic region and found an 8-fold difference in skin cancer prevalence between the highest level of arsenic exposure to the lowest, with an increasing trend in skin cancer prevalence from low to high (62). In a retrospective cohort study of Taiwan’s arsenic-endemic villages, skin cancer risk was related to the duration of living in the endemic area, duration of arsenic well-water consumption, average concentration of arsenic in the drinking water, and an index for cumulative exposure to arsenic (Table 1B; ref. 63).

The association between environmental arsenic exposure and keratinocyte carcinoma has subsequently been reported in Asia, Eastern Europe, Latin America, and the United States (36, 42, 56, 64–67). Several ecologic studies in endemic regions have found elevated standard mortality ratios (SMR) of skin cancer among populations exposed to drinking water with high arsenic concentrations (11, 37, 68–73). In Chile, SMRs for keratinocyte carcinoma have ranged from 3.2 [95% confidence interval (CI) = 2.1–4.8; ref. 73] to 7.7 [95% CI = 1.3–6.6; ref. 37]. In Taiwan, increased SMRs of skin cancer among people in arsenic-endemic areas have also been reported (68–72).

A summary of cohort, case–control, and cross-sectional studies of arsenic and skin cancer is in Table 1B. Multiple studies were conducted within Asian countries. Two hospital-based case–control studies in Taiwan revealed increased percentages of urinary methylarsonic acid (MMA), an organoarsenic compound commonly used in herbicides, and increased urinary levels of other arsenic species among patients with keratinocyte carcinoma compared with controls (74, 75). In the United States, a population-based case–control study found no association between toenail arsenic levels and risk of SCC and BCC among residents in New Hampshire (76, 77). In another population-based case–control study among residents in New Hampshire, a positive association was found between urinary measures of arsenic exposure and risk of SCC (77). A case–control study in Hungary, Romania, and Slovakia found a positive association between residential water arsenic concentration and BCC risk (78).

Table 1A. Epidemiologic studies of arsenic exposure and cutaneous melanoma (A) and keratinocyte carcinoma (B) listed by study design and year (Cont’d)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Demographics</th>
<th>Cases/controls or total participants</th>
<th>Exposures</th>
<th>Results (RR/OR/HR and 95% CI)</th>
<th>Covariate adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td>Overall KC 17/1,836</td>
<td>Drinking water arsenic consumption &gt;50 μg/day compared with &lt;5 μg/day; Overall KC RR = 3.28 (2.17–4.40)</td>
<td>Age and sex</td>
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</tbody>
</table>

NOTE: Age given in years.
Abbreviation: MM, cutaneous malignant melanoma; KC, keratinocyte carcinoma; NS, not specified.

As a carcinogen, cadmium’s mechanism of action is multifaceted, not fully understood, and ranges from aberrant gene expression (96) and errors in DNA methylation (97, 98), to apoptosis blockage (99, 100) and differentiation disruption (101). Cadmium can activate oncogenes and increase mitogenesis (102, 103). Cadmium can also act in synergy with other human carcinogens like tobacco smoke and UV (104). After exposure to UV, cadmium can interfere with the removal of thymine dimers (104). Cadmium has been hypothesized to play a role in melanogenesis through methylation and inactivation of caspase 8 in the extrinsic apoptotic pathway (105). In uveal melanoma, cadmium has been found to alter the cell cycle through methylation and silencing of p16INK4A (105, 106). Absorption of cadmium has been found to be higher through the skin than in...
Table 2. Epidemiologic studies of cadmium/chromium (A), iron (B), copper exposure and cutaneous melanoma (C), and copper exposure and keratinocyte carcinoma listed by study design and year (D)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Demographics</th>
<th>Cases/controls or total participants</th>
<th>Exposures</th>
<th>Results (RR/OR/HR and 95% CI)</th>
<th>Covariate Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cadmium/Chromium Melanoma Cohort</td>
<td>Weinlich and colleagues, 2003 (111)</td>
<td>Prospective cohort</td>
<td>Sex: M/F Mean age: 56.3 Country/region: Austria (Innsbruck)</td>
<td>520 MM</td>
<td>IHC overexpression of metallothionein in melanoma</td>
<td>Progression: RR = 2.9 (1.45-5.76) Survival: RR = 4.19 (1.73-10.19)</td>
</tr>
<tr>
<td></td>
<td>Vinceti and colleagues, 2005 (25)</td>
<td>Case-control study (population-based)</td>
<td>Sex: M/F Age: NS Country (region): Italy (Modena province) Ethnicity: NS</td>
<td>58 MM/58 Controls matched by sex and age</td>
<td>Toenail cadmium concentration</td>
<td>For ≥ median cadmium levels compared with the remaining category: Chromium: OR = 0.9 (0.2-3.2)</td>
</tr>
<tr>
<td>B. Iron Melanoma Case-control</td>
<td>Stryker and colleagues, 1990 (141)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: M/F Mean age: Cases M/F: 48/42 Controls M/F: 48/38 Country (region): US (Massachusetts) Ethnicity: Caucasian</td>
<td>204 MM/248 Controls visited dermatology clinic</td>
<td>Total iron intake</td>
<td>For highest quintile compared with lowest: OR = 0.8 (0.5-1.4)</td>
</tr>
<tr>
<td></td>
<td>Bain and colleagues, 1993 (142)</td>
<td>Case-control study (population-based)</td>
<td>Sex: 4F Mean age: 50 Country (region): Australia (Brisbane) Ethnicity: NS</td>
<td>41 MM/297 Controls matched for age</td>
<td>Dietary iron intake</td>
<td>For highest tertile compared with lowest: OR = 0.39 (0.15-0.97) ( P = 0.04 ) Calories, age, number of painful sunburns, and years of schooling</td>
</tr>
<tr>
<td></td>
<td>Vinceti and colleagues, 2005 (25)</td>
<td>Case-control study (population-based)</td>
<td>Sex: M/F Age: NS Country (region): Italy (Modena Province) Ethnicity: NS</td>
<td>58 MM/58 Controls matched by sex and age</td>
<td>Toenail Iron concentration</td>
<td>For ≥ median levels of iron exposure compared with the remaining category: OR = 0.4 (0.1-1.4) ( P_{\text{trend}} = 0.15 ) Education, sun exposure, and total number of atypical nevi</td>
</tr>
<tr>
<td>C. Copper Melanoma Case-control</td>
<td>Ros-Bullon and colleagues, 1998 (157)</td>
<td>Case-control study (hospital-based)</td>
<td>Sex: M/F Age: NS Country (region): Spain (Murcia) Ethnicity: NS</td>
<td>35 MM/39 Control sera obtained from healthy blood donors</td>
<td>Serum copper levels</td>
<td>Median copper levels: MM:38.3 ± 25.3 ( \mu )g/dL Controls: 117.9 ± 28.0 ( \mu )g/dL ( P &gt; 0.05 )</td>
</tr>
<tr>
<td></td>
<td>Vinceti and colleagues, 2005 (25)</td>
<td>Case-control study (population-based)</td>
<td>Sex: M/F Age: NS Country (Region): Italy (Modena province) Ethnicity: NS</td>
<td>58 MM/58 Controls matched by sex and age</td>
<td>Toenail copper concentration</td>
<td>For ≥ median levels of copper exposure compared with the remaining category: OR = 15.5 (1.7-142.6) Education, sun exposure, and total number of atypical nevi</td>
</tr>
<tr>
<td>D. Copper Keratinocyte carcinoma Case-control</td>
<td>Sahl and colleagues, 1995 (158)</td>
<td>Case-control (hospital-based)</td>
<td>Sex: M/F Mean age: 65 Country (region): United States (South Dakota) Ethnicity: NS</td>
<td>46 BCC/46 Controls matched by age, skin type, and sex</td>
<td>Mean daily copper intake</td>
<td>KC cases: 1.9 ± 0.1 mg Controls: 1.9 ± 0.9 mg ( P = 0.88 )</td>
</tr>
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plasma (107), and is partly mediated through complexing with metallothionein, a heavy metal-binding protein involved in protective stress responses (108). Metallothionein overexpression in cancers has been implicated in poorer prognosis by anticancer drug and radiotherapy resistance (109, 110).

**Melanoma**

The present epidemiologic literature regarding cadmium exposure and risk of melanoma is limited. In an Austrian cohort study, metallothionein overexpression was a significant prognostic factor for patients with primary melanoma (111). In an Italian case-control study examining trace elements in the toenails of 58 melanoma cases and 58 controls, higher levels of copper and lower levels of iron were found in patients with cutaneous melanoma, but no differences for cadmium (Table 2A; ref. 25). In a melanoma cell line study, low concentrations of hexavalent chromium were found to increase cell proliferation (20). In a murine study, exposure to potassium chromate was associated with a dose-dependent increase in UV-induced SCCs (124, 125). In the same study, chromium (IV) delivered in concentrations as low as 0.5 ppm was able to induce skin tumors with UV, but chromate alone was a weak skin carcinogen (124, 125).

In experimental studies, metallothionein expression is associated with melanoma progression and has been suggested to be a poor prognostic indicator (109, 112, 113). In murine organ samples exposed to cadmium, melanoma cell invasion was enhanced through the induction of metallothioneins (110), suggesting a possible role for metallothioneins in malignancy and metastasis (110).

**Keratinocyte carcinoma**

Despite cadmium being considered a comutagen with UVR (104), relatively little has been studied with regard to cadmium and keratinocyte carcinoma. To our knowledge, there are no epidemiologic studies investigating cadmium and keratinocyte carcinoma. Lansdown and Sampson administered percutaneous cadmium chloride solutions to shaved rats and found dermal hyperkeratosis and acanthosis and increased mitotic indices in epidermal cells (114), suggesting a possible interaction between cadmium and keratinocytes (108, 115).

**Chromium**

Chromium occurs primarily in the stable, nontoxic trivalent state (III), or in the strongly oxidizing hexavalent state (VI; ref. 116). Humans are exposed to trace levels of chromium in the air, soil, water, and food including green beans, broccoli, high-bran breakfast cereals, and certain beers and wines (117). Hexavalent chromium is found mostly in air and water. While trivalent chromium is an essential trace metal, hexavalent chromium is a known carcinogen (13). The IARC concluded that chromium (VI) causes lung as well as nasopharyngeal cancers (11).

While it is unknown whether chromate can induce skin cancer, chromate does cause skin toxicity including allergic contact dermatitis and skin ulcers (118–122). Despite dermal exposure of workers to chromate, there are limited epidemiologic studies evaluating chromate exposure and skin cancer (11, 123). A population-based case-control study in Italy examined trace elements in the toenails of melanoma cases and controls and found no differences for chromium levels (Table 2A; ref. 25). In a melanoma cell line study, low concentrations of hexavalent chromium were found to increase cell proliferation (20). In a murine study, exposure to potassium chromate was associated with a dose-dependent increase in UV-induced SCCs (124, 125).

In the same study, chromium (IV) delivered in concentrations as low as 0.5 ppm was able to induce skin tumors with UV, but chromate alone was a weak skin carcinogen (124, 125). There is no human skin data about chromate and UV exposure (126). Further studies must be conducted to better understand the potential carcinogenic effects of chromium on skin.

**Iron**

Iron is the second most abundant metal on earth, after aluminum. Foods rich in heme iron include meats and fish, and nonheme sources including green leafy vegetables, legumes, and fortified foods (127). In humans, iron plays a key role in cell growth, respiration, and replication (128–131).

Iron is also involved in catalyzing redox reactions, which in the presence of UVA radiation, can produce reactive oxygen species (ROS) and play an important role in UVA-mediated skin cell damage (132). Iron could be carcinogenic due to its catalytic effect on the formation of ROS like hydroxyl radicals, suppression of host defense cell activity, and promotion of cancer cell multiplication (133–136). In both animals and humans, primary neoplasms have developed at sites of excessive iron deposits (136). Cancerous cells uptake iron at a higher rate (135, 137, 138), and generally have higher numbers of iron-binding cell receptors than their noncancer counterparts (134, 139, 140). Despite potential links between iron and carcinogenesis, and iron and UVA-mediated skin damage, relatively little data exist about iron and skin cancer.

**Melanoma**

Only three epidemiologic studies were found investigating iron exposure and risk of melanoma. A case-control study in the United States investigated dietary intake of various vitamins and minerals, and found a nonsignificant inverse trend toward reduced risk of melanoma with increased dietary iron intake (Table 2B; ref. 141). A case-control study in Australia evaluating nutrient intake also found an inverse association between dietary iron intake and risk of melanoma (Table 2B; ref. 142). Furthermore, an inverse association between toenail iron concentrations and melanoma risk was observed in an Italian case-control study (Table 2B; ref. 25). These epidemiologic studies contrast with
experimental studies suggesting a possible protective role for iron in melanoma development (132). Further studies on the possible relation between reduced iron status and melanoma etiology are necessary.

Keratinocyte carcinoma

There are no epidemiologic studies investigating iron exposure and keratinocyte carcinoma. In a study measuring levels of iron, copper, and zinc in the skin with noninvasive diagnostic

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
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<th>Cases/controls or total participants</th>
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<th>Results (RR/OR/HR and 95% CI)</th>
<th>Covariate adjustment</th>
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<tbody>
<tr>
<td><strong>Zinc</strong></td>
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<tr>
<td><strong>A. Melanoma</strong></td>
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<tr>
<td>Horcicko &amp; Pantucek, 1983 (184)</td>
<td>Case–control study Population-based</td>
<td>Sex: NS</td>
<td>Age: NS</td>
<td>Country (region): Czech Republic</td>
<td>Ethnicity: NS</td>
<td>93 MM/64</td>
</tr>
<tr>
<td>Gorodetsky and colleagues, 1986 (143)</td>
<td>Case–control (hospital-based)</td>
<td>Sex: M/F</td>
<td>Age: NS</td>
<td>Country (region): Israel</td>
<td>Ethnicity: NS</td>
<td>71 samples (3 MM patients, 42 controls)</td>
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<tr>
<td>Siu and colleagues, 1991 (185)</td>
<td>Case–control (hospital-based)</td>
<td>Sex: MM: 6M/16F Controls: 7M/10F</td>
<td>Age: adults, not otherwise specified</td>
<td>Country (region): NS</td>
<td>Ethnicity: NS</td>
<td>22 MM and 17 BCC as controls</td>
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<tr>
<td>Bain and colleagues, 1993 (142)</td>
<td>Case–control (population-based)</td>
<td>Sex: 4F</td>
<td>Mean age: 50</td>
<td>Country (region): Australia (Brisbane)</td>
<td>Ethnicity: NS</td>
<td>41 MM/ 297 Controls matched for sex and age</td>
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<tr>
<td>Ros-Bullón and colleagues, 1998 (157)</td>
<td>Case–control (hospital-based)</td>
<td>Sex: M/F</td>
<td>Age: NS</td>
<td>Country (region): Murcia, Spain</td>
<td>Ethnicity: NS</td>
<td>35 MM/39 controls. Control serum obtained from healthy blood donors</td>
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<tr>
<td>Vinceti and colleagues, 2005 (25)</td>
<td>Case–control study (population-based)</td>
<td>Sex: M/F</td>
<td>Age: NS</td>
<td>Country (region): Modena, Italy</td>
<td>Ethnicity: NS</td>
<td>58/58 Controls matched for sex and age</td>
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<td><strong>B. Keratinocyte carcinoma</strong></td>
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<tr>
<td>Sahl and colleagues, 1995 (158)</td>
<td>Case–control study (hospital-based)</td>
<td>Sex: M/F</td>
<td>Mean age: Cases: 65 Controls: 64</td>
<td>Country (region): US (South Dakota)</td>
<td>Ethnicity: NS</td>
<td>46 BCC / 46 Cancer-free controls matched by age, skin type, and sex</td>
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</tbody>
</table>

**NOTE:** Age given in years. Abbreviation: MM, cutaneous malignant melanoma.
Table 4. Epidemiologic studies of selenium and cutaneous melanoma (A) and keratinocyte carcinoma (B)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Demographics</th>
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<tr>
<td><strong>A. Melanoma</strong></td>
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<tr>
<td>Dufﬁeld-Lillico and colleagues, 2002 (235)</td>
<td>Randomized controlled trial</td>
<td>Sex: M/F Mean age: 63 Country (region): US (East) Ethnicity: NS</td>
<td>11 MM/621 in supplement group and 9 MM/629 in placebo group</td>
<td>Supplementation of 200 µg/d of selenium versus placebo</td>
<td>RR = 1.21 (0.46–3.30) HR = 1.18 (0.49–2.85)</td>
<td>RR was unadjusted, HR was adjusted for sex, age, and smoking status</td>
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<tr>
<td><em>Nested case–control and cohort</em></td>
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<tr>
<td>Garland and colleagues, 1995 (209)</td>
<td>Nested case-control study (1976–1982)</td>
<td>Sex: F Age: 30–55 Country (Region): II States within the US Ethnicity: NS</td>
<td>63 MM/63 Controls were matched by year of birth and month of toenail return</td>
<td>Toenail selenium concentration</td>
<td>Highest tertile compared with lowest tertile of selenium exposure: OR = 1.66 (0.73–3.85)</td>
<td>Smoking status</td>
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<tr>
<td>Vinceti and colleagues, 1998 (213)</td>
<td>Prospective cohort study (1975–1985)</td>
<td>Sex: 1,021M/1,044F Age: ≥ 5 Country (region): Italy (Reggio Emilia) Ethnicity: NS</td>
<td>8 MM/2,065 exposed</td>
<td>Exposure to high levels of inorganic selenium in tap water</td>
<td>Standardized morbidity ratio</td>
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<td>Asgari and colleagues, 2009 (210)</td>
<td>Prospective cohort study (2000–2006)</td>
<td>Sex: M/F Age range: 50–76 Country (region): US (Washington State) Ethnicity: Caucasian</td>
<td>461/69,671</td>
<td>Supplemental selenium use over 10 years</td>
<td>≥50 µg/day selenium compared with none: RR = 0.98 (0.69–1.41)</td>
<td>Age, sex, education, family history of melanoma, personal history of KC, history of mole removal, freckles between ages 10 and 20 years, ≥3 severe sunburns between ages 10 and 20 years, natural red or blonde hair, reaction to 1 hour in strong sunlight</td>
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<td><strong>Case–control</strong></td>
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<tr>
<td>Breslow and colleagues, 1995 (212)</td>
<td>Case-control study (population-based)</td>
<td>Sex: 55M/44F Age: ≥18 Country (Region): US (Washington county, Maryland) Ethnicity: Caucasian</td>
<td>30 MM/60 Controls matched by age, sex</td>
<td>Serum selenium level</td>
<td>Highest tertile compared with lowest tertile of selenium exposure: OR = 0.9 (0.3–2.5)</td>
<td>Smoking, education, and hours between last meal and blood donation did not change results</td>
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<tr>
<td>Vinceti and colleagues, 2012 (214)</td>
<td>Case-control study (population-based)</td>
<td>Sex: 26M/28F Age: 25–79 Country (region): Italy (Modena province) Ethnicity: NS</td>
<td>54 MM/56 Controls selected from regional population and matched for sex and age</td>
<td>Toenail, plasma, and dietary selenium concentration</td>
<td>Toenail (≥ 73 µg/g): OR = 0.77 (0.26–2.28) Plasma (≥ 105 µg/L): OR = 6.42 (1.94–21.24) Dietary (≥ 71 µg/d): OR = 0.59 (0.19–1.83)</td>
<td>Age and sex</td>
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<tr>
<td>Le Marchand and colleagues, 2006 (211)</td>
<td>Case-control study (population-based)</td>
<td>Sex: M/F Mean age: Cases: 53 Controls: 52 Country (region): US (Oahu, Hawaii) Ethnicity: Caucasian</td>
<td>278 MM/278 Controls matched by age, ethnicity and sex</td>
<td>Plasma, erythrocyte and toenail concentrations of selenium</td>
<td>Plasma (µg/mL): ≥ 0.14 vs. ≤ 0.12 Males: OR = 1.2 (0.7–2.2) (P trend = 0.53) Females: OR = 0.8 (0.4–1.6) (P trend = 0.49) Erythrocyte (µg): ≥ 0.15 vs. ≤ 0.12</td>
<td>Height, education, hair color, number of blistering sunburns at ages 10–17 years, ability to tan and lifetime ethanol intake. Selenium-containing shampoo was</td>
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Table 4. Epidemiologic studies of selenium and cutaneous melanoma (A) and keratinocyte carcinoma (B) (Cont’d)

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<tr>
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<tr>
<td>B. Keratinocyte Carcinoma</td>
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<tr>
<td>Duffield-Lillico and colleagues, 2003 (28)</td>
<td>Randomized controlled trial</td>
<td>Sex: M/F Median age: 65 Country (region): Eastern US Ethnicity: NS</td>
<td>621 in selenium and 629 in placebo group</td>
<td>Supplementation of 200 μg/day of selenium versus placebo</td>
<td>Males: OR = 0.4 (0.4-14) (P_{trend} = 0.40) for males; Females: OR = 1.0 (0.5-2.0) (P_{trend} = 0.90)</td>
<td>Toenail (μg/g): ≥1.0 vs. &lt;0.86 Males: OR = 0.9 (0.5-1.6) (P_{trend} = 0.63) Females: OR = 1.0 (0.4-2.1) (P_{trend} = 0.99) additionally adjusted for toenail selenium</td>
</tr>
<tr>
<td>Dreno, 2007 (218)</td>
<td>Placebo-controlled randomized trial with recent organ transplant recipients (2 years)</td>
<td>Sex: 127 M/57 F Median age: 44 Country (region): France Ethnicity: 89% Caucasians</td>
<td>6/91 in selenium and 2/95 in placebo group</td>
<td>Supplementation of 200 μg/day of selenium versus placebo</td>
<td>OR = 3.08, P = 0.15</td>
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<tr>
<td>Reid and colleagues, 2008 (217)</td>
<td>Double-blind, placebo-controlled randomized trial with KC history (1983-1993). Substudy of the Nutritional Prevention of Cancer Trial</td>
<td>Sex: M/F Mean age: 64 Country (region): US (Georgia) Ethnicity: NS</td>
<td>98 KC/210 in selenium group and 108 KC/215 in placebo group</td>
<td>Selenium supplementation with 400 μg/day or 200 μg/day selenium yeast vs. placebo</td>
<td>400 μg/day: Overall KC: HR = 0.91 (0.69-1.20) BCC: HR = 0.95 (0.69-1.29) SCC: HR = 1.05 (0.72-1.53) 200 μg/day: Overall KC: HR = 1.5 (1.3-2.04), P_{trend} = 0.006 BCC: HR = 1.22 (0.88-1.70) SCC: HR = 1.9 (1.28-2.79), P_{trend} = 0.001</td>
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<tr>
<td>Knekt and colleagues, 1990 (221)</td>
<td>Nested case-control study</td>
<td>Sex: M/F Age range: 15-99 Country (region): Finland Ethnicity: NS</td>
<td>126 BCC/252</td>
<td>Serum selenium levels</td>
<td>Highest quintile compared with lowest quintile levels: Males: RR = 0.86 (0.35-2.12) Females: RR = 1.54 (0.64-3.73)</td>
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</tr>
<tr>
<td>Breslow and colleagues, 1995 (212)</td>
<td>Nested case-control study (population-based)</td>
<td>Sex: M/F Age: ≥18 Country (region): Maryland, US Ethnicity: Caucasian</td>
<td>32/64 for BCC, 37/74 for SCC</td>
<td>Serum selenium levels</td>
<td>Highest tertile compared with lowest tertile levels: BCC: OR = 0.9 (0.1-4.5) SCC: OR = 0.6 (0.2-1.5)</td>
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### Table 4. Epidemiologic studies of selenium and cutaneous melanoma (A) and keratinocyte carcinoma (B) (Cont’d)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
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<th>Results (RR/OR/HR and 95% CI)</th>
<th>Covariate Adjustment</th>
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</thead>
<tbody>
<tr>
<td>Karagas and colleagues, 1997 (224)</td>
<td>Nested case–control study in a clinical trial of those with history of KC Skin Cancer Prevention Trial</td>
<td>Sex: 89%M/11%F, Mean age: 67, Country (region): US (New Hampshire, Minnesota, California), Ethnicity: NS</td>
<td>132 SCC/ 246 controls</td>
<td>Plasma selenium levels</td>
<td>For the highest quartile versus lowest quartile selenium levels and SCC: OR = 0.86 (0.47-1.58)</td>
<td>Controls were chosen at random and matched by age, sex, and study center</td>
</tr>
<tr>
<td>Davies and colleagues, 2002 (219)</td>
<td>Nested case–control study EPIC-Norfolk Study</td>
<td>Sex: M/F, Mean age: 67M/ 65F, Country (region): Britain (Norfolk), Ethnicity: NS</td>
<td>14 SCC, 109 BCC/ 247 controls</td>
<td>Dietary selenium intake</td>
<td>For each 20 μg selenium intake and overall KC: OR = 1.07 (0.86–1.34)</td>
<td>Adjusted for body mass index and red hair</td>
</tr>
<tr>
<td>McNaughton and colleagues, 2005 (222)</td>
<td>Nested case–control study The Nambour Skin Cancer Study</td>
<td>Sex: Cases: 39M/51F, Controls: 39M/51F, Mean age: 55, Country (region): Australia (Nambour), Ethnicity: NS</td>
<td>90 BCC/90 Controls matched for age and sex</td>
<td>Dietary selenium intake and serum selenium levels</td>
<td>Highest quartile compared with lowest selenium intake and BCC: Dietary intake: OR = 1.13 (0.47–2.74) Serum level: OR = 0.86 (0.38–1.96)</td>
<td>Age, sex, and self-prescribed supplement use</td>
</tr>
<tr>
<td>Heinen and colleagues, 2007 (220)</td>
<td>Prospective cohort study (1996–2004) Nambour Skin Cancer Study</td>
<td>Sex: 454M/547F, Mean age: SCC: 65 BCC: 61, Country (region): Australia (Nambour), Ethnicity: NS</td>
<td>116 SCC, 149 BCC/ 1001</td>
<td>Dietary selenium intake</td>
<td>For highest tertile compared with lowest tertile selenium intake: SCC: RR = 1.30 (0.77–2.30) BCC: RR = 0.95 (0.59–1.5)</td>
<td>Age, sex, energy intake, skin color, elastosis of the neck, smoking, treatment allocation, use of dietary supplements, history of skin cancer before 1996</td>
</tr>
<tr>
<td>Van der Pols and colleagues, 2009 (223)</td>
<td>Subset of prospective cohort study (1996–2004) Nambour Skin Cancer Study</td>
<td>Sex: 223M/262F, Mean age: SCC: 63 BCC: 61, Controls: 54 Country (region): Australia (Queensland), Ethnicity: NS</td>
<td>77 BCC, 59 SCC/ 485</td>
<td>Serum selenium concentration</td>
<td>For highest tertile compared with lowest tertile: BCC: RR = 0.58 (0.32 – 1.07) SCC: RR = 0.49 (0.24 – 0.99)</td>
<td>Age, sex, pack-years of smoking, alcohol intake; time spent outdoors on weekdays, and history of skin cancer before 1996</td>
</tr>
<tr>
<td>Case–control/Clark, 1984 (236)</td>
<td>Case–control study (hospital-based)</td>
<td>Sex: M/F, Age: &lt;76 years, Country (region): US (Wilson, North Carolina), Ethnicity: NS</td>
<td>142 BCC, 48 SCC, 50 BCC = SCC/103</td>
<td>Plasma selenium levels</td>
<td>High vs. low selenium levels and overall KC: OR = 2.11 (1.25–3.56)</td>
<td>Age and sun damage</td>
</tr>
<tr>
<td>Sahl and colleagues, 1995 (158)</td>
<td>Case–control study (hospital)</td>
<td>Sex: M/F, Mean age: Cases: 65 Controls: 64, Country (region): US (South Dakota), Ethnicity: NS</td>
<td>46 BCC/46 Controls matched by age, skin type, and sex</td>
<td>Mean daily selenium intake</td>
<td>BCC cases: 99 ± 6 (μg) Controls: 72 ± 6 (μg) P = 0.14</td>
<td>Age and sun damage</td>
</tr>
</tbody>
</table>

NOTE: Age given in years. Abbreviations: MM, cutaneous malignant melanoma; KC, keratinocyte carcinoma; NS, not specified.
X-ray spectrometry, all three elements were increased in both BCCs and SCCs compared with skin of healthy controls (143). In another histochemical examination of invasive BCCs and SCCs, only copper, not iron or zinc, were detected (144). In untransformed HaCaT and transformed A431 human keratinocytes, coexposure with arsenic and iron was found to synergistically promote malignant transformation of untransformed keratinocytes, and progression of transformed keratinocytes (145). Despite possible associations between iron and UVA-induced skin damage, further studies are needed to elucidate a relation between iron and keratinocyte carcinoma.

**Copper**

Copper is an essential trace element found in water and in certain foods including seafood, red meat, legumes, and whole grains (146, 147). Copper plays a key role in many biological processes (148–154), often as an intermediate or cofactor in enzymes like cytochrome c oxidase and Cu/Zn superoxide dismutase (Cu/ZnSOD; ref. 148). Thus, copper contributes to mitochondrial ATP production and detoxification of reactive oxygen species (149–151). Copper also plays roles in gene expression regulation (148) and melanin formation (152). Elevated serum and tissue copper levels have been observed in patients with cancer, including breast, ovarian, hematologic, lung, colorectal, head and neck, and prostate suggesting altered systemic copper homeostasis (153). Copper promotes angiogenesis (154), activates enzymes involved in tumor cell migration and metastasis (154), and promotes oncogenic BRAF signaling and tumorigenesis (155). Given its contribution to cancer progression and increased uptake by malignant cells, cellular copper is a new potential target for novel anticancer therapeutics (154, 156). Some studies have also suggested that a lower level of copper may confer a risk of keratinocyte carcinoma, particularly lower levels of copper as a cofactor for antioxidant enzymes. IHC stains of skin cancer biopsies have demonstrated reduced levels of CuZnSOD in AKs and SCCs, but increased levels in BCCs (160). Others have also found lower levels of CuZnSOD in SCCs and BCCs and surrounding tissues compared with younger-aged control skin (161). In a murine study, promotion and progression of papillomas, keratoacanthomas, and SCCs were found to be inhibited by pretreating with copper(II) (3,5-diisopropylsalicylate) 2, a superoxide dismutase agent with copper as a cofactor (162).

**Melanoma**

To our knowledge, there are only two small population-based studies on environmental copper exposure and risk of melanoma. An Italian case–control study found increased risk of melanoma with higher toenail copper levels (Table 2C; ref. 25). Another case–control study in Spain found no association between serum copper levels and melanoma (Table 2C; ref. 157). Further studies are needed to better elucidate a potential connection between copper consumption and melanoma.

**Keratinocyte carcinoma**

The epidemiologic literature on copper and keratinocyte carcinoma in humans is limited. In a case–control study, copper levels were measured in 46 patients with BCCs and controls, and no difference was found in dietary consumption of zinc or copper (Table 2D; ref. 158). In another case–control study, ceruloplasmin, a major copper-carrying protein in the blood, was noted to be decreased in patients with actinic keratosis and BCCs compared with controls (159). Further epidemiologic studies are needed to better elucidate the potential relationship between copper and keratinocyte carcinoma.

**Zinc**

Zinc is an essential trace element found in water, soil, foods including meat, eggs, whole grains, and dairy, building products, fertilizers, pesticides, and cosmetic products, and sunscreen...
Zinc is involved in over 200 enzymatic functions (167). At a cellular level, zinc is necessary for cell survival by playing key roles in signal transduction, transcription, and replication (168–170).

In cultured skin fibroblasts exposed to UVA and UVB, zinc protects against UV damage and reduces cytotoxicity and lipid peroxidation (171–173). When zinc was added to an immortalized human keratinocyte cell line, it decreased both the amount of DNA damage following UVB exposure and also the number of nucleosomes observed, a marker of apoptosis (174).

Topical zinc in the form of zinc oxide (ZnO) is an increasingly popular ingredient used in commercial sunscreen formulations for UV protection. Controversies regarding these nanoparticles involve concern of reactive oxygen species (ROS) development and penetration into the epidermis (175, 176). There is conflicting evidence regarding absorption of zinc through the skin. Some in vivo and in vitro studies reported that nanoparticles are confined to the stratum corneum (175, 177–179), while human studies have found increased amounts of zinc in blood and urine after ZnO sunscreen application (180, 181). Longitudinal studies must be conducted on ZnO nanoparticles to better understand possible cytotoxic effects and long-term health implications. As of now, the health benefits of melanoma and keratinocyte carcinoma risk reduction from sunscreen outweigh the current understood risk of these topical zinc formulations (182).

Melanoma

There are six epidemiologic studies on environmental trace zinc exposure and risk of melanoma. Some studies have found an inverse association between zinc exposure and risk of melanoma. In a U.S. ecologic study using state-averaged cancer mortality rate data for Caucasian Americans during 1970 to 1994, indices for dietary zinc were found to be inversely correlated with melanoma mortality rate (183). In a population-based case–control study in the Czech Republic, lower serum zinc concentrations were found among subjects with melanoma (Table 3A; ref. 184). In another case–control study, an inverse association was found between dietary zinc intake and risk of melanoma in Australians (Table 3A; ref. 142).

Conversely, there are studies that have found positive associations between zinc exposure and risk of melanoma. Two hospital-based case–control studies found increased serum zinc concentrations among patients with melanoma (157, 185). Another hospital-based case–control study found increased zinc concentrations in melanoma lesions compared with uninvolved skin of cases and skin of healthy controls (Table 3A; ref. 143). There are also studies that have found no significant associations between zinc intake and melanoma (Table 3A; ref. 25).

Keratinocyte carcinoma

There is limited epidemiologic data regarding trace environmental zinc exposure and keratinocyte carcinoma. In the same U.S. ecological study investigating zinc and melanoma mortality, zinc and state-averaged keratinocyte carcinoma mortality rate data was examined, and the dietary zinc index was also found to be inversely correlated with keratinocyte carcinoma (183). In a case–control study, zinc levels were examined in patients with BCCs and cancer-free controls, and no difference in dietary consumption of zinc or copper was found between both groups (Table 3B; ref. 158). Further studies are needed to better elucidate a potential connection between zinc exposure and keratinocyte carcinoma.

Experimental study results are also mixed. As discussed with copper, IHC stains of actinic keratosis, SCC, and BCC biopsies have shown reduced levels of CuZnSOD compared with skin of controls (161). Conversely, increased levels of zinc in BCCs and SCCs compared with skin of healthy controls have been demonstrated using noninvasive diagnostic X-ray spectrometry (143). In another histochemical examination of invasive BCCs and SCCs, zinc was not detected (144).

Selenium

Selenium is an essential trace element found mainly in soil, water, and foods including grains, mushrooms, asparagus, garlic, and animal products (186, 187). Selenium has a narrow range for safe intake (188–190), and toxic levels (>400 μg/day) can induce alopecia, gastroenteritis (191, 192), neurologic dysfunction (193–196), infertility, and dermatitis (197, 198). The average content of selenium in the daily diet is far from the recommended amount (55 μg/day for persons 14 years or older in the United States; ref. 199), and 0.5–1 billion people worldwide are deficient in this metalloid (187, 200). Selenium is genetically encoded into proteins as the amino acid selenocysteine; selenium-containing proteins include antioxidant enzymes that play essential roles in protecting against oxidation of lipid membranes, reduction of hydrogen peroxide, and organic peroxides (201–203). Selenium plays key roles in numerous essential cell and organ functions (202–208), and has been implicated in multiple diseases including diabetes mellitus (204, 205) and cancer (206, 207).

The association between selenium and cancer is controversial. Selenium has been implicated to have both anticancer and carcinogenic properties. Cancers that have been implicated involve nearly every organ system, including gynecologic, gastrointestinal, urinary, respiratory, hematologic, endocrine, and skin (207, 208). Limited skin cancer studies were included in these reviews. A recent meta-analysis on selenium exposure and cancer risk reported a pooled OR of 1.09 (95% CI, 0.98–1.21) for high selenium exposure and melanoma and keratinocyte carcinoma combined, based on 6 effect estimates from 4 studies (206).

Melanoma

There have been seven epidemiologic studies of selenium and melanoma (Table 4A). In a U.S. double-blind randomized placebo controlled trial among those with a history of cutaneous BCC or SCC, 200 μg/day of selenium supplementation was not effective in reducing melanoma risk (28). In two U.S. prospective studies, no association was found between either toenail selenium concentrations or self-reported selenium supplement use and melanoma (209, 210). Two case–control studies similarly revealed no association between plasma and toenail selenium concentrations and melanoma (209, 210). Two case–control studies similarly revealed no association between plasma and toenail selenium concentrations and melanoma (25, 211, 212). Conversely, some studies have found an association between selenium exposure and melanoma, although these studies in comparison with RCTs and cohort studies are more prone to bias given limitations in study design. An Italian prospective study found that exposure to tap water with high selenium levels was associated with melanoma risk (Table 4A; ref. 213). In a case–control study, increased concentrations of plasma selenium were associated with increased risk of melanoma among an Italian population (214). In the same study, toenail and dietary selenium exhibited no evidence of a relation with melanoma risk; this difference could have been in part due to differences in specific selenium compounds (Table 4A; ref. 214).
On the basis of these studies, selenium has not shown any beneficial role against melanoma risk. A few studies suggested potential adverse effects of selenium. In a murine study, a dose-dependent difference was found with selenium and melanoma development, with moderate dosage increasing tumor growth, and high dosage effectively treating and preventing recurrence of fully malignant tumors (215). In vitro studies have shown selenium inducing dose-dependent apoptosis in human A375 melanoma cell lines by inducing mitochondria-mediated oxidative stress (216). Taken together, these studies demonstrate the need to further investigate the exposure classification of selenium biomarkers, and metabolism of selenium to elucidate the potential relation between selenium exposure and melanoma risk.

**Keratinocyte carcinoma**

There are multiple epidemiologic studies investigating selenium exposure and risk of keratinocyte carcinoma, including RCTs and prospective cohort studies. A double-blind RCT investigated whether 200 μg/day selenium, as selenized yeast could prevent keratinocyte carcinoma among patients with BCC and SCC from the Eastern United States (28). They found that selenium supplementation in fact elevated risk for SCC [relative risk (RR) = 1.25; 95% CI = 1.03–1.51] and total KC [RR = 1.17; 95% CI = 1.02–1.34], but not BCC (Table 4B; ref. 28). A sub-study of the trial then tested 400 μg/day of selenium supplementation and found no effect, while those who continued to receive 200 μg/day of selenium maintained a higher risk of SCC (RR = 1.88; 95% CI = 1.28–2.79) and keratinocyte carcinoma (RR = 1.50; 95% CI = 1.13–2.04; Table 4B; ref. 217). In a small trial among 184 French organ graft recipients, 200 μg/day selenium supplementation had no effect on skin cancer (218). Case-control or cohort studies in the United Kingdom or United States have not found an association between dietary, serum, or supplemental selenium and BCC (158, 212, 218–223) or SCC (212, 220, 223, 224) (Table 4B). A meta-analysis evaluating selenium supplementation and cancer risk found nonsignificant positive associations between selenium and keratinocyte carcinoma with 4 included studies [RR = 1.23; 95% CI, 0.73–2.08; ref. 207]. In summary, the effect of selenium exposure on risk of keratinocyte carcinoma is inconclusive despite relatively large numbers of existing epidemiologic studies, while there is some suggestion of positive association with SCC risk.

The suggested positive association contradicts some experimental studies. Selenomethionine, a selenium organic compound, when applied topically for two weeks at increasing concentrations was effective in protecting against acute UV damage to the skin (225). In human keratinocytes, p53 activation was significantly diminished when incubated in selenomethionine both pre- and post-UVR irradiation (226). In another in vitro study with human keratinocytes exposed to UVR, a reduction in apoptosis was found by 71% when cells were incubated with selenomethionine or sodium selenite (227). A similar reduction in apoptosis had been noted in prior studies (228). Given selenium’s increasingly popular role as a dietary supplement (207), it is important to better understand the relation of this element to skin cancer.

**Conclusion**

Of all environmental trace elements, we identified published epidemiologic studies on exposure to arsenic, cadmium, chromium, copper, iron, selenium, and zinc and risk of skin cancer (Table 5). Some of these elements such as copper, (trivalent) chromium, iron, selenium, and zinc are essential and necessary for healthy biologic function. Other metals including arsenic, cadmium, and hexavalent chromium are toxic and carcinogenic. Exposures to these metals are mainly through soil and water sources affecting foods and drinking water, as well as occupational, including pesticides, and field-specific activities such as welding and electroplating.

There were several epidemiologic studies that reported a positive association between arsenic exposure and keratinocyte carcinoma (both SCC and BCC), which was concluded as causally related with keratinocyte carcinoma by the IARC. However, the studies on arsenic exposure and melanoma are still too limited to draw considerable conclusions.

Although biologically plausible, only a few epidemiologic studies exist on exposure to cadmium, chromium, copper, iron, and zinc and skin cancer. Among them, cadmium and chromium are considered carcinogens for other cancers, but have insufficient evidence to conclude an association with skin cancer. While copper, iron, and zinc are essential nutrients in certain concentrations, they may adversely affect skin cancer at higher concentrations. Studies investigating exposure to zinc and risk of melanoma found associations in both directions. However, there is insufficient evidence to draw any definitive conclusions with no prospective data available on zinc and skin cancer.

Selenium has been more extensively investigated with both melanoma and keratinocyte carcinoma. While selenium is hypothesized to reduce risk of other cancers, studies of selenium exposure and skin cancer risk did not find any inverse associations. A few studies, including evidence from RCTs, suggested a positive association between selenium exposure and keratinocyte carcinoma risk.

In general, the literature on exposure to these elements and cutaneous malignancies has been quite limited, with studies of predominantly small sample sizes and study designs more prone to biases such as case-control and cross-sectional studies. It is necessary that more studies are conducted, with larger sample sizes and prospective study designs.

Effective methods to prevent and reduce environmental trace metal exposure requires sustainable broad public health initiatives, including testing drinking water sources and soil for heavy metal contamination, surveying vulnerable populations like pregnant women and at-risk workers (e.g., chromate plant workers; ref. 229), creating and enacting legislation that bans pesticides with heavy metals and other toxins, and encouraging organic farming and dietary practices (230–232). For high-risk activities, enacting and enforcing strict clothing and equipment practices is necessary (233, 234).

The current body of literature provides the groundwork from which future studies can build upon. In the setting of rising melanoma incidence and the markedly high prevalence of keratinocyte carcinoma, it is imperative that environmental risk factors are identified and better understood for investigation of etiopathogenesis and preventative strategies.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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