HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2019 January ; 28(1): 3–21. doi:10.1158/1055-9965.EPI-18-0286.

Exposure to trace elements and risk of skin cancer: A systematic review of epidemiologic studies.

Natalie H. Matthews[1,2], **Katherine Fitch**[1], **Wen-Qing Li**[1,3], **J. Steven Morris**[4], **David C. Christiani**[5,6,7], **Abrar A. Qureshi**[1,3,8,9], and **Eunyoung Cho**[1,3,8]

[1]Department of Dermatology, The Warren Alpert Medical School, Brown University, Providence, RI, USA

[2]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US

[3]Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA

[4]Research Reactor Center, University of Missouri-Columbia and Harry S Truman Memorial Veterans Hospital, Columbia, MO, USA

[5]Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, MA, USA

[6]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

[7]Pulmonary and Critical Care Unit, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA.

[8]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[9]Department of Dermatology, Rhode Island Hospital, Providence, RI, USA

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 5 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,

Corresponding Author: Eunyoung Cho, 339 Eddy St, Department of Dermatology, The Warren Alpert Medical School, Brown University, Providence, RI 02903; eunyoung_cho@brown.edu; Phone: 401-863-5895; Fax:401-863-5799.

Conflict of Interest: The authors declare no potential conflicts of interest.

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

Melanoma is a malignant skin tumor that arises from melanocytes (8). Though 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 KCs 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 non-human 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 since 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 epidemiological 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.

Non-epidemiologic studies, including non-human experiments, were discussed in the text to supplement discussion of cancer risk. We included randomized controlled trials (RCTs), cohort, case-control, and cross-sectional studies. Ecological 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, ecological studies often investigated exposure to metals indirectly. However, some ecological 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, flow charts of available studies were provided in supplementary material (Supplementary Figures 1–3). Based on quality of study design, more emphasis was placed on RCTs, followed by cohort studies, then case-control and cross-sectional studies, as the later 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/d (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, neurological 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 – 8 μg/kg body weight/d is estimated to result in a 1 % increased risk of KC, lung, and bladder tumors (46).

Arsenic is also a co-carcinogen with ultraviolet radiation (UVR) (47,48), which can cause both keratinocyte and melanocyte damage (49–51). Compared to 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 poly ADP ribose polymerase 1, susceptibility to UVR damage becomes similarly enhanced in both cell types (52). The co-carcinogenic effects of arsenic and UVR could partly account for the epidemiologic findings suggesting an increased risk of melanoma and KC 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 US cohort study found no association between exposure to arsenic-containing pesticides and melanoma (Table 1a) (53). Similarly, in a Danish cohort study, no association was found between exposure to arsenic in drinking water and risk for melanoma (Table 1a) (54). A US case-control study examined toenail arsenic exposure and melanoma using colorectal cancer patients as controls, and found an increased risk of melanoma with increasing toenail arsenic concentrations (Table 1a) (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).

KC

The link between arsenic exposure and KC has been more extensively evaluated (11,43–45), though to our knowledge, there are no RCTs, and existing studies are largely ecological 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 were among patients 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 KC (11). For example, in 1968, Tseng et al. conducted an ecologic analysis of arsenic-contaminated drinking water and KC 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 artesian well-water consumption, average concentration of arsenic in the drinking water, and an index for cumulative exposure to arsenic (Table 1b)(63).

The association between environmental arsenic exposure and KC has subsequently been reported in Asia, Eastern Europe, Latin America, and the US (36,42,56,64–67). Several ecological studies in endemic regions have found elevated standard mortality ratios (SMRs) of skin cancer among populations exposed to drinking water with high arsenic concentrations (11,37,68–73). In Chile, SMRs for KC have ranged from 3.2 (95% CI = 2.1 – 4.8) (73) to 7.7 (95% CI = 1.3 – 6.6) (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 KC compared with controls (74,75). In the US, 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). Increased incidence and prevalence of KC has also been reported among residents of Wisconsin's Fox River Valley, which contains arsenic-rich minerals in its bedrock layers (79,80), as well as in Eastern Europe (64), Mexico (81), and Vietnam (66). Taken together, epidemiologic studies from different geographical regions have consistently supported the positive association between arsenic exposure and KC risk. Studies which have evaluated BCC and SCC separately have reported similar positive associations.

Future directions for arsenic exposure and KC investigation include developing a better understanding of pathogenesis and genetic susceptibility. Individuals can vary in their susceptibility to arsenic toxicity (82). For example, only 15–20% of exposed individuals show evidence of arsenic induced skin damage (82). This variability may be influenced by a combination of inherited genetic factors and environmental and lifestyle factors. For example, the chromosomal region that contains the arsenite methyltransferase (*AS3MT*) gene is subject to multiple variants, which can affect an individual's ability to metabolize and excrete arsenic (82–87). Variations in this gene could ultimately impact that individual's susceptibly to arsenic exposure and degree of toxicity and carcinogenicity (82,86,87). As

emerging data supports a role for genetic variation in arsenic metabolism, it may become a promising method of skin cancer risk evaluation.

Cadmium

Cadmium is a highly toxic heavy metal that is present in air, water, soil, sediment (11,88), and foods including green leafy vegetables (89–92). Cigarettes are a significant source of cadmium exposure (93). For non-smokers, diet and house dust are the main routes of cadmium exposure (94). Cadmium is considered a group I carcinogen by the IARC (12,93), and has been associated with tumors of the lung, testes, prostate, pancreas, adrenals, liver, kidney, blood, and pituitary (95).

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 UVR (104). After exposure to UVR, cadmium can interfere with the removal of thymine dimers (104). Cadmium has been hypothesized to play a role in melanomagenesis 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 $p16^{INK4A}$ (105,106). Absorption of cadmium has been found to be higher through the skin than in 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 epidemiological literature regarding cadmium exposure and risk of melanoma is limited. In an Austrian cohort study, metallothionein overexpression was a significant prognostic factor for primary melanoma patients (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) (25).

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).

KC

Despite cadmium being considered a co-mutagen with UVR (104), relatively little has been studied with regard to cadmium and KC. To our knowledge, there are no epidemiologic studies investigating cadmium and KC. 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) (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 epidemiological 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) (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 0.5ppm 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 non-cancer counterparts (134,139,140). Despite potential links between iron and carcinogenesis, and iron and UVA-mediated skin damage, relatively little data exists about iron and skin cancer.

Melanoma

Only three epidemiological studies were found investigating iron exposure and risk of melanoma. A case-control study in the US investigated dietary intake of various vitamins and minerals, and found a non-significant inverse trend toward reduced risk of melanoma with increased dietary iron intake (Table 2b) (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) (142). Furthermore, an inverse association between toenail iron concentrations and melanoma risk was observed in an Italian case-control study (Table 2b) (25). These epidemiological 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.

KC

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

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 (CuZnSOD) (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 cancer patients, 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 anti-cancer therapeutics (154,156). Despite emerging research on cellular copper, relatively little is understood about environmental copper consumption and potential risk for skin cancers.

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) (25). Another case-control study in

Spain found no association between serum copper levels and melanoma (Table 2c) (157). Further studies are needed to better elucidate a potential connection between copper consumption and melanoma.

KC

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

Given the potential role of copper in tumorigenesis, as seen in other cancer patients, one would expect increased risk of skin cancer with increased copper levels (153). Studies measuring levels of copper in BCCs and SCCs both noninvasively and using histochemical techniques have detected increased amounts of copper compared with uninvolved skin or skin of healthy controls (143,144). A murine study noted incidental development of SCCs at or near sites of nickel-copper alloy ear tags in 8.8% of mice compared with 0% in the untagged ears, suggesting that chronic topical exposure to one or both of the metals is carcinogenic (21). Some studies have also suggested that a lower level of copper may confer a risk of KC, particularly lower levels of copper as a cofactor for antioxidant enzymes. Immunohistochemical 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).

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 (163–166). 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 KC 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 US ecological study using state-averaged cancer mortality rate data for Caucasian Americans during 1970–94, 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) (184). In another case-control study, an inverse association was found between dietary zinc intake and risk of melanoma in Australians (Table 3a) (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 melanoma patients (157,185). Another hospital-based case-control study found increased zinc concentrations in melanoma lesions compared to uninvolved skin of cases and skin of healthy controls (Table 3a) (143). There are also studies that have found no significant associations between zinc intake and melanoma (Table 3a) (25).

KC

There is limited epidemiologic data regarding trace environmental zinc exposure and KC. In the same US ecological study investigating zinc and melanoma mortality, zinc and state-averaged KC mortality rate data was examined, and the dietary zinc index was also found to be inversely correlated with KC (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) (158). Further studies are needed to better elucidate a potential connection between zinc exposure and KC.

Experimental study results are also mixed. As discussed with copper, immunohistochemical stains of AK, SCC, and BCC biopsies have shown reduced levels of CuZnSOD compared to skin of controls (161). Conversely, increased levels of zinc in BCCs and SCCs compared with skin of healthy controls has 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 US) (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, hematological, 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 odds ratio of 1.09 (95% CI 0.98–1.21) for high selenium exposure and melanoma and KC combined, based on 6 effect estimates from 4 studies (206).

Melanoma

There have been 7 epidemiological studies of selenium and melanoma (Table 4a). In a US double-blind randomized placebo controlled trial among those with a history of cutaneous BCC or SCC, 200 μg/d of selenium supplementation was not effective in reducing melanoma risk (28). In two US 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 (25,211,212). Conversely, some studies have found an association between selenium exposure and melanoma, though these studies in comparison to 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) (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) (214).

Based on 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.

KC

There are multiple epidemiologic studies investigating selenium exposure and risk of KC, including RCTs and prospective cohort studies. A double-blind RCT investigated whether 200 μg/d selenium as selenized yeast could prevent KC among BCC and SCC patients from the Eastern US (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) (28). A sub-study of the trial then tested 400 ug/d of selenium supplementation and found no effect, while those who continued to receive 200 μg/d of selenium maintained a higher risk of SCC (RR = 1.88, 95% CI = 1.28 – 2.79) and KC (RR = 1.50, 95% CI = 1.13–2.04) (Table 4b)(217). In a small trial among 184 French organ graft recipients, 200 μg/d selenium-supplementation had no effect on skin cancer (218). Case-control or cohort studies in the UK or US 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 non-significant positive associations between selenium and KC with 4 included studies (RR=1.23 [95% CI 0.73–2.08]) (207). In summary, the effect of selenium exposure on risk of KC is inconclusive despite relatively large numbers of existing epidemiological 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, iron, selenium, and zinc are essential and necessary for healthy biologic function. Other metals including arsenic, cadmium, and 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 epidemiological studies that reported a positive association between arsenic exposure and KC (both SCC and BCC), which was concluded as causally related

with KC 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 epidemiological 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 KC. 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 KC 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) (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 KC, it is imperative that environmental risk factors are identified and better understood for investigation of etiopathogenesis and preventative strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Acknowledgements: NIH: CA198216, E.Cho; NIEHS: ES000002, D.C. Christiani

References

1. Surveillance, Epidemiology, and End Results (SEER) 1975–2013 04 April. Program Cancer Statistics Review. National Cancer Institute <http://seer.cancer.gov/csr/1975_2013/>. Accessed 2017 04 April.

2. Alam M, Nanda S, Mittal BB, Kim NA, Yoo S. The use of brachytherapy in the treatment of nonmelanoma skin cancer: a review. J Am Acad Dermatol 2011;65(2):377–88 doi 10.1016/j.jaad.2010.03.027. [PubMed: 21496952]

3. Samarasinghe V, Madan V. Nonmelanoma skin cancer. J Cutan Aesthet Surg 2012;5(1):3–10 doi 10.4103/0974-2077.94323. [PubMed: 22557848]

4. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. J Cutan Med Surg 2005;9(1):10–5 doi 10.1177/120347540500900104. [PubMed: 16208438]

5. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. J Am Acad Dermatol 1991;24(5 Pt 1):715–9. [PubMed: 1869642]

6. Samarasinghe V, Madan V, Lear JT. Management of high-risk squamous cell carcinoma of the skin. Expert Rev Anticancer Ther 2011;11(5):763–9 doi 10.1586/era.11.36. [PubMed: 21554051]

7. Macbeth AE, Grindlay DJ, Williams HC. What's new in skin cancer? An analysis of guidelines and systematic reviews published in 2008–2009. Clin Exp Dermatol 2011;36(5):453–8 doi 10.1111/j.1365-2230.2011.04087.x. [PubMed: 21671988]

8. Zhang XY, Zhang PY. Genetics and epigenetics of melanoma. Oncol Lett 2016;12(5):3041–4 doi 10.3892/ol.2016.5093. [PubMed: 27899960]

9. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. Br J Dermatol 2014;170(1):11–9 doi 10.1111/bjd.12492. [PubMed: 23815297]

10. Guy GP, Jr, Thomas CC, Thompson T, Watson M, Massetti GM, Richardson LC. Vital signs: melanoma incidence and mortality trends and projections - United States, 1982–2030. MMWR Morb Mortal Wkly Rep 2015;64(21):591–6. [PubMed: 26042651]

11. IARC working group on the evaluation of carcinogenic risks to humans. Arsenic, metals, fibres and dusts. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans 2012;100c:11–465.

12. IARC working group on the evaluation of carcinogenic risks to humans. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC monographs on the evaluation of carcinogenic risks to humans 1993;58:119–237. [PubMed: 8022055]

13. IARC working group on the evaluation of carcinogenic risks to humans. Chromium, nickel, and welding. IARC monographs on the evaluation of carcinogenic risks to humans 1990;49:105–782.

14. Payette MJ, Whalen J, Grant-Kels JM. Nutrition and nonmelanoma skin cancers. Clin Dermatol 2010;28(6):650–62 doi 10.1016/j.clindermatol.2010.03.033. [PubMed: 21034989]

15. Lansdown AB. Metal ions affecting the skin and eyes. Metal ions in life sciences 2011;8:187–246. [PubMed: 21473382]

16. Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R. Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings. IARC Sci Publ 1984(53):105–15. [PubMed: 6532976]

17. Sauni R, Oksa P, Uitti J, Linna A, Kerttula R, Pukkala E. Cancer incidence among Finnish male cobalt production workers in 1969–2013: a cohort study. BMC cancer 2017;17(1):340 doi 10.1186/s12885-017-3333-2. [PubMed: 28521771]

18. Zhang Q, Pan E, Liu L, Hu W, He Y, Xu Q, et al. Study on the relationship between manganese concentrations in rural drinking water and incidence and mortality caused by cancer in Huai'an city. BioMed research international 2014;2014:645056 doi 10.1155/2014/645056. [PubMed: 25530966]

19. Spangler JG, Reid JC. Environmental manganese and cancer mortality rates by county in North Carolina: an ecological study. Biological trace element research 2010;133(2):128–35 doi 10.1007/s12011-009-8415-9. [PubMed: 19495573]

20. Rizzi M, Cravello B, Reno F. Textile industry manufacturing by-products induce human melanoma cell proliferation via ERK1/2 activation. Cell Prolif 2014;47(6):578–86 doi 10.1111/cpr.12132. [PubMed: 25224575]

21. Baron BW, Langan G, Huo D, Baron JM, Montag A. Squamous cell carcinomas of the skin at ear tag sites in aged FVB/N mice. Comp Med 2005;55(3):231–5. [PubMed: 16089170]

22. Carpenter RL, Jiang BH. Roles of EGFR, PI3K, AKT, and mTOR in heavy metal-induced cancer. Curr Cancer Drug Targets 2013;13(3):252–66. [PubMed: 23297824]

23. Perez-Gomez B, Aragones N, Gustavsson P, Plato N, Lopez-Abente G, Pollan M. Cutaneous melanoma in Swedish women: Occupational risks by anatomic site. American journal of industrial medicine 2005;48(4):270–81 doi 10.1002/ajim.20212. [PubMed: 16142745]
24. Magnani C, Coggon D, Osmond C, Acheson ED. Occupation and five cancers: a case-control study using death certificates. British journal of industrial medicine 1987;44(11):769–76. [PubMed: 3689708]
25. Vinceti M, Bassissi S, Malagoli C, Pellacani G, Alber D, Bergomi M, et al. Environmental exposure to trace elements and risk of cutaneous melanoma. J Expo Anal Environ Epidemiol 2005;15(5):458–62 doi 10.1038/sj.jea.7500423. [PubMed: 15785778]
26. Thiese MS. Observational and interventional study design types; an overview. Biochemia medica 2014;24(2):199–210 doi 10.11613/bm.2014.022. [PubMed: 24969913]
27. Hsueh YM, Cheng GS, Wu MM, Yu HS, Kuo TL, Chen CJ. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. Br J Cancer 1995;71(1):109–14. [PubMed: 7819025]
28. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF, Jr, Slate EH, Fischbach LA, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev 2002;11(7):630–9. [PubMed: 12101110]
29. European Food Safety A Dietary exposure to inorganic arsenic in the European population. EFSA Journal 2014;12(3):3597–n/a doi 10.2903/j.efsa.2014.3597.
30. Abedin MJ, Cresser MS, Meharg AA, Feldmann J, Cotter-Howells J. Arsenic accumulation and metabolism in rice (Oryza sativa L.). Environ Sci Technol 2002;36(5):962–8. [PubMed: 11918027]
31. Abedin MJ, Feldmann J, Meharg AA. Uptake kinetics of arsenic species in rice plants. Plant Physiol 2002;128(3):1120–8 doi 10.1104/pp.010733. [PubMed: 11891266]
32. Watanabe T, Hirano S. Metabolism of arsenic and its toxicological relevance. Arch Toxicol 2013;87(6):969–79 doi 10.1007/s00204-012-0904-5. [PubMed: 22811022]
33. Murcott S Arsenic contamination in the world: an international sourcebook 2012. London, UK: IWA Publishing; 2012.
34. Smedley PL KD. Arsenic in goundwater and the environment In: Selinus OAB, Centeno JA, et al., editor. Essentials of Medical Geology. United Kingdom: Springer; 2013 p 279–310.
35. McCarty KM, Hanh HT, Kim KW. Arsenic geochemistry and human health in South East Asia. Rev Environ Health 2011;26(1):71–8. [PubMed: 21714384]
36. Bundschuh J, Litter MI, Parvez F, Roman-Ross G, Nicolli HB, Jean JS, et al. One century of arsenic exposure in Latin America: a review of history and occurrence from 14 countries. Sci Total Environ 2012;429:2–35 doi 10.1016/j.scitotenv.2011.06.024. [PubMed: 21959248]
37. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. Am J Epidemiol 1998;147(7):660–9. [PubMed: 9554605]
38. Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. Br J Cancer 1992;66(5):888–92. [PubMed: 1419632]
39. Brouwer OF, Onkenhout W, Edelbroek PM, de Kom JF, de Wolff FA, Peters AC. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. Clin Neurol Neurosurg 1992;94(4):307–10. [PubMed: 1335858]
40. Rahman M, Tondel M, Ahmad SA, Chowdhury IA, Faruquee MH, Axelson O. Hypertension and arsenic exposure in Bangladesh. Hypertension 1999;33(1):74–8. [PubMed: 9931084]
41. Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiology 1996;7(2):117–24. [PubMed: 8834549]
42. Bardach AE, Ciapponi A, Soto N, Chaparro MR, Calderon M, Briatore A, et al. Epidemiology of chronic disease related to arsenic in Argentina: A systematic review. Sci Total Environ 2015;538:802–16 doi 10.1016/j.scitotenv.2015.08.070. [PubMed: 26340583]

43. IARC working group on the evaluation of carcinogenic risks to humans. Arsenic and inorganic arsenic compounds. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans 1973;2:48–73.
44. IARC working group on the evaluation of carcinogenic risks to humans. Arsenic and arsenic compounds. Some metals and metallic compounds. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans 1980;23:39–141.
45. IARC working group on the evaluation of carcinogenic risks to humans. Arsenic and arsenic compounds. Some drinking water disinfectants and contaminants, including arsenic. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans 2004;84:39–70.
46. Chain EPoCitF. Scientific Opinion on Arsenic in Food. EFSA Journal 2009;7(10):1351–n/a doi 10.2903/j.efsa.2009.1351.
47. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol 2008;82(8):493–512 doi 10.1007/s00204-008-0313-y. [PubMed: 18496671]
48. Germolec DR, Yang RS, Ackermann MF, Rosenthal GJ, Boorman GA, Blair P, et al. Toxicology studies of a chemical mixture of 25 groundwater contaminants. II. Immunosuppression in B6C3F1 mice. Fundam Appl Toxicol 1989;13(3):377–87. [PubMed: 2515087]
49. Cunha ES, Kawahara R, Kadowaki MK, Amstalden HG, Noleto GR, Cadena SM, et al. Melanogenesis stimulation in B16-F10 melanoma cells induces cell cycle alterations, increased ROS levels and a differential expression of proteins as revealed by proteomic analysis. Exp Cell Res 2012;318(15):1913–25 doi 10.1016/j.yexcr.2012.05.019. [PubMed: 22668500]
50. Jenkins NC, Grossman D. Role of melanin in melanocyte dysregulation of reactive oxygen species. BioMed research international 2013;2013:908797 doi 10.1155/2013/908797. [PubMed: 23555101]
51. Suzukawa AA, Vieira A, Winnischofer SM, Scalfo AC, Di Mascio P, Ferreira AM, et al. Novel properties of melanins include promotion of DNA strand breaks, impairment of repair, and reduced ability to damage DNA after quenching of singlet oxygen. Free Radic Biol Med 2012;52(9):1945–53 doi 10.1016/j.freeradbiomed.2012.02.039. [PubMed: 22401857]
52. Cooper KL, Yager JW, Hudson LG. Melanocytes and keratinocytes have distinct and shared responses to ultraviolet radiation and arsenic. Toxicology letters 2014;224(3):407–15 doi 10.1016/j.toxlet.2013.11.010. [PubMed: 24270004]
53. Dennis LK, Lynch CF, Sandler DP, Alavanja MC. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environmental health perspectives 2010;118(6):812–7 doi 10.1289/ehp.0901518. [PubMed: 20164001]
54. Baastrup R, Sorensen M, Balstrom T, Frederiksen K, Larsen CL, Tjonneland A, et al. Arsenic in drinking-water and risk for cancer in Denmark. Environmental health perspectives 2008;116(2):231–7 doi 10.1289/ehp.10623. [PubMed: 18288323]
55. Beane Freeman LE, Dennis LK, Lynch CF, Thorne PS, Just CL. Toenail arsenic content and cutaneous melanoma in Iowa. Am J Epidemiol 2004;160(7):679–87 doi 10.1093/aje/kwh267. [PubMed: 15383412]
56. Karagas MR, Gossai A, Pierce B, Ahsan H. Drinking Water Arsenic Contamination, Skin Lesions, and Malignancies: A Systematic Review of the Global Evidence. Curr Environ Health Rep 2015;2(1):52–68 doi 10.1007/s40572-014-0040-x. [PubMed: 26231242]
57. Maresca V, Flori E, Picardo M. Skin phototype: a new perspective. Pigment Cell Melanoma Res 2015;28(4):378–89 doi 10.1111/pcmr.12365. [PubMed: 25786343]
58. Matthews NH, Li WQ, Qureshi AA, Weinstock MA, Cho E. Epidemiology of Melanoma In: Ward WH, Farma JM, editors. Cutaneous Melanoma: Etiology and Therapy. Brisbane (AU): Codon Publications, 2017.
59. Neubauer O Arsenical cancer; a review. Br J Cancer 1947;1(2):192–251. [PubMed: 20266457]
60. Yeh S, How SW, Lin CS. Arsenical cancer of skin. Histologic study with special reference to Bowen's disease. Cancer 1968;21(2):312–39. [PubMed: 4952508]
61. Neumann E, Schwank R. Multiple malignant and benign epidermal and dermal tumours following arsenic. Acta Derm Venereol 1960;40:400–9. [PubMed: 13728543]

62. Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. Journal of the National Cancer Institute 1968;40(3):453–63. [PubMed: 5644201]
63. Hsueh YM, Chiou HY, Huang YL, Wu WL, Huang CC, Yang MH, et al. Serum beta-carotene level, arsenic methylation capability, and incidence of skin cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1997;6(8):589–96.
64. Surdu S, Fitzgerald EF, Bloom MS, Boscoe FP, Carpenter DO, Haase RF, et al. Occupational exposure to arsenic and risk of nonmelanoma skin cancer in a multinational European study. Int J Cancer 2013;133(9):2182–91 doi 10.1002/ijc.28216. [PubMed: 23595521]
65. Huang L, Wu H, van der Kuijp TJ. The health effects of exposure to arsenic-contaminated drinking water: a review by global geographical distribution. Int J Environ Health Res 2015;25(4):432–52 doi 10.1080/09603123.2014.958139. [PubMed: 25365079]
66. Huy TB, Tuyet-Hanh TT, Johnston R, Nguyen-Viet H. Assessing health risk due to exposure to arsenic in drinking water in Hanam Province, Vietnam. Int J Environ Res Public Health 2014;11(8):7575–91 doi 10.3390/ijerph110807575. [PubMed: 25062276]
67. Mayer JE, Goldman RH. Arsenic and skin cancer in the USA: the current evidence regarding arsenic-contaminated drinking water. Int J Dermatol 2016;55(11):e585–e91 doi 10.1111/ijd.13318. [PubMed: 27420023]
68. Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res 1985;45(11 Pt 2):5895–9. [PubMed: 3965150]
69. Chen CJ, Kuo TL, Wu MM. Arsenic and cancers. Lancet 1988;1(8582):414–5.
70. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol 1989;130(6):1123–32. [PubMed: 2589305]
71. Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res 1990;50(17):5470–4. [PubMed: 2386951]
72. Tsai SM, Wang TN, Ko YC. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 1999;54(3):186–93 doi 10.1080/00039899909602258. [PubMed: 10444040]
73. Rivara MI, Cebrian M, Corey G, Hernandez M, Romieu I. Cancer risk in an arsenic-contaminated area of Chile. Toxicol Ind Health 1997;13(2–3):321–38 doi 10.1177/074823379701300217. [PubMed: 9200798]
74. Yu RC, Hsu KH, Chen CJ, Froines JR. Arsenic methylation capacity and skin cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2000;9(11):1259–62.
75. Chen YC, Guo YL, Su HJ, Hsueh YM, Smith TJ, Ryan LM, et al. Arsenic methylation and skin cancer risk in southwestern Taiwan. Journal of occupational and environmental medicine 2003;45(3):241–8. [PubMed: 12661181]
76. Karagas MR, Stukel TA, Morris JS, Tosteson TD, Weiss JE, Spencer SK, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol 2001;153(6):559–65. [PubMed: 11257063]
77. Gilbert-Diamond D, Li Z, Perry AE, Spencer SK, Gandolfi AJ, Karagas MR. A population-based case-control study of urinary arsenic species and squamous cell carcinoma in New Hampshire, USA. Environmental health perspectives 2013;121(10):1154–60 doi 10.1289/ehp.1206178. [PubMed: 23872349]
78. Leonardi G, Vahter M, Clemens F, Goessler W, Gurzau E, Hemminki K, et al. Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: a case-control study. Environ Health Perspect 2012;120(5):721–6 doi 10.1289/ehp.1103534. [PubMed: 22436128]
79. Knobeloch LM, Zierold KM, Anderson HA. Association of arsenic-contaminated drinking-water with prevalence of skin cancer in Wisconsin's Fox River Valley. J Health Popul Nutr 2006;24(2):206–13. [PubMed: 17195561]

80. Haupert TA, Wiersma JH, Goldring JM. Health effects of ingesting arsenic-contaminated groundwater. Wis Med J 1996;95(2):100–4. [PubMed: 8819705]
81. Rosales-Castillo JA, Acosta-Saavedra LC, Torres R, Ochoa-Fierro J, Borja-Aburto VH, Lopez-Carrillo L, et al. Arsenic exposure and human papillomavirus response in non-melanoma skin cancer Mexican patients: a pilot study. Int Arch Occup Environ Health 2004;77(6):418–23 doi 10.1007/s00420-004-0527-0. [PubMed: 15235918]
82. Paul S, Majumdar S, Giri AK. Genetic susceptibility to arsenic-induced skin lesions and health effects: a review. Genes Environ 2015;37:23 doi 10.1186/s41021-015-0023-7. [PubMed: 27350818]
83. Agusa T, Fujihara J, Takeshita H, Iwata H. Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms. Int J Mol Sci 2011;12(4):2351–82 doi 10.3390/ijms12042351. [PubMed: 21731446]
84. Pierce BL, Kibriya MG, Tong L, Jasmine F, Argos M, Roy S, et al. Genome-wide association study identifies chromosome 10q24.32 variants associated with arsenic metabolism and toxicity phenotypes in Bangladesh. PLoS Genet 2012;8(2):e1002522 doi 10.1371/journal.pgen.1002522. [PubMed: 22383894]
85. Pierce BL, Tong L, Argos M, Gao J, Farzana J, Roy S, et al. Arsenic metabolism efficiency has a causal role in arsenic toxicity: Mendelian randomization and gene-environment interaction. Int J Epidemiol 2013;42(6):1862–71 doi 10.1093/ije/dyt182. [PubMed: 24536095]
86. Hernandez A, Marcos R. Genetic variations associated with interindividual sensitivity in the response to arsenic exposure. Pharmacogenomics 2008;9(8):1113–32 doi 10.2217/14622416.9.8.1113. [PubMed: 18681785]
87. De Chaudhuri S, Ghosh P, Sarma N, Majumdar P, Sau TJ, Basu S, et al. Genetic variants associated with arsenic susceptibility: study of purine nucleoside phosphorylase, arsenic (+3) methyltransferase, and glutathione S-transferase omega genes. Environmental health perspectives 2008;116(4):501–5 doi 10.1289/ehp.10581. [PubMed: 18414634]
88. M S. Cadmium In: E M, editor. Metals and their Compounds in the Environment. New York: Weinheim; 1991 p 803–51.
89. Peijnenburg W, Baerselman R, de Groot A, Jager T, Leenders D, Posthuma L, et al. Quantification of metal bioavailability for lettuce (Lactuca sativa L.) in field soils. Arch Environ Contam Toxicol 2000;39(4):420–30. [PubMed: 11031301]
90. Sahmoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and prostate cancer: a critical epidemiologic analysis. Cancer Invest 2005;23(3):256–63. [PubMed: 15945511]
91. Winge DR, Miklossy KA. Domain nature of metallothionein. J Biol Chem 1982;257(7):3471–6. [PubMed: 6801048]
92. Huang Y, He C, Shen C, Guo J. Toxicity of cadmium and its health risks from leafy vegetable consumption. 2017 doi 10.1039/c6fo01580h.
93. Cadmium and cadmium compounds. IARC monographs on the evaluation of carcinogenic risks to humans 1993;58:119–237. [PubMed: 8022055]
94. Schwartz GG, Reis IM. Is cadmium a cause of human pancreatic cancer? Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2000;9(2):139–45.
95. Waalkes MP. Cadmium carcinogenesis. Mutat Res 2003;533(1–2):107–20. [PubMed: 14643415]
96. Fabbri M, Urani C, Sacco MG, Procaccianti C, Gribaldo L. Whole genome analysis and microRNAs regulation in HepG2 cells exposed to cadmium. Altex 2012;29(2):173–82. [PubMed: 22562489]
97. Zhou ZH, Lei YX, Wang CX. Analysis of aberrant methylation in DNA repair genes during malignant transformation of human bronchial epithelial cells induced by cadmium. Toxicol Sci 2012;125(2):412–7 doi 10.1093/toxsci/kfr320. [PubMed: 22112500]
98. Yuan D, Ye S, Pan Y, Bao Y, Chen H, Shao C. Long-term cadmium exposure leads to the enhancement of lymphocyte proliferation via down-regulating p16 by DNA hypermethylation. Mutat Res 2013;757(2):125–31 doi 10.1016/j.mrgentox.2013.07.007. [PubMed: 23948183]
99. Hart BA, Potts RJ, Watkin RD. Cadmium adaptation in the lung - a double-edged sword? Toxicology 2001;160(1–3):65–70. [PubMed: 11246125]

100. Achanzar WE, Achanzar KB, Lewis JG, Webber MM, Waalkes MP. Cadmium induces c-myc, p53, and c-jun expression in normal human prostate epithelial cells as a prelude to apoptosis. Toxicol Appl Pharmacol 2000;164(3):291–300 doi 10.1006/taap.1999.8907. [PubMed: 10799339]
101. Zhou XD, Sens MA, Garrett SH, Somji S, Park S, Gurel V, et al. Enhanced expression of metallothionein isoform 3 protein in tumor heterotransplants derived from As+3- and Cd+2-transformed human urothelial cells. Toxicol Sci 2006;93(2):322–30 doi 10.1093/toxsci/kfl065. [PubMed: 16854967]
102. Spruill MD, Song B, Whong WZ, Ong T. Proto-oncogene amplification and overexpression in cadmium-induced cell transformation. J Toxicol Environ Health A 2002;65(24):2131–44 doi 10.1080/00984100290071379. [PubMed: 12515591]
103. Huang C, Zhang Q, Li J, Shi X, Castranova V, Ju G, et al. Involvement of Erks activation in cadmium-induced AP-1 transactivation in vitro and in vivo. Mol Cell Biochem 2001;222(1–2): 141–7. [PubMed: 11678596]
104. Hartwig A, Schwerdtle T. Interactions by carcinogenic metal compounds with DNA repair processes: toxicological implications. Toxicology letters 2002;127(1–3):47–54. [PubMed: 12052640]
105. Venza M, Visalli M, Biondo C, Oteri R, Agliano F, Morabito S, et al. Epigenetic effects of cadmium in cancer: focus on melanoma. Curr Genomics 2014;15(6):420–35 doi 10.2174/1389202915061501061459 32. [PubMed: 25646071]
106. Venza M, Visalli M, Biondo C, Oteri R, Agliano F, Morabito S, et al. Epigenetic marks responsible for cadmium-induced melanoma cell overgrowth. Toxicol In Vitro 2015;29(1):242–50 doi 10.1016/j.tiv.2014.10.020. [PubMed: 25448810]
107. Wester RC, Maibach HI, Sedik L, Melendres J, DiZio S, Wade M. In vitro percutaneous absorption of cadmium from water and soil into human skin. Fundam Appl Toxicol 1992;19(1): 1–5. [PubMed: 1397789]
108. Fasanya-Odewumi C, Latinwo LM, Ikediobi CO, Gilliard L, Sponholtz G, Nwoga J, et al. The genotoxicity and cytotoxicity of dermally-administered cadmium: effects of dermal cadmium administration. Int J Mol Med 1998;1(6):1001–6. [PubMed: 9852638]
109. Zelger B, Hittmair A, Schir M, Ofner C, Ofner D, Fritsch PO, et al. Immunohistochemically demonstrated metallothionein expression in malignant melanoma. Histopathology 1993;23(3): 257–63. [PubMed: 8225244]
110. Haga A, Nagase H, Kito H, Sato T. Enhanced invasiveness of tumour cells after host exposure to heavy metals. Eur J Cancer 1996;32a(13):2342–7. [PubMed: 9038619]
111. Weinlich G, Bitterlich W, Mayr V, Fritsch PO, Zelger B. Metallothionein-overexpression as a prognostic factor for progression and survival in melanoma. A prospective study on 520 patients. Br J Dermatol 2003;149(3):535–41. [PubMed: 14510986]
112. Yokouchi M, Hiramatsu N, Hayakawa K, Kasai A, Takano Y, Yao J, et al. Atypical, bidirectional regulation of cadmium-induced apoptosis via distinct signaling of unfolded protein response. Cell Death Differ 2007;14(8):1467–74 doi 10.1038/sj.cdd.4402154. [PubMed: 17464326]
113. Koropatnick J, Pearson J. Zinc treatment, metallothionein expression, and resistance to cisplatin in mouse melanoma cells. Somat Cell Mol Genet 1990;16(6):529–37. [PubMed: 2267627]
114. Lansdown AB, Sampson B. Dermal toxicity and percutaneous absorption of cadmium in rats and mice. Lab Anim Sci 1996;46(5):549–54. [PubMed: 8905589]
115. Deschamps F, Moulin JJ, Wild P, Labriffe H, Haguenoer JM. Mortality study among workers producing chromate pigments in France. Int Arch Occup Environ Health 1995;67(3):147–52. [PubMed: 7591171]
116. Barceloux DG. Chromium. J Toxicol Clin Toxicol 1999;37(2):173–94. [PubMed: 10382554]
117. Anderson RA, Bryden NA, Polansky MM. Dietary chromium intake. Freely chosen diets, institutional diet, and individual foods. Biological trace element research 1992;32:117–21. [PubMed: 1375047]
118. Shelnutt SR, Goad P, Belsito DV. Dermatological toxicity of hexavalent chromium. Crit Rev Toxicol 2007;37(5):375–87 doi 10.1080/10408440701266582. [PubMed: 17612952]

119. Biedermann KA, Landolph JR. Role of valence state and solubility of chromium compounds on induction of cytotoxicity, mutagenesis, and anchorage independence in diploid human fibroblasts. Cancer Res 1990;50(24):7835–42. [PubMed: 2253225]
120. Wise JP, Leonard JC, Patierno SR. Clastogenicity of lead chromate particles in hamster and human cells. Mutat Res 1992;278(1):69–79. [PubMed: 1370121]
121. Ha L, Ceryak S, Patierno SR. Generation of S phase-dependent DNA double-strand breaks by Cr(VI) exposure: involvement of ATM in Cr(VI) induction of gamma-H2AX. Carcinogenesis 2004;25(11):2265–74 doi 10.1093/carcin/bgh242. [PubMed: 15284180]
122. Xie H, Holmes AL, Wise SS, Young JL, Wise JT, Wise JP, Sr. Human Skin Cells Are More Sensitive than Human Lung Cells to the Cytotoxic and Cell Cycle Arresting Impacts of Particulate and Soluble Hexavalent Chromium. Biological trace element research 2015;166(1): 49–56 doi 10.1007/s12011-015-0315-6. [PubMed: 25805272]
123. Occupational safety and health administration, Department of Labor. Ocupational Exposure to hexavalent chromium. Final rule. United States Department of Labor Occupational Safety and Health Administration 2006;71(39):10099–385.
124. Davidson T, Kluz T, Burns F, Rossman T, Zhang Q, Uddin A, et al. Exposure to chromium (VI) in the drinking water increases susceptibility to UV-induced skin tumors in hairless mice. Toxicol Appl Pharmacol 2004;196(3):431–7 doi 10.1016/j.taap.2004.01.006. [PubMed: 15094314]
125. Uddin AN, Burns FJ, Rossman TG, Chen H, Kluz T, Costa M. Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice. Toxicol Appl Pharmacol 2007;221(3):329–38 doi 10.1016/j.taap.2007.03.030. [PubMed: 17499830]
126. Costa M, Klein CB. Toxicity and carcinogenicity of chromium compounds in humans. Crit Rev Toxicol 2006;36(2):155–63. [PubMed: 16736941]
127. Miret S, Simpson RJ, McKie AT. Physiology and molecular biology of dietary iron absorption. Annu Rev Nutr 2003;23:283–301 doi 10.1146/annurev.nutr.23.011702.073139. [PubMed: 12626689]
128. Richardson DR, Ponka P. The molecular mechanisms of the metabolism and transport of iron in normal and neoplastic cells. Biochim Biophys Acta 1997;1331(1):1–40. [PubMed: 9325434]
129. Le NT, Richardson DR. The role of iron in cell cycle progression and the proliferation of neoplastic cells. Biochim Biophys Acta 2002;1603(1):31–46. [PubMed: 12242109]
130. Darnell G, Richardson DR. The potential of iron chelators of the pyridoxal isonicotinoyl hydrazone class as effective antiproliferative agents III: the effect of the ligands on molecular targets involved in proliferation. Blood 1999;94(2):781–92. [PubMed: 10397746]
131. Gao J, Lovejoy D, Richardson DR. Effect of iron chelators with potent anti-proliferative activity on the expression of molecules involved in cell cycle progression and growth. Redox Rep 1999;4(6):311–2 doi 10.1179/135100099101534990. [PubMed: 10772072]
132. Vile GF, Tyrrell RM. UVA radiation-induced oxidative damage to lipids and proteins in vitro and in human skin fibroblasts is dependent on iron and singlet oxygen. Free Radic Biol Med 1995;18(4):721–30. [PubMed: 7750796]
133. Richardson DR. Iron chelators as therapeutic agents for the treatment of cancer. Crit Rev Oncol Hematol 2002;42(3):267–81. [PubMed: 12050019]
134. Chitambar CR, Massey EJ, Seligman PA. Regulation of transferrin receptor expression on human leukemic cells during proliferation and induction of differentiation. Effects of gallium and dimethylsulfoxide. J Clin Invest 1983;72(4):1314–25 doi 10.1172/jci111087. [PubMed: 6313760]
135. Richardson D, Baker E. Two mechanisms of iron uptake from transferrin by melanoma cells. The effect of desferrioxamine and ferric ammonium citrate. J Biol Chem 1992;267(20):13972–9. [PubMed: 1629195]
136. Weinberg ED. The role of iron in cancer. Eur J Cancer Prev 1996;5(1):19–36.
137. Richardson DR, Baker E. The uptake of iron and transferrin by the human malignant melanoma cell. Biochim Biophys Acta 1990;1053(1):1–12. [PubMed: 2364114]
138. Trinder D, Zak O, Aisen P. Transferrin receptor-independent uptake of differic transferrin by human hepatoma cells with antisense inhibition of receptor expression. Hepatology 1996;23(6): 1512–20 doi 10.1053/jhep.1996.v23.pm0008675172. [PubMed: 8675172]

139. Larrick JW, Cresswell P. Modulation of cell surface iron transferrin receptors by cellular density and state of activation. J Supramol Struct 1979;11(4):579–86 doi 10.1002/jss.400110415. [PubMed: 232525]
140. Morgan EH. Transferrin, biochemistry, physiology and clinical significance. Molecular Aspects of Medicine 1981;4(1):1–123 doi 10.1016/0098-2997(81)90003-0.
141. Stryker WS, Stampfer MJ, Stein EA, Kaplan L, Louis TA, Sober A, et al. Diet, plasma levels of beta-carotene and alpha-tocopherol, and risk of malignant melanoma. Am J Epidemiol 1990;131(4):597–611. [PubMed: 2316493]
142. Bain C, Green A, Siskind V, Alexander J, Harvey P. Diet and melanoma. An exploratory case-control study. Ann Epidemiol 1993;3(3):235–8. [PubMed: 8275194]
143. Gorodetsky R, Sheskin J, Weinreb A. Iron, copper, and zinc concentrations in normal skin and in various nonmalignant and malignant lesions. Int J Dermatol 1986;25(7):440–5. [PubMed: 3771040]
144. Bedrick AE, Ramaswamy G, Tchertkoff V. Histochemical determination of copper, zinc, and iron in some benign and malignant tissues. Am J Clin Pathol 1986;86(5):637–40. [PubMed: 3776915]
145. Kumasaka MY, Yamanoshita O, Shimizu S, Ohnuma S, Furuta A, Yajima I, et al. Enhanced carcinogenicity by coexposure to arsenic and iron and a novel remediation system for the elements in well drinking water. Arch Toxicol 2013;87(3):439–47 doi 10.1007/s00204-012-0964-6. [PubMed: 23100159]
146. Copper Development Association. Copper in Human Health. http://www.copper.org/consumers/health/cu_health_uk.html>. Accessed 2017 04 April.
147. Shorrocks VM, Alloway BJ. Copper in Plant, Animal and Human Nutrition Potters Bar, UK: Copper Development Association; 1986; 84.
148. Uauy R, Olivares M, Gonzalez M. Essentiality of copper in humans. Am J Clin Nutr 1998;67(5 Suppl):952s–9s. [PubMed: 9587135]
149. Pena MM, Lee J, Thiele DJ. A delicate balance: homeostatic control of copper uptake and distribution. J Nutr 1999;129(7):1251–60. [PubMed: 10395584]
150. Horn D, Barrientos A. Mitochondrial copper metabolism and delivery to cytochrome c oxidase. IUBMB Life 2008;60(7):421–9 doi 10.1002/iub.50. [PubMed: 18459161]
151. Fukai T, Ushio-Fukai M. Superoxide dismutases: role in redox signaling, vascular function, and diseases. Antioxid Redox Signal 2011;15(6):1583–606 doi 10.1089/ars.2011.3999. [PubMed: 21473702]
152. JR T. Copper. In: Shills ME SM, Ross AC, Caballero B, Cousins RJ editor. Modern nutrition in health and disease. 10 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006 p 289–99.
153. Gupte A, Mumper RJ. Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. Cancer Treat Rev 2009;35(1):32–46 doi 10.1016/j.ctrv.2008.07.004. [PubMed: 18774652]
154. Park KC, Fouani L, Jansson PJ, Wooi D, Sahni S, Lane DJ, et al. Copper and conquer: copper complexes of di-2-pyridylketone thiosemicarbazones as novel anti-cancer therapeutics. Metallomics 2016;8(9):874–86 doi 10.1039/c6mt00105j. [PubMed: 27334916]
155. Brady DC, Crowe MS, Turski ML, Hobbs GA, Yao X, Chaikuad A, et al. Copper is required for oncogenic BRAF signalling and tumorigenesis. Nature 2014;509(7501):492–6 doi 10.1038/nature13180. [PubMed: 24717435]
156. Liu H, Zhang Y, Zheng S, Weng Z, Ma J, Li Y, et al. Detention of copper by sulfur nanoparticles inhibits the proliferation of A375 malignant melanoma and MCF-7 breast cancer cells. Biochem Biophys Res Commun 2016;477(4):1031–7 doi 10.1016/j.bbrc.2016.07.026. [PubMed: 27392714]
157. Ros-Bullon MR, Sanchez-Pedreno P, Martinez-Liarte JH. Serum zinc levels are increased in melanoma patients. Melanoma Res 1998;8(3):273–7. [PubMed: 9664150]
158. Sahl WJ, Glore S, Garrison P, Oakleaf K, Johnson SD. Basal cell carcinoma and lifestyle characteristics. Int J Dermatol 1995;34(6):398–402. [PubMed: 7657438]
159. Vural P, Canbaz M, Selcuki D. Plasma antioxidant defense in actinic keratosis and basal cell carcinoma. J Eur Acad Dermatol Venereol 1999;13(2):96–101. [PubMed: 10568487]

160. Kobayashi T, Matsumoto M, Iizuka H, Suzuki K, Taniguchi N. Superoxide dismutase in psoriasis, squamous cell carcinoma and basal cell epithelioma: an immunohistochemical study. Br J Dermatol 1991;124(6):555–9. [PubMed: 2064938]
161. Sander CS, Hamm F, Elsner P, Thiele JJ. Oxidative stress in malignant melanoma and non-melanoma skin cancer. Br J Dermatol 2003;148(5):913–22. [PubMed: 12786821]
162. Duran HA, Lanfranchi H, Palmieri MA, de Rey BM. Inhibition of benzoyl peroxide-induced tumor promotion and progression by copper(II)(3,5-diisopropylsalicylate)2. Cancer Lett 1993;69(3):167–72. [PubMed: 8513442]
163. Barceloux DG. Zinc. J Toxicol Clin Toxicol 1999;37(2):279–92. [PubMed: 10382562]
164. Association IZ. 2017 Zinc in the environment. <http://www.zinc.org/environment/>.
165. McSweeney PC. The safety of nanoparticles in sunscreens: An update for general practice. Aust Fam Physician 2016;45(6):397–9. [PubMed: 27622230]
166. Holmes AM, Song Z, Moghimi HR, Roberts MS. Relative Penetration of Zinc Oxide and Zinc Ions into Human Skin after Application of Different Zinc Oxide Formulations. ACS Nano 2016;10(2):1810–9 doi 10.1021/acsnano.5b04148. [PubMed: 26741484]
167. Sandstead HH. Understanding zinc: recent observations and interpretations. J Lab Clin Med 1994;124(3):322–7. [PubMed: 8083574]
168. Prasad AS. Zinc: an overview. Nutrition 1995;11(1 Suppl):93–9. [PubMed: 7749260]
169. Vallee BL, Falchuk KH. The biochemical basis of zinc physiology. Physiol Rev 1993;73(1):79–118. [PubMed: 8419966]
170. Coleman JE. Zinc proteins: enzymes, storage proteins, transcription factors, and replication proteins. Annu Rev Biochem 1992;61:897–946 doi 10.1146/annurev.bi.61.070192.004341. [PubMed: 1497326]
171. Leccia MT, Richard MJ, Beani JC, Faure H, Monjo AM, Cadet J, et al. Protective effect of selenium and zinc on UV-A damage in human skin fibroblasts. Photochem Photobiol 1993;58(4):548–53. [PubMed: 8248330]
172. Richard MJ, Guiraud P, Leccia MT, Beani JC, Favier A. Effect of zinc supplementation on resistance of cultured human skin fibroblasts toward oxidant stress. Biological trace element research 1993;37(2–3):187–99 doi 10.1007/bf02783794. [PubMed: 7688532]
173. Leccia MT, Richard MJ, Favier A, Beani JC. Zinc protects against ultraviolet A1-induced DNA damage and apoptosis in cultured human fibroblasts. Biological trace element research 1999;69(3):177–90. [PubMed: 10468155]
174. Parat MO, Richard MJ, Pollet S, Hadjur C, Favier A, Beani JC. Zinc and DNA fragmentation in keratinocyte apoptosis: its inhibitory effect in UVB irradiated cells. J Photochem Photobiol B 1997;37(1–2):101–6. [PubMed: 9043099]
175. Jansen R, Osterwalder U, Wang SQ, Burnett M, Lim HW. Photoprotection: part II. Sunscreen: development, efficacy, and controversies. J Am Acad Dermatol 2013;69(6):867.e1–14; quiz 81–2 doi 10.1016/j.jaad.2013.08.022.
176. Tran DT, Salmon R. Potential photocarcinogenic effects of nanoparticle sunscreens. Australas J Dermatol 2011;52(1):1–6 doi 10.1111/j.1440-0960.2010.00677.x.
177. Cross SE, Innes B, Roberts MS, Tsuzuki T, Robertson TA, McCormick P. Human skin penetration of sunscreen nanoparticles: in-vitro assessment of a novel micronized zinc oxide formulation. Skin Pharmacol Physiol 2007;20(3):148–54 doi 10.1159/000098701. [PubMed: 17230054]
178. Kimura E, Kawano Y, Todo H, Ikarashi Y, Sugibayashi K. Measurement of skin permeation/penetration of nanoparticles for their safety evaluation. Biol Pharm Bull 2012;35(9):1476–86. [PubMed: 22975498]
179. Monteiro-Riviere NA, Wiench K, Landsiedel R, Schulte S, Inman AO, Riviere JE. Safety evaluation of sunscreen formulations containing titanium dioxide and zinc oxide nanoparticles in UVB sunburned skin: an in vitro and in vivo study. Toxicol Sci 2011;123(1):264–80 doi 10.1093/toxsci/kfr148. [PubMed: 21642632]
180. Gulson B, McCall M, Korsch M, Gomez L, Casey P, Oytam Y, et al. Small amounts of zinc from zinc oxide particles in sunscreens applied outdoors are absorbed through human skin. Toxicol Sci 2010;118(1):140–9 doi 10.1093/toxsci/kfq243. [PubMed: 20705894]

181. James SA, Feltis BN, de Jonge MD, Sridhar M, Kimpton JA, Altissimo M, et al. Quantification of ZnO nanoparticle uptake, distribution, and dissolution within individual human macrophages. ACS Nano 2013;7(12):10621–35 doi 10.1021/nn403118u. [PubMed: 24187959]
182. US food and drug administration. Rulemaking History for OTC Sunscreen Drug Products. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm072134.htm#zinc>. Accessed 2007 04 April.
183. Grant WB. An ecological study of cancer mortality rates including indices for dietary iron and zinc. Anticancer Res 2008;28(3b):1955–63. [PubMed: 18630488]
184. Horcicko J, Pantucek M. Hypozincemia in patients with malignant melanoma. Clin Chim Acta 1983;130(3):279–82. [PubMed: 6872261]
185. Siu TO, Basu T, Jerry LM. Zinc, carotene, and retinol in melanoma and non-melanoma skin cancer. In Vivo 1991;5(1):65–8. [PubMed: 1932628]
186. Bialy TL, Rothe MJ, Grant-Kels JM. Dietary factors in the prevention and treatment of nonmelanoma skin cancer and melanoma. Dermatol Surg 2002;28(12):1143–52. [PubMed: 12472495]
187. Holben DH, Smith AM. The diverse role of selenium within selenoproteins: a review. J Am Diet Assoc 1999;99(7):836–43 doi 10.1016/s0002-8223(99)00198-4. [PubMed: 10405682]
188. Rayman MP. Selenium and human health. Lancet 2012;379(9822):1256–68 doi 10.1016/s0140-6736(11)61452-9. [PubMed: 22381456]
189. Vinceti M, Crespi CM, Bonvicini F, Malagoli C, Ferrante M, Marmiroli S, et al. The need for a reassessment of the safe upper limit of selenium in drinking water. Sci Total Environ 2013;443:633–42 doi 10.1016/j.scitotenv.2012.11.025. [PubMed: 23220755]
190. Vinceti M, Crespi CM, Malagoli C, Del Giovane C, Krogh V. Friend or foe? The current epidemiologic evidence on selenium and human cancer risk. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013;31(4):305–41 doi 10.1080/10590501.2013.844757. [PubMed: 24171437]
191. Fordyce F Selenium geochemistry and health. Ambio 2007;36(1):94–7. [PubMed: 17408199]
192. Zagrodzki P, Laszczyk P. [Selenium and cardiovascular disease: selected issues]. Postepy Hig Med Dosw (Online) 2006;60:624–31. [PubMed: 17199104]
193. Navarro-Alarcon M, Cabrera-Vique C. Selenium in food and the human body: a review. Sci Total Environ 2008;400(1–3):115–41 doi 10.1016/j.scitotenv.2008.06.024. [PubMed: 18657851]
194. Tanguy S, Grauzam S, de Leiris J, Boucher F. Impact of dietary selenium intake on cardiac health: experimental approaches and human studies. Mol Nutr Food Res 2012;56(7):1106–21 doi 10.1002/mnfr.201100766. [PubMed: 22760983]
195. Berthold HK, Michalke B, Krone W, Guallar E, Gouni-Berthold I. Influence of serum selenium concentrations on hypertension: the Lipid Analytic Cologne cross-sectional study. J Hypertens 2012;30(7):1328–35 doi 10.1097/HJH.0b013e32835414df. [PubMed: 22573120]
196. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S. Selenium supplementation for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews 2013(1):Cd009671 doi 10.1002/14651858.CD009671.pub2. [PubMed: 23440843]
197. Li S, Xiao T, Zheng B. Medical geology of arsenic, selenium and thallium in China. Sci Total Environ 2012;421-422:31–40 doi 10.1016/j.scitotenv.2011.02.040. [PubMed: 21440288]
198. Nazemi L, Nazmara S, Eshraghyan MR, Nasseri S, Djafarian K, Yunesian M, et al. Selenium status in soil, water and essential crops of Iran. Iranian J Environ Health Sci Eng 2012;9(1):11 doi 10.1186/1735-2746-9-11. [PubMed: 23369199]
199. World Health organization. Vitamin and mineral requirements in human nutrition. In: Cataloguing WL, editor. 2nd ed: World Health Organization and Food and Agriculture Organization of the United Nations; 2004.
200. Kieliszek M, Blazejak S. Current Knowledge on the Importance of Selenium in Food for Living Organisms: A Review. Molecules 2016;21(5) doi 10.3390/molecules21050609.
201. Jovanovic IB, Velickovic M, Vukovic D, Milanovic S, Valcic O, Gvozdic D. Effects of Different Amounts of Supplemental Selenium and Vitamin E on the Incidence of Retained Placenta, Selenium, Malondialdehyde, and Thyronines Status in Cows Treated with Prostaglandin F2alpha

for the Induction of Parturition. J Vet Med 2013;2013:867453 doi 10.1155/2013/867453. [PubMed: 26464914]

202. Ruseva B, Himcheva I, Nankova D. Importance of selenoproteins for the function of the thyroid gland. Medicine 2013;3(1).
203. Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for human health. Metallomics 2014;6(1):25–54 doi 10.1039/c3mt00185g. [PubMed: 24185753]
204. Park K, Rimm EB, Siscovick DS, Spiegelman D, Manson JE, Morris JS, et al. Toenail selenium and incidence of type 2 diabetes in U.S. men and women. Diabetes Care 2012;35(7):1544–51 doi 10.2337/dc11-2136. [PubMed: 22619078]
205. Stranges S, Sieri S, Vinceti M, Grioni S, Guallar E, Laclaustra M, et al. A prospective study of dietary selenium intake and risk of type 2 diabetes. BMC public health 2010;10:564 doi 10.1186/1471-2458-10-564. [PubMed: 20858268]
206. Cai X, Wang C, Yu W, Fan W, Wang S, Shen N, et al. Selenium Exposure and Cancer Risk: an Updated Meta-analysis and Meta-regression. Sci Rep 2016;6:19213 doi 10.1038/srep19213. [PubMed: 26786590]
207. Vinceti M, Filippini T, Del Giovane C, Dennert G, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. Cochrane Database Syst Rev 2018;1–CD005195 doi 10.1002/14651858.CD005195.pub4.
208. Dennert G, Zwahlen M, Brinkman M, Vinceti M, Zeegers MP, Horneber M. Selenium for preventing cancer. The Cochrane database of systematic reviews 2011(5):Cd005195 doi 10.1002/14651858.CD005195.pub2. [PubMed: 21563143]
209. Garland M, Morris JS, Stampfer MJ, Colditz GA, Spate VL, Baskett CK, et al. Prospective study of toenail selenium levels and cancer among women. Journal of the National Cancer Institute 1995;87(7):497–505. [PubMed: 7707436]
210. Asgari MM, Maruti SS, Kushi LH, White E. Antioxidant supplementation and risk of incident melanomas: results of a large prospective cohort study. Arch Dermatol 2009;145(8):879–82 doi 10.1001/archdermatol.2009.176. [PubMed: 19687417]
211. Le Marchand L, Saltzman BS, Hankin JH, Wilkens LR, Franke AA, Morris SJ, et al. Sun exposure, diet, and melanoma in Hawaii Caucasians. Am J Epidemiol 2006;164(3):232–45 doi 10.1093/aje/kwj115. [PubMed: 16524953]
212. Breslow RA, Alberg AJ, Helzlsouer KJ, Bush TL, Norkus EP, Morris JS, et al. Serological precursors of cancer: malignant melanoma, basal and squamous cell skin cancer, and prediagnostic levels of retinol, beta- carotene, lycopene, alpha-tocopherol, and selenium. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1995;4(8):837–42.
213. Vinceti M, Rothman KJ, Bergomi M, Borciani N, Serra L, Vivoli G. Excess melanoma incidence in a cohort exposed to high levels of environmental selenium. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1998;7(10):853–6.
214. Vinceti M, Crespi CM, Malagoli C, Bottecchi I, Ferrari A, Sieri S, et al. A case-control study of the risk of cutaneous melanoma associated with three selenium exposure indicators. Tumori 2012;98(3):287–95 doi 10.1700/1125.12394. [PubMed: 22825502]
215. Cassidy PB, Fain HD, Cassidy JP, Jr., Tran SM, Moos PJ, Boucher KM, et al. Selenium for the prevention of cutaneous melanoma. Nutrients 2013;5(3):725–49 doi 10.3390/nu5030725. [PubMed: 23470450]
216. Chen T, Wong YS. Selenocystine induces apoptosis of A375 human melanoma cells by activating ROS-mediated mitochondrial pathway and p53 phosphorylation. Cell Mol Life Sci 2008;65(17): 2763–75 doi 10.1007/s00018-008-8329-2. [PubMed: 18661100]
217. Reid ME, Duffield-Lillico AJ, Slate E, Natarajan N, Turnbull B, Jacobs E, et al. The nutritional prevention of cancer: 400 mcg per day selenium treatment. Nutr Cancer 2008;60(2):155–63 doi 10.1080/01635580701684856. [PubMed: 18444146]
218. Dreno B, Euvrard S, Frances C, Moyse D, Nandeuil A. Effect of selenium intake on the prevention of cutaneous epithelial lesions in organ transplant recipients. Eur J Dermatol 2007;17(2):140–5 doi 10.1684/ejd.2007.0127. [PubMed: 17337398]

219. Davies TW, Treasure FP, Welch AA, Day NE. Diet and basal cell skin cancer: results from the EPIC-Norfolk cohort. Br J Dermatol 2002;146(6):1017–22. [PubMed: 12072070]

220. Heinen MM, Hughes MC, Ibiebele TI, Marks GC, Green AC, van der Pols JC. Intake of antioxidant nutrients and the risk of skin cancer. Eur J Cancer 2007;43(18):2707–16 doi 10.1016/j.ejca.2007.09.005. [PubMed: 17988857]

221. Knekt P, Aromaa A, Maatela J, Alfthan G, Aaran RK, Hakama M, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. Journal of the National Cancer Institute 1990;82(10):864–8. [PubMed: 2332904]

222. McNaughton SA, Marks GC, Green AC. Role of dietary factors in the development of basal cell cancer and squamous cell cancer of the skin. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2005;14(7):1596–607 doi 10.1158/1055-9965.epi-05-0026.

223. van der Pols JC, Heinen MM, Hughes MC, Ibiebele TI, Marks GC, Green AC. Serum antioxidants and skin cancer risk: an 8-year community-based follow-up study. Cancer Epidemiol Biomarkers Prev 2009;18(4):1167–73 doi 10.1158/1055-9965.epi-08-1211. [PubMed: 19336544]

224. Karagas MR, Greenberg ER, Nierenberg D, Stukel TA, Morris JS, Stevens MM, et al. Risk of squamous cell carcinoma of the skin in relation to plasma selenium, alpha-tocopherol, beta-carotene, and retinol: a nested case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1997;6(1):25–9.

225. Burke KE, Burford RG, Combs GF, Jr, French IW, Skeffington DR. The effect of topical L-selenomethionine on minimal erythema dose of ultraviolet irradiation in humans. Photodermatol Photoimmunol Photomed 1992;9(2):52–7. [PubMed: 1489715]

226. Traynor NJ, McKenzie RC, Beckett GJ, Gibbs NK. Selenomethionine inhibits ultraviolet radiation-induced p53 transactivation. Photodermatol Photoimmunol Photomed 2006;22(6):297–303 doi 10.1111/j.1600-0781.2006.00256.x. [PubMed: 17100737]

227. Rafferty TS, Beckett GJ, Walker C, Bisset YC, McKenzie RC. Selenium protects primary human keratinocytes from apoptosis induced by exposure to ultraviolet radiation. Clin Exp Dermatol 2003;28(3):294–300. [PubMed: 12780718]

228. Rafferty TS, McKenzie RC, Hunter JA, Howie AF, Arthur JR, Nicol F, et al. Differential expression of selenoproteins by human skin cells and protection by selenium from UVB-radiation-induced cell death. Biochem J 1998;332 (Pt 1):231–6. [PubMed: 9576872]

229. Hu G, Wang T, Liu J, Chen Z, Zhong L, Yu S, et al. Serum Protein Expression Profiling and Bioinformatics Analysis in Workers Occupationally Exposed to Chromium (VI). Toxicology letters 2017 doi 10.1016/j.toxlet.2017.05.026.

230. Haby MM, Soares A, Chapman E, Clark R, Korc M, Galvao LA. Interventions that facilitate sustainable development by preventing toxic exposure to chemicals: an overview of systematic reviews. Revista panamericana de salud publica = Pan American journal of public health 2016;39(6):378–86. [PubMed: 27706431]

231. King KE, Darrah TH, Money E, Meentemeyer R, Maguire RL, Nye MD, et al. Geographic clustering of elevated blood heavy metal levels in pregnant women. BMC public health 2015;15:1035 doi 10.1186/s12889-015-2379-9. [PubMed: 26449855]

232. Katner A, Lackovic M, Streva K, Paul V, Trachtman WC. Evaluation of available data sources to prioritize parishes for arsenic monitoring and outreach related to private well drinking water. Journal of public health management and practice : JPHMP 2015;21 Suppl 2:S93–101 doi 10.1097/phh.0000000000000177.

233. Nawrot TS, Staessen JA, Roels HA, Munters E, Cuypers A, Richart T, et al. Cadmium exposure in the population: from health risks to strategies of prevention. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine 2010;23(5):769–82 doi 10.1007/s10534-010-9343-z.

234. Barry S Levy GRW, Kathleen M. Rest, Weeks James L, editor. Preventing Occupational Disease and Injury. Second ed. Washington, DC: American Public Health Association; 2005.

235. Clark LC, Combs GF, Jr., Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized

controlled trial. Nutritional Prevention of Cancer Study Group. Jama 1996;276(24):1957–63. [PubMed: 8971064]

236. Clark LC, Graham GF, Crounse RG, Grimson R, Hulka B, Shy CM. Plasma selenium and skin neoplasms: a case-control study. Nutr Cancer 1984;6(1):13–21. [PubMed: 6545569]

Table 1.

Epidemiologic studies of arsenic exposure and ([A]) cutaneous melanoma and ([B]) keratinocyte carcinoma listed by study design and year.

Reference	Study Design	Demographics	Cases/ controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
A. Melanoma						
Cohort						
Dennis et al., 2010 (53)	Prospective cohort study (1993–2005) Agricultural Health Study	Sex: NS Mean age: Cases: 57 Controls: 48 Country (Region): US (Iowa, North Carolina) Ethnicity: NS	150MM/24,704	Arsenic pesticide	OR = 1.3 (0.7–2.4) for never used vs. ever used	Age at enrollment, sex
Baastrup et al., 2008 (54)	Prospective cohort study	Sex: 26,876M/ 29,502F Median age: 56 Country (Region): Denmark (Copenhagen, Aarhus)	147MM/56,378	Level of arsenic in the drinking water by time-weighted average exposure and by cumulated exposure	RR: 0.80 (0.59–1.08) for time-weighted average exposure of arsenic (per ug/L) RR: 0.96 (0.89–1.04) for cumulated arsenic exposure (per 5 mg)	Education, skin reaction to sun, suntanned during summer, area of enrollment
Case-Control						
Beane Freeman et al., 2004 (55)	Case control study (population-based)	Sex: M/F Cases: 205M/ 163F Controls: 240M/ 133F Median age: Cases: 60 Controls: 62 Country (Region): US (Iowa) Ethnicity: Caucasian	326MM/329 Controls diagnosed with colorectal cancer and frequency matched for sex and age	Toenail arsenic concentration	MM associated with highest quartile (≥0.084 ug/g) compared to lowest quartile (≤ 0.020 ug/g): OR = 2.1 (1.4–3.3) P_{trend} 0.001	Age, sex, education
B. Keratinocyte Carcinoma						
Cohort						

Reference	Study Design	Demographics	Cases/ controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
Hsueh et al., 1997 (63)	Retrospective cohort study	Sex:468M/613F Age: ≥30 Country: Taiwan	26KC/497	Cumulative arsenic exposure	Cumulative arsenic exposure (mg/L-yr) OR = 2.82 (0.25–31.87) for 0.1–10.6 2.61 (0.30–22.90) for 10.7–17.7 7.58 (0.95–60.3) for ≥17.7	Age, sex, education level
Baastrup et al., 2008 (54)	Prospective cohort study	Sex: 26,876M/ 29,502F Median age: 56 Country (Region): Denmark (Copenhagen, Aarhus)	1,010 KC/56,378	Level of arsenic in the drinking water by time-weighted average exposure and by cumulated exposure	RR: 0.99 (0.94–1.06) for time weighted average exposure of arsenic (per ug/L) RR: 0.99 (0.97–1.01) for cumulated arsenic exposure (per 5 mg)	Adjusted: education, skin reaction to sun, suntanned during summer, occupation, area of enrollment
Case-Control						
Yu et al., 2000 (74)	Case-control study (hospital-based)	Sex: 28M/24F Mean age: 63 Country (Region): Taiwan (Southwest region) Ethnicity: NS	2BCC, 19 Bowen's diseases (SCC in situ), 6 hyperkeratosis/ hyperpigmentation/26 Controls matched by age and sex	Urine levels of inorganic arsenic (InAs), methylarsonic acid (MMA) and dimethylarsinic acid (DMA)	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)	Sex, age, cigarette smoking, hepatitis B surface antigen, alcohol consumption, and regular tea intake.
Karagas et al., 2001 (76)	Case-control study (population-based)	Sex: BCC:182M/ 102F SCC: 388M/ 249F Controls: 315M/ 209F Age range: 25–74	587 BCC, 284 SCC/524 Controls matched by age and sex	Toenail arsenic concentration	Above the 97th percentile (≥0.345ug/g) compared to median (≤ 0.089 ug/g) SCC OR = 2.07 (0.92–4.66)	Age and sex

Reference	Study Design	Demographics	Cases/ controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
		Country (Region): US, New Hampshire Ethnicity: NS			BCC OR = 1.44 (0.74–2.81)	
Chen et al., 2003 (75)	Case-control study (hospital-based; 1996–1999)	Sex: Case: 48M/28F Control: 131M/ 93F Age range: >30 Country (Region): Taiwan (Southwest region) Ethnicity: NS	76KC/224	Percentage of urinary arsenic species, arsenic methylation ability, and cumulative arsenic exposure	Mean cumulative arsenic exposure (mg/L-year): Cases: 15.33 ± 18.8 Controls: 8.14 ± 15.48 $P = 0.002$	Age, sex, body-mass index (BMI), cigarette smoking, the use of hair dye, and education
Rosales-Castillo et al, 2004 (81)	Case-control study (hospital-based)	Sex: Case: 71% male Control: 21% male Age: mean 63 for cases and 47 for controls Country (Region): Mexico Ethnicity: NS	42 KC/48	Historical arsenic exposure (arsenic concentration in the drinking water in the town of residency*years lived in the town/age)	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	Age, gender, and sun exposure
Leonardi et al, 2012 (78)	Case-control study (hospital-based)	Sex: Case: 237M/ 292F Control: 278M/262 F Age range: >30 Country (Region): Hungary, Romania, and Slovakia	529 BCC/540	Lifetime average inorganic arsenic (iAs) concentration in residential drinking water, peak daily dose rate, cumulative iAs dose	OR=3.03 (1.70–5.41) for 19.5–167.3 vs. <0.68 lifetime average iAs concentration (ug/L) P_{trend} 0.001 OR=2.50 (1.39–4.49) for 32.2–	County, age, sex, education, skin response to 1-hr midday sun, and skin complexion.

Reference	Study Design	Demographics	Cases/ controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
		Ethnicity: NS			242.1 vs <0.73 peak daily iAs dose rate (ug/d) P_{trend} 0.001 OR=2.63 (1.45–4.78) for 0.55–4.46 vs. <0.01 cumulative iAs dose (g) P_{trend} 0.001	
Gilbert-Diamond et al., 2013 (77)	Case-control study (population-based)	Sex: SCC: 284M/186F Control: 258M/189F Age range: 25–74 Country (Region): US, New Hampshire Ethnicity: Caucasian	323 SCC/319 Controls matched by age, sex and state of residence	Urinary levels of InAs, MMA, and DMA, sum (ΣAs) of the species	For each ln-transformed μg/L increase: ln(ΣInAs) OR = 1.37 (1.04–1.80) ln(iAs) OR = 1.20 (0.97–1.49) ln(MMA) OR = 1.34 (1.04–1.71) ln(DMA) OR = 1.34 (1.03–1.74)	Age, sex, BMI, education, smoking status, skin reaction to chronic sun exposure, and urinary creatinine concentration
Surdu et al., 2013 (64)	Case-control study (hospital-based)	Sex: BCC: 231M/284F SCC: 38M/32F Controls: 272M/255F Age range 30–79 Countries (Region): Hungary, Romania, Slovakia Ethnicity: NS	515 BCC, 70 SCC/527 controls matched to by county of residence, sex and 5-year-age group	Cumulative lifetime workplace dust/fume arsenic exposure (>232.5hr)	≥7,232.5hr vs ≤105hr KC: OR = 1.94 (0.76–4.95) BCC: OR = 1.90 (0.72–4.99) SCC: OR = 2.69 (0.50–14.59)	Sex, age, county of residence, family history of cancer, skin propensity to sunburns and lifetime average arsenic concentration in drinking water
Cross-sectional						
Haupert et al., 1996 (80)	Cross-sectional study	Sex: 727M/731F Age: All ages Country (Region): US (Outagamie and Winnebago counties, Wisconsin) Ethnicity: NS	Overall KC 17/1,836	Drinking water arsenic consumption	>50 μg/day compared to <5 μg/day: Overall KC RR = 3.28 (2.17–4.40)	Age and sex

Age given in years; RR = relative risk; HR = hazard ratio; OR = odds ratio; CI = confidence Interval; NS=Not specified

[A] MM = cutaneous malignant melanoma

[B] KC = Keratinocyte carcinoma; SCC = cutaneous squamous cell carcinoma; BCC = cutaneous basal cell carcinoma

Table 2.

Epidemiologic studies of ([A]) cadmium/chromium, ([B]) iron, and ([C]) copper exposure and cutaneous melanoma, and ([D]) copper exposure and keratinocyte carcinoma listed by study design and year.

Reference	Study design	Demographics	Cases/controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
A. Cadmium/Chromium						
Melanoma						
Cohort						
Weinlich et al., 2003 (111)	Prospective Cohort	Sex: M/F Mean Age: 56.3 Country (Region): Austria (Innsbruck)	520 MM	Immunohistochemical overexpression of metallothionein in melanoma	Progression: RR= 2.9 (1.46–5.76) Survival: RR = 4.19 (1.73–10.19)	
Case-control						
Vinceti et al., 2005 (25)	Case-control study (population-based)	Sex: M/F Age: NS Country (Region): Italy (Modena province) Ethnicity: NS	58MM/58 Controls matched by sex and age	Toenail cadmium concentration	For ≥ median cadmium levels compared to the remaining category: Cadmium : OR = 0.7 (0.3–1.9) Chromium : OR = 0.9 (0.2–3.2)	Education, sun exposure and total number of atypical nevi
B. Iron						
Melanoma						
Case-control						
Stryker et al., 1990 (141)	Case-control study (hospital-based)	Sex: M/F Mean age: Cases M/F: 48/42 Controls M/F: 48/38 Country (Region): US (Massachusetts) Ethnicity: Caucasian	204MM/ 248 Controls visited dermatology clinic	Total iron intake	For highest quintile compared to lowest: OR = 0.8 (0.5–1.4)	Age, sex and total energy intake
Bain et al., 1993 (142)	Case-control study (population-based)	Sex: 41F Mean age: 50 Country (Region): Australia (Brisbane) Ethnicity: NS	41MM/ 297 Controls matched for age	Dietary iron intake	For highest tertile compared to lowest: OR = 0.39 (0.15–0.97) $P = 0.04$	Calories, age, number of painful sunburns, years of schooling

Reference	Study design	Demographics	Cases/controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
Vinceti et al., 2005 (25)	Case-control study (population-based)	Sex: M/F Age: NS Country (Region): Italy (Modena Province) Ethnicity: NS	58MM/58 Controls matched by sex and age	Toenail Iron concentration	For ≥ median levels of iron exposure compared to the remaining category: OR = 0.4 (0.1–1.4) P_{trend} = 0.15	Education, sun exposure, and total number of atypical nevi
C. Copper						
Melanoma						
Case-control						
Ros-Bullón et al., 1998 (157)	Case-control (hospital-based)	Sex: M/F Age: NS Country (Region): Spain (Murcia) Ethnicity: NS	35MM/39 Control serum obtained from healthy blood donors	Serum copper levels	Median copper levels: MM:118.3 ± 25.3 µg/dl Controls: 117.9 ± 28.0 µg/dl P > 0.05	
Vinceti et al., 2005 (25)	Case-control study (population-based)	Sex: M/F Age: NS Country (Region): Italy (Modena province) Ethnicity: NS	58MM/58 Controls matched by sex and age	Toenail copper concentration	For ≥ median levels of copper exposure compared to the remaining category: OR = 15.5 (1.7–142.6)	Education, sun exposure and total number of atypical nevi
D. Copper						
Keratinocyte Carcinoma						
Case-control						
Sahl et al., 1995 (158)	Case-Control (hospital-based)	Sex: M/F Mean age: 65 Country (Region): United States (South Dakota) Ethnicity: NS	46BCC/46 Controls matched by age, skin-type and sex	Mean daily copper intake	KC cases: 1.9 ± 0.1 mg Controls: 1.9 ± 0.9 mg P = 0.88	
Vural et al., 1999 (159)	Case-Control (hospital-based)	Sex: 5M/7F Median age: 61 Country (Region): Turkey (Istanbul) Ethnicity: NS	12 BCC, 13 AK/16 Healthy controls matched by age, sex and	Plasma cerulopasmin	BCC: 219.1 ± 34.2(units/l) Controls: 251.7 ± 27.3 (units/l) P<0.05	

Reference	Study design	Demographics	Cases/controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
			average daily sun exposure			

Age given in years; RR = relative risk; HR = hazard ratio; OR = odds ratio; CI = confidence Interval; NS=Not specified

A, B, C. MM = cutaneous malignant melanoma

D. KC = Keratinocyte carcinoma; SCC = cutaneous squamous cell carcinoma; BCC = cutaneous basal cell carcinoma; AK = Actinic Keratosis

Table 3.

Epidemiologic studies of zinc exposure and ([A]) cutaneous melanoma and ([B]) keratinocyte carcinoma

Reference	Study design	Demographics	Cases/controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
Zinc						
A. Melanoma						
Case-control						
Horcicko & Pantucek, 1983 (184)	Case-control study Population-based	Sex: NS Age: NS Country (Region): Czech Republic Ethnicity: NS	93MM/64	Mean serum zinc concentration	MM: 13.0 ± 2.4 µmol/l Controls: 17.0±2.8 µmol/l (P<0.01)	
Gorodetsky et al., 1986 (143)	Case-control (hospital-based)	Sex: M/F Age: NS Country (Region): Israel Ethnicity: NS	71 samples (3 MM patients, 42 controls)	Wet weight concentration of zinc determined in vivo by diagnostic x-ray spectrometry	In malignant melanoma lesions: 13.9 ± 9.3ppm In uninvolved skin near melanoma lesion: 7.7 ± 3.5ppm In healthy controls: 6.7 ± 1.1 ppm (face and upper neck); 4.5 ± 1.7 ppm (chest, abdomen, arm, axilla, and lower neck)	
Siu et al., 1991 (185)	Cast-control (hospital-based)	Sex: MM: 6M/16F Controls: 7M/10F Age: Adults, not otherwise specified Country (Region): NS Ethnicity: NS	22MM and 17 BCC as controls	Mean serum zinc levels	MM: 22.5 ± 1.2 µmol/l (mean levels) Controls: 17.6 ± 0.8 µmol/l (mean levels) P < 0.001	
Bain et al., 1993 (142)	Case-control (population-based)	Sex: 41F Mean age: 50 Country (Region): Australia (Brisbane) Ethnicity: NS	41MM/ 297 Controls matched for sex and age	Dietary zinc intake	For highest tertile compared to lowest zinc intake and MM: OR = 0.36 (0.15–0.88) P=0.02	Calories, age, number of painful sunburns, years of schooling
Ros-Bullón et al., 1998 (157)	Case-control (hospital-based)	Sex: M/F Age: NS Country (Region): Murcia, Spain	35 MM/39 controls Control serum obtained from	Serum zinc levels	Median zinc levels: MM: 82.3 ± 25.34µg/dl	

Reference	Study design	Demographics	Cases/controls or total participants	Exposures	Results (RR/OR/HR and 95% confidence interval)	Covariate Adjustment
		Ethnicity: NS	healthy blood donors		Controls: 56.7 ± 11.8 μg/dl $P < 0.0001$	
Vinceti et al., 2005 (25)	Case-control study (population-based)	Sex: M/F Age: NS Country (Region): Modena, Italy Ethnicity: NS	58/58 Controls matched for sex and age	Toenail zinc concentration	For ≥ median zinc levels compared to the remaining category and MM: OR = 3.5 (1.0–12.6) $P_{trend} = 0.48$	Education, sun exposure and total number of atypical nevi
B. Keratinocyte Carcinoma						
Case-control						
Sahl et al., 1995 (158)	Case-control study (hospital-based)	Sex: M/F Mean age: Cases: 65 Controls: 64 Country (Region): US (South Dakota) Ethnicity: NS	46 BCC/ 46 Cancer-free controls matched by age, skin-type and sex	Mean daily zinc consumption	BCC: 12.2 ± 0.8mg Controls: 12.3 ± 0.7mg $P = 0.71$	

Age given in years; RR = relative risk; HR = hazard ratio; OR = odds ratio; CI = confidence Interval

A. MM = cutaneous malignant melanoma

B. KC = Keratinocyte carcinoma; SCC = cutaneous squamous cell carcinoma; BCC = cutaneous basal cell carcinoma

Table 4.

Epidemiologic studies of selenium and ([A]) cutaneous melanoma and ([B]) keratinocyte carcinoma

Selenium						
Reference	**Study Design**	**Demographics**	**Cases/controls or total participants**	**Exposures**	**Results (RR/OR/HR and 95% confidence interval)**	**Covariate Adjustment**
A. Melanoma						
Randomized controlled trial						
Duffield-Lillico et al., 2002 (235)	Double-blind, placebo-controlled randomized trial with KC history (1983–1996) The Nutritional Prevention of Cancer Trial	Sex: M/F Mean age: 63 Country (Region): US (East) Ethnicity: NS	11MM/621 in supplement group and 9MM/629 in placebo group	Supplementation of 200μg/d of Se versus placebo	RR = 1.21 (0.46–3.30) HR = 1.18 (0.49–2.85)	RR was unadjusted, HR was adjusted for sex, age, and smoking status
Nested Case-Control & Cohort						
Garland et al., 1995 (209)	Nested case-control study (1976–1982)	Sex: F Age: 30–55 Country (Region): 11 States within the US Ethnicity: NS	63MM/63 controls were matched by year of birth and month of toenail return	Toenail selenium concentration	Highest tertile compared to lowest tertile of selenium exposure: OR = 1.66 (0.71–3.85)	Smoking status
Vinceti et al., 1998 (213)	Prospective cohort study (1975–1985)	Sex: 1021M/1044F Age: > 5 Country (Region): Italy (Reggio Emilia) Ethnicity: NS	8MM/2,065 exposed	Exposure to high levels of inorganic selenium in tap water	Standardized morbidity ratio: Male = 5.0 (1.6–12.0) Female = 3.2 (1.0–7.7)	
Asgari et al., 2009 (210)	Prospective cohort study (2000–2006)	Sex: M/F Age range: 50–76 Country (Region): US (Washington State) Ethnicity: Caucasian	461/69,671	Supplemental selenium use over 10 years	≥50 μg/day Se compared to none: RR = 0.98 (0.69–1.41)	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 blond hair, reaction to 1 hour in strong sunlight

Selenium						
Reference	**Study Design**	**Demographics**	**Cases/controls or total participants**	**Exposures**	**Results (RR/OR/HR and 95% confidence interval)**	**Covariate Adjustment**
Case-control						
Breslow et al., 1995 (212)	Case-control study (population-based) 000000000000000ppppppp77777	Sex: 55M/44F Age: >18 Country (Region): US (Washington county, Maryland) Ethnicity: Caucasian	30MM/60 Controls matched by age, sex	Serum selenium level	Highest tertile compared to lowest tertile of selenium exposure: OR = 0.9 (0.3–2.5)	Smoking, education, and hours between last meal and blood donation did not change results
Vinceti et al., 2012 (214)	Case-control study (population-based)	Sex: 26M/28F Age: 25 – 79 Country (Region): Italy (Modena province) Ethnicity: NS	54MM/56 Controls selected from regional population and matched for sex and age	Toenail, plasma, and dietary selenium concentration	Toenail (≥ 73 μg/g): OR: 0.77 (0.26–2.28) P_{trend} = 0.633 Plasma (≥ 105 μg/l): OR: 6.42 (1.94–21.24) P_{trend} = 0.002 Dietary (≥ 71 μg/d): OR: 0.59 (0.19–1.83) P_{trend} = 0.34	Age, sex
Le Marchand et al., 2006 (211)	Case-control study (population-based)	Sex: M/F Mean age: Cases: 53 Controls: 52 Country (Region): US (Oahu, Hawaii) Ethnicity: Caucasian	278MM/278 Controls matched by age, ethnicity and sex	Plasma, erythrocyte and toenail concentrations of selenium	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 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) Toenail (μg/g): ≥1. 0 vs ≤0.86 Males: OR=0.9 (0.5–1.6)	Height, education, hair color, number of blistering sunburns at ages 10–17 years, ability to tan and lifetime ethanol intake. selenium-containing shampoo was additionally adjusted for toenail Se

Selenium						
Reference	**Study Design**	**Demographics**	**Cases/controls or total participants**	**Exposures**	**Results (RR/OR/HR and 95% confidence interval)**	**Covariate Adjustment**
					(P_{trend} = 0.61) Females: OR = 1.0 (0.4–2.1) (P_{trend} = 0.99)	
B. Keratinocyte Carcinoma						
Randomized controlled trial						
Duffield-Lillico et al., 2003 (28)	Double-blind, placebo-controlled randomized clinical trial with history of KC (1983–1996) The Nutritional Prevention of Cancer Trial	Sex: M/F Median age: 65 Country (Region): Eastern US Ethnicity: NS	621 in selenium and 629 in placebo group	Supplementation of 200 μg/day of selenium versus placebo	By baseline Se concentrations: ≤ 105 μg/mL: 0.87 (0.02–1.22) 106–122: 1.49 (1.05–2.12) ≥122: 1.59 (1.11–2.30) BCC RR = 1.17 (1.02–1.35) HR = 1.09 (0.94–1.26) SCC RR = 1.32 (1.09–1.60) HR = 1.25 (1.03–1.51)	RRs are unadjusted, HRs are adjusted for sex, age, smoking status, clinic site, plasma selenium concentration, clinical sun damage, sunscreen use at baseline, and number of previous BCCs, SCCs, or total NMSCs in the 12 months before randomization
Dreno, 2007(218)	Placebo-controlled randomized trial with recent organ transplant recipients (2 years)	Sex: 127 M/57 F Median age: 44 Country (Region): France Ethnicity: 89% Caucasians	6/91 in selenium and 2/93 in placebo group	Supplementation of 200 μg/day of selenium versus placebo	OR=3.08, p=0.15	
Reid et al., 2008 (217)	Double-blind, placebo-controlled randomized trial with KC history (1983–1993). Sub-study of the Nutritional Prevention of Cancer Trial (1989–1996)	Sex: M/F Mean age:64 Country (Region): US (Georgia) Ethnicity: NS	98KC/210 in Se group 108 KC/213 in placebo group	Selenium supplementation with 400 μg/day or 200 μg/day selenized yeast versus placebo	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 (1.13–2.04), P_{trend} = 0.006 BCC: HR = 1.22 (0.88–1.70)	Age, smoking status, sex

Selenium						
Reference	**Study Design**	**Demographics**	**Cases/controls or total participants**	**Exposures**	**Results (RR/OR/HR and 95% confidence interval)**	**Covariate Adjustment**
					SCC: HR = 1.88 (1.28–2.79), P_{trend} = 0.001	
Nested Case-Control & Cohort						
Knekt et al., 1990 (221)	Nested case-control study	Sex: M/F Age range: 15–99 Country (Region): Finland Ethnicity: NS	126 BCC/252 Controls matched by age, sex and municipality	Serum selenium levels	Highest quintile compared to lowest selenium levels: Males: RR = 0.86 (0.35–2.12) Females: RR = 1.54 (0.64–3.73)	Smoking status, occupation, BMI, parity, cholesterol, hematocrit
Breslow et al., 1995 (212)	Nested case-control study (population-based)	Sex: M/F Age: >18 Country (Region): Maryland, US Ethnicity: Caucasian	32/64 for BCC, 37/74 for SCC Controls matched by age and sex	Serum selenium levels	Highest tertile compared lowest selenium levels: BCC: 0.8 (0.1–4.5) SCC: 0.6 (0.2–1.5)	Smoking, education, and the hours between last meal and blood donation did not change the results
Karagas et al., 1997 (224)	Nested case-control study in a clinical trial of those with history of KC Skin Cancer Prevention Trial	Sex: 89%M/ 11%F Mean age: 67 Country (Region): US (New Hampshire, Minnesota, California) Ethnicity: NS	132 SCC/ 246 controls Controls were chosen at random and matched by age, sex, and study center	Plasma selenium levels	For the highest quartile versus lowest quartile selenium levels and SCC: OR =0.86 (0.47–1.58)	
Davies et al., 2002 (219)	Nested case-control study EPIC-Norfolk Study	Sex: M/F Median age: M: 67 F: 65 Country (Region): Britain (Norfolk) Ethnicity: NS	14 SCC, 109 BCC/247 controls	Dietary selenium intake	For each 20 ug Se intake and overall KC: RR =1.07 (0.86–1.34)	Adjusted for body mass index and red hair
McNaughton et al., 2005 (222)	Nested case-control study The Nambour Skin Cancer Study	Sex: Cases: 39M/51F Controls: 39M/51F Mean age: 55	90 BCC/90 Controls matched for age and sex	Dietary selenium intake and serum selenium levels	Highest quartile compared to lowest selenium intake and BCC:	Age, sex and self-prescribed supplement use

Selenium						
Reference	**Study Design**	**Demographics**	**Cases/controls or total participants**	**Exposures**	**Results (RR/OR/HR and 95% confidence interval)**	**Covariate Adjustment**
		Country (Region): Australia (Nambour) Ethnicity: NS			Dietary intake: OR = 1.13 (0.47–2.74) Serum level: OR = 0.86 (0.38–1.96)	
Heinen et al., 2007 (220)	Prospective cohort study (1996–2004) Nambour Skin Cancer Study	Sex: 454M/ 547F Median age: SCC: 65 BCC: 61 Country (Region): Australia (Nambour) Ethnicity: NS	116 SCC, 149 BCC / 1001	Dietary selenium intake	For highest tertile compared to lowest tertile selenium intake: SCC: RR = 1.30 (0.77–2.30) BCC: RR = 0.95 (0.59–1.5)	Age, sex, energy intake, skin color, elastosis of the neck, smoking, treatment allocation, use of dietary supplements, history of skin cancer before 1996
Van der Pols et al., 2009 (223)	Sub-set of prospective cohort study (1996–2004) Nambour Skin Cancer Study	Sex: 223M/262F Mean age: SCC: 63 BCC: 61 Controls: 54 Country (Region): Australia (Queensland) Ethnicity: NS	77 BCC, 59 SCC/485	Serum selenium concentration	For highest tertile compared to lowest tertile: BCC: RR = 0.58 (0.32 – 1.07) SCC: RR = 0.49 (0.24 – 0.99)	Age, sex, pack-years of smoking, alcohol intake; time spent outdoors on weekdays, and history of skin cancer before 1996
Case-control						
Clark., 1984 (236)	Case control study (hospital-based)	Sex: M/F Age: <76 years Country (Region): US (Wilson, North Carolina) Ethnicity: NS	142 BCC, 48 SCC, 50 BCC +SCC/ 103	Plasma selenium levels	High vs low selenium levels and overall KC: OR = 2.11 (1.25–3.56)	Age and sun damage
Sahl et al., 1995 (158)	Case-control study (hospital)	Sex: M/F Mean age: Cases: 65 Controls: 64 Country (Region): US (South Dakota) Ethnicity: NS	46 BCC/46 Controls matched by age, skin-type and sex	Mean daily selenium intake	BCC cases: 99 ± 6 (μg) Controls: 112 ± 6 (μg) *P* = 0.14	

Age given in years; RR = relative risk; HR = hazard ratio; OR = odds ratio; CI = confidence Interval; NS=Not specified

A. MM = cutaneous malignant melanoma

[B] KC = Keratinocyte carcinoma; SCC = cutaneous squamous cell carcinoma; BCC = cutaneous basal cell carcinoma

Table 5.

Summary of number of epidemiologic studies of metals and skin cancer*

Metal	Type of skin cancer	Number of case-control studies	Number of cohort studies and nested case-control studies	Number of clinical trials
Arsenic	Melanoma	1	2	0
	KC	7	2 (one retrospective and one prospective cohort)	0
Cadmium/Chromium	Melanoma	1	1 (cadmium only and among melanoma cases)	0
	KC	0	0	0
Iron	Melanoma	3	0	0
	KC	0	0	0
Copper	Melanoma	2	0	0
	KC	2	0	0
Zinc	Melanoma	6	0	0
	KC	1	0	0
Selenium	Melanoma	3	3	1
	KC	2	5	2

* The numbers are based on number of studies, not number of publications. Some studies had multiple publications.

Arsenic and KC also had one cross-sectional study.