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Trace elements and cancer risk: a review of the epidemiologic evidence

Stephanie A. Navarro Silvera
Montclair State University, silveras@montclair.edu

Thomas E. Rohan
Albert Einstein College of Medicine, thomas.rohan@einsteinmed.org

REVIEW

Trace elements and cancer risk: a review of the epidemiologic evidence

Stephanie A. Navarro Silvera · Thomas E. Rohan

Abstract Worldwide, there are more than 10 million new cancer cases each year, and cancer is the cause of approximately 12% of all deaths. Given this, a large number of epidemiologic studies have been undertaken to identify potential risk factors for cancer, amongst which the association with trace elements has received considerable attention. Trace elements, such as selenium, zinc, arsenic, cadmium, and nickel, are found naturally in the environment, and human exposure derives from a variety of sources, including air, drinking water, and food. Trace elements are of particular interest given that the levels of exposure to them are potentially modifiable. In this review, we focus largely on the association between each of the trace elements noted above and risk of cancers of the lung, breast, colorectum, prostate, urinary bladder, and stomach. Overall, the evidence currently available appears to support an inverse association between selenium exposure and prostate cancer risk, and possibly also a reduction in risk with respect to lung cancer, although additional prospective studies are needed. There is also limited evidence for an inverse association between zinc and breast cancer, and again, prospective studies are needed to confirm this. Most studies have reported no association between selenium and risk of breast, colorectal, and stomach cancer, and between zinc and prostate cancer risk. There is compelling evidence in support of positive associations between arsenic and risk of both lung and bladder cancers, and between cadmium and lung cancer risk.

Keywords Trace elements · Selenium · Zinc · Arsenic · Cadmium · Nickel · Neoplasms

Abbreviations

ATBC	Alpha-Tocopherol Beta-Carotene Cancer Prevention Cohort
As	arsenic
AAS	atomic absorption spectrophotometry
AES	atomic emission spectrophotometry
AR	attributable risk
Cd	cadmium
EMR	excessive mortality rate
FAA	flame atomic absorption
GC	gastric cardia adenocarcinoma
ICP-MS	inductively coupled plasma mass spectometry
IARC	International Agency for Research on Cancer
NAA	neutron activation analysis
Ni	nickel
OG	non-cardia gastric adenocarcinoma
ppb	part per billion
Se	selenium
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SELECT	The Selenium and Vitamin E Cancer Prevention Trial
ATSDR	United States Department of Health and Human Services Agency for Toxic Substances & Disease Registry
Zn	zinc

S. A. N. Silvera (✉) · T. E. Rohan
Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Room 1301a, New York, NY 10461, USA
e-mail: ssilvera@aecom.yu.edu

Introduction

There were an estimated 10.9 million new cancer cases and 6.7 million cancer deaths worldwide in 2002 [1]. Of these, cancers of the lung, breast, colorectum, and stomach were the most common [1]. Additionally, prostate cancer was the fifth most common cancer overall and the second most common among men, and bladder cancer, ranked ninth in terms of incidence, was more common in developed countries (63% of all new bladder cancer cases) and among men (77% of new bladder cancer cases occur in men) [1]. Given the burden of disease associated with these cancers, a large number of epidemiologic studies have been undertaken to identify potential risk factors. Amongst the many factors that have been explored, the association with trace elements has received considerable attention. Trace elements are of particular interest given that levels of exposure to them are potentially modifiable.

The term 'trace element' refers to chemical elements present or required in minute quantities. Trace elements are found naturally in the environment and human exposure derives from a variety of sources, including air, drinking water, and food (Table 1). The World Health Organization has classified 19 trace elements as being important to human health, including arsenic (As), cadmium (Cd), nickel (Ni), selenium (Se), and zinc (Zn), amongst others (Table 1) [2].

There is a large body of literature on the role of trace elements in the development of cancer. Arsenic exposure has been examined in relation to cancer risk, generally focusing on exposure via drinking water. In addition, a number of studies of Cd, and Ni have been conducted, with a primary focus on work-place exposures. Finally, there is substantial interest in the role of Se and Zn with respect to a number of cancer sites. While Se tends to be inversely associated with cancer risk [3, 4], Zn appears to be protective when Zn deficient individuals are compared to those who are Zn sufficient [5], whereas it appears harmful when those who have Zn overload as a result of environmental exposure are compared to those who are Zn sufficient [6]. Cd, Ni, and As are generally associated with increased risk of many cancers [7] and each of them has been designated as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC) [8–10] and the US National Toxicology Program.

In this review, we focus on the association between each of the trace elements noted above and risk of cancers of the lung, breast, colorectum, prostate, urinary bladder, and stomach, the anatomical sites that have been studied most commonly. We precede our review of the epidemiologic literature with a brief discussion of the sources of exposure to trace elements, methods for measuring trace element exposure, and the biological samples in which trace elements can be measured.

Methods

Search strategy

We aimed to identify all epidemiologic evidence relevant to the research question. Therefore, epidemiologic literature regarding trace element exposure and risk of cancers of the breast, lung, colorectum, prostate, bladder, and stomach, was searched for, obtained, and reviewed.

A systematic search of Medline (1966-present) was carried out for the relevant epidemiologic literature. In

Table 1 Average exposure to trace elements from common sources

Trace element[a]	Average exposure by source		
	Water (/day)[b]	Diet (/day)	Air (/m³)
Arsenic	<1 ng–7200 μg, depending on geographic locale [11, 14, 16]	50 μg–200 μg (3.5 μg of inorganic arsenic) [2, 11]	1–2000 ng [11, 12]
Cadmium	0.01–0.2 μg (50 μg in heavily polluted areas) [13, 14]	3 μg–160 μg, approximately 1–3 μg is absorbed [13, 14]	1–40 ng [13, 14]
Nickel	10–20 μg (up to 200 μg in mining areas) [14, 15]	8 μg–170 μg, < 2% is absorbed [14, 15]	7–12 ng [14, 15]
Selenium	<1 μg–300 μg [18]	71–152 μg [2, 18][c]	Not a common source of exposure
Zinc	Varies depending on zinc content of pipes	5.2–16.2 mg [2, 17]	0.1–1.7 μg [17]

[a] Source: World Health Organization. Trace elements in human nutrition and health. Geneva: World Health Organization, 1996

[b] Assuming an intake of 2 l water/day

[c] Varies depending on soil concentrations in which foods were grown

addition, we followed-up on references from relevant papers and prior reviews of trace elements. Appendices 1 and 2 show the search strategy employed for each of the cancers and trace elements in Medline.

Study selection

Epidemiologic studies of men and women were included in this review. Each of the articles reviewed reported on the effect of exposure to at least one of the trace elements listed in Table 1 and reported on the incidence, prevalence, and/or death from lung, bladder, breast, colorectal, prostate, or stomach cancer. Epidemiologic studies not published in English were excluded from this review, as were published abstracts and non-peer-reviewed literature.

Data extraction and analysis

All relevant epidemiologic studies were read in full and the data were extracted. Details on study design, study population, exposure source and exposure measures, outcome, results, and conclusions were recorded. Included studies were summarized in Tables 3–8 and described briefly in the text. We considered issues related to exposure measurement, along with considerations of study design, sample size, and magnitude of effect, in drawing conclusions from the literature.

Sources of trace element exposure

Trace elements are found naturally in the environment and human exposure derives from a variety of sources, including air, drinking water, and food.

Concentrations of trace elements in the air are generally low. Levels of As in the air range from approximately 1 to 2,000 ng/m^3 [11, 12], levels of Cd generally range from 1 to 40 ng/m^3 [13] but can reach up to 100 ng/m^3 near emission sources [14], and levels of Ni in cities and rural areas range from 7 to 12 ng/m^3 [15] (Table 1). Welders, workers in the smelting and refining industries, and those employed in the

production of batteries, coatings, and plastics, can be exposed to much higher levels of airborne Cd and Ni [14, 15].

Each of the trace elements under consideration here is found in drinking water supplies. The average amount of Cd in drinking water is approximately 1 part per billion (ppb) and intakes from drinking water range from 0.01 $\mu g/day$ in more remote geographic locations to 25 $\mu g/day$ in heavily polluted areas [14]. The average concentration of Ni in water ranges from 3 to 7 ppb [14, 15]. With respect to As, which is found naturally in ground water, the Agency for Toxic Substances and Disease Registry (ATSDR) in the United States estimates that 80% of the US water supply has less than 2 ppb, but about 2% has greater than 20 ppb [11]. Internationally, levels of As in water range from as low as <1 ng/m^3 in remote locations (e.g., the Canadian arctic) to as high as 2,000–3,600 $\mu g/l$ in Bangladesh and India [14, 16].

Diet is the primary source of Zn and a major source of Se exposure. Average Zn consumption from food ranges from 5.2 to 16.2 mg/day [14, 17] and Zn levels in animal products vary depending on the soil and water concentrations where the animals were raised [17]. Average Se consumption from food ranges from 71 to 152 $\mu g/day$ [18]. Fish and seafood are the main sources of dietary As exposure [11]. However, the As in these foods is mainly in the form of organic As, which is considered less harmful than inorganic As [11]. With respect to Cd, the average individual consumes 30 $\mu g/day$, but only 1–3 $\mu g/day$ is absorbed into the body [13, 14]. Likewise, while average Ni consumption from foods is 170 $\mu g/day$ in the United States [15] and between 200 and 300 $\mu g/day$ internationally [14], less than 2% is absorbed [15].

Methods for measuring trace element exposure

Exposure to many trace elements (e.g., As, Cd, and Ni) is largely from occupational sources. Studies of exposure to such trace elements have utilized various exposure assessment methods including job histories

Table 2 Analytical methods for measuring trace element exposure in biological specimens	Method	Elements commonly tested
	Atomic absorption spectrophotometry (AAS)	Arsenic, Cadmium, Nickel, Zinc
	Atomic emission spectroscopy (AES)	Cadmium, Nickel
	Inductively coupled plasma mass spectrometry (ICP-MS)	Cadmium, Arsenic, Zinc, Selenium, Nickel
	Neutron activation analysis (NAA)	Arsenic, Cadmium, Nickel, Selenium
	Fluorometry	Arsenic, Zinc, Selenium

Table 3 Summary of epidemiologic studies of high level arsenic exposure (≥100 μg/l) and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Lung						
Chen et al. [37]	Case–control	444 (79)	Taiwan	Years of water consumption	>40 vs. 0 years	OR = 3.01
Ferreccio et al. [38]	Case–control	571 (152)	Chile	Water–As concentrations from 1950 to 1994—lifetime residential exposure	200–400 vs. 0–10 μg/l	$OR_{cancer\ controls}$ = 9.5 (4.0–22.6)[d] $OR_{noncancer\ controls}$ 8.5 (3.6–20.2)[d]
Chiou et al. [39]	Cohort	2,556 (27)	Taiwan	Cumulative exposure to As in drinking water	20+ vs. 0 mg/l × years	RR = 4.01 (1.00–16.12)
Lewis et al. [41]	Cohort	4,058 (34)[a]	United States	Drinking water	General population	SMR_{men} = 0.57 (0.38–0.82) SMR_{women} = 0.44 (0.16–0.95)
Chen et al. [40]	Cohort	65,876[a]	Bangladesh	Drinking water[c]	≥ 599 vs < 50 μg/l	RR_{men} = 4.22 RR_{women} = 9.00
Bladder						
Chen et al. [37]	Case–control	444 (79)	Taiwan	Years of water consumption	> 40 vs. 0 years	OR = 4.10
Bates et al. [42]	Case–control	128 (114)	Argentina	Drinking water[b]	>200 vs. 0–50 μg/l years of well-water use 61–70 years (yes vs. no)	OR = 0.60 (0.2–1.7) $OR_{never\ smokers}$ = 1.28 (0.4–4.1) $OR_{smokers}$ = 2.54 (1.0–6.4)
Chiou et al. [39]	Cohort	2,556 (29)	Taiwan	Cumulative exposure to As in drinking water	20+ vs. 0 mg/l × year	RR = 3.58 (1.05–12.19)
Kurttio et al. [44]	Case-cohort	336 (61)	Finland	Cumulative exposure to As in drinking water	> 2.0 mg vs. < 0.05 mg	$RR_{short\ latency}$ = 1.50 (0.71–3.15)[d] $RR_{long\ latency}$ = 0.53 (0.25–1.10)
Lewis et al. [41]	Cohort	4,058 (5)[a]	United States	Drinking water	General population	SMR_{men} = 0.42 (0.08–1.22) SMR_{women} = 0.81 (0.10–2.93)
Chen et al. [40]	Cohort	65,876[a]	Bangladesh	Drinking water[c]	≥ 599 vs < 50 μg/l	RR_{men} = 16.87 RR_{women} = 25.79
Chiou et al. [43]	Cohort	4,074 (10)	Taiwan	Drinking water[b]	Arseniasis-endemic area vs. general population	SIR = 1.96 (0.94–3.61)
Stomach						
Lewis et al. [41]	Cohort	4,058 (19)[a]	United States	Drinking water	General population	SMR_{men} = 0.88 (0.47–1.50) SMR_{women} = 0.72 (0.26–1.57)
Prostate						
Lewis et al. [41]	Cohort	4,058 (50)[a]	United States	Drinking water	General population	SMR = 1.45 (1.07–1.91)

[a] Number in parentheses represents number of deaths; [b] As determined using atomic absorption spectroscopy (AAS); [c] Method of determining As content of water not provided; [d] Statistically significant dose–response relationship reported; SMR = standardized mortality ratio; SIR = standardized incidence ratio

(yielding subjective assessments of exposure as high, medium, or low), measurement of airborne and static dust, and personal monitoring devices. Often, these measures are combined with job history information, such as the number of years employed in a particular area, to develop an estimate of cumulative exposure. Between-study differences in the method of exposure assessment make it difficult to compare results across studies. Further, assessments based on type of employment (e.g., production versus maintenance)

Table 4 Summary of epidemiologic studies of low level arsenic exposure (< 100 μg/l) and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Breast						
Garland et al. [45]	Nested case–control	892 (433)	USA	Toenail [b]	>0.139 vs. < 0.059 μg/g	OR = 1.12 (0.66–1.91)
Lung						
Coggon et al. [49]	Case–control	1,778	UK	Job records	Exposed vs. unexposed	OR = 1.1 (0.8–1.5)
Pershagen, [46]	Case–control	636 (212)	Sweden	Job & residential history	Exposed vs. unexposed	OR $_{residents}$ = 2.0 (1.2–3.4) OR $_{miners}$ = 4.1 (1.7–9.7) OR $_{smelter\ workers}$ = 3.0 (2.0–4.7)
Hazelton et al. [47]	Cohort	12,011 (842)	China	Cumulative work exposure–work records	General population	AR = 15.8% As alone AR = 11% As & radon AR = 8.7% combined As, radon & tobacco
Mabuchi et al. [48]	Cohort	1,393 (23)[a]	USA	Job records	General population	SMR = 1.6 (p < 0.05)
Bladder						
Bates et al. [50]	Case–control	231 (71)	Utah, USA	Drinking water[c]	≥ 75 vs. < 19 mg (cum. dose) ≥ 74 vs. < 33 mg/l × years	OR = 1.41 (0.7–2.9) OR = 1.00 (0.5–2.1)
Steinmaus et al. [51]	Case–control	509 (181)	Western USA	Drinking water[d]	> 80 vs ≤ 80 μg/d	OR = 0.94 (0.56–1.57) OR $_{exposure > 40\ years\ ago, among\ smokers}$ = 3.67 (1.43–9.42)
Michaud et al. [52]	Nested case–control	573 (280)	Finland	Toenail[b]	> 0.161 vs. < 0.050 μg/g	OR = 1.13 (0.70–1.81)

[a] Number in parentheses represents number of deaths; [b] As content determined using Neutron Activation Analysis (NAA); [c] As determined using X-ray emission spectroscopy; [d] As exposure based on Nevada State Health Division and California Department of Health Services measures of community-supplied drinking water; AR = attributable risk; SMR = standardized mortality ratio

assume that emissions are confined to specific locations, which may not always be the case. In addition, many of the occupational studies have (of necessity) relied on historical data, which are limited due to possible changes in production techniques and ventilation systems over time.

Several other methods for measuring trace element exposure have been tested and utilized, including assessment of dietary intake and analytical assessment of trace element levels in biological and environmental samples. Methods to assess intake of trace elements from dietary sources (and via supplement use) include 24-h and 7-day dietary recalls, diet histories, and food frequency questionnaires (FFQ) [19]. To date, these methods have been used mostly to estimate dietary intake of Zn and Se. Diet measurement methods are limited due to the possibility of recall bias (particularly in case–control studies), by the possibility of misclassification of exposure due to the inherent inaccuracy of such methods (for example, Se intake is measured inaccurately by food frequency questionnaires [20]), due to potential differences in absorption of trace elements depending upon food preparation methods, and due to variation by geographic locale in the levels of trace elements in the soil in which foods are grown [21]. However, this is less of an issue in developed countries where most people do not eat locally grown produce.

The various analytical methods for measuring the content of trace elements in biological and environmental samples are listed in Table 2. It should be noted that the ability of each of these methods to detect trace elements in biological specimens is dependent, in large part, on the specimen (e.g., blood, urine, hair, or nail), the methods used to prepare the specimen for analysis, and the trace element of interest [22]. A comprehensive discussion of the methods utilized for each trace element is beyond the scope of the present review—more information (described under the ToxFaq for each trace element) can be found at the United States Department of Health and Human Services ATSDR website http://www.atsdr.cdc.gov/toxfaq.html.

Table 5 Summary of epidemiologic studies of cadmium (Cd) and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Lung						
Lemen et al. [59]	Cohort	292 (12)[a]	USA	Job history	General population	SMR^b = 235 ($p = 0.05$)
Sorahan et al. [60]	Cohort	3,025 (89)	UK	Job history (Ni–Cd)	General population	$SMR_{all\ employees}$ = 127 ($p < 0.05$)
Elinder et al. [61]	Cohort	522 (195)[a]	Sweden	Job history (Ni–Cd)	General population	SMR = No association
Sorahan et al. [62]	Cohort	3,025 (110)	UK	Job records/ survey & airborne Cd measurement	General population ≥ 15 vs. 0 yrs	SMR = 130 ($p < 0.01$) RR = 1.5 ($p = ns$)
Kazantzis et al. [63]	Cohort	7,000 (277)[a]	UK	Occupational exposure	General population	SMR = 115 (101–129)
Stayner et al. [64]	Cohort	606 (24)[a]	USA	Job history	General population	SMR = 149 (95–222) $SMR_{among\ highest\ exposure\ group}$ = 272 (123–513)
Sorahan [65]	Cohort	1,492 (92)	UK	Job history (Ni–Cd)	General population	$SMR_{alloy\ workers}$ = 101 ($p = ns$) $SMR_{vicinity\ workers}$ = 160 ($p < 0.01$) $SMR_{brass/iron\ foundry\ workers}$ = 107 ($p = ns$)
Stomach						
Kazantzis et al. [63]	Cohort	7,000 (98)[a]	UK	Occupational exposure	General population	SMR = 139 (111–166)
Bladder						
Lemen et al. [59]	Cohort	292 (12)[a]	USA	Job history	General population	$SMR_{total\ cohort}$ = 347 ($p = ns$) $SMR_{≥ 20\ years/latency}$ = 452 ($p = 0.05$)
Prostate						
West et al. [66]	Case–control	1,037 (358)	Utah, USA	Diet	>61 vs. < 36 µg/day	$OR_{68–74\ years\ old}$ = 1.8 (1.1–3.1)
Armstrong et al. [68]	Nested case–control	6,995 (39)	USA	Job category	Medium vs. low High vs. low	OR = 1.55 (0.49–4.93) OR = 1.35 (0.31–5.91)
Platz et al. [67]	Nested case–control	342 (115)	USA	Toenail[c]	5th vs. 1st quintile	OR = 0.70 (0.36–1.37)
Sorahan et al. [60]	Cohort	3,025 (5)[a]	UK	Occupational history (Ni–Cd)	General population	SMR = 127 ($p < 0.05$)
Kazantzis et al. [63]	Cohort	7,000 (30)[a]	UK	Occupational exposure	General population	SMR = 90 (61–129)

[a] Number in parentheses represents number of deaths; [b] SMR = standardized mortality ratio; [c] Cd content determined using Flame atomic absorption (FAA)

Use of biological specimens for measuring trace element exposure

Estimates of trace element exposure are often determined by sampling biological specimens such as blood (including whole blood, serum, plasma, and erythrocytes), urine, hair, and nails, each of which differs in terms of the exposure period represented. In relation to the etiology of cancer, cumulative exposure is usually of interest. Plasma and serum measures tend to reflect short-term exposures, while trace element levels in erythrocytes represent long-term exposure [23]. Toenails are often preferable to other biological samples (e.g., blood, urine) for the measurement of trace element levels because they reflect longer-term exposure. A number of studies have assessed the validity/ reproducibility of toenails as a surrogate measure of selenium intake [20, 24–26] and have shown good or strong correlations between toenail measures and intake. Although analytical methods for determining

Table 6 Summary of epidemiologic studies of nickel (Ni) and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Colorectal						
Karjalainen et al. [80]	Cohort	1,388 (3)	Finland	Job exposure	General population	SIR[b] $_{Employed\ after\ 5/1/60}$ = 1.4 (0.2–5.0)
Lung						
Grimsrud et al. [78]	Case–control	465 (213)	Norway	Job-exposure matrix	>1.43 vs. 0 mg/m³-yr >12.6 vs. 0 mg/m³-yr >2.3 vs. 0 mg/m³-yr	OR $_{Sulfidic\ Ni}$ = 1.2 (0.5–3.3) OR$_{Oxidic\ Ni}$ = 15 (0.4–2.5) OR $_{Metalic\ Ni}$ = 0.3 (0.3–2.4)
Grimsrud et al. [79]	Nested case–control	5,297 (267)[a]	Norway	Work history	General population	SMR[c] $_{total\ Ni}$ = 3.3 (2.8–3.8) SIR $_{water-soluble\ Ni}$ = 4.5 (3.6–5.5)
Elinder et al. [61]	Cohort	522 (195)[a]	Sweden	Job history	General population	SMR = No association
Sorahan [62]	Cohort	3,025 (102)	United Kingdom	Job history	≥ 15 vs. 0 yrs. exposed	RR = No association
Karjalainen et al. [80]	Cohort	1,388 (18)	Finland	Job exposure	General population	SIR $_{Employed\ before\ 5/1/60}$ = 1.0 (0.4–1.9) SIR $_{Employed\ after\ 5/1/60}$ = 1.1 (0.5–2.0)
Pang et al. [81]	Cohort	(5)[a]	United Kingdom	Job history	≥ 1 vs. < 1 yrs. exposed	RR = 1.25 (0.36–4.33)
Andersen et al. [83]	Cohort	125,000 (203) 125,000 (55)	Norway	Job exposure	≥ 15 vs. 0 yrs. exposed	SIR = 3.0 (2.6–3.4) RR $_{soluble\ Ni}$ = 3.1 (2.1–4.8)[d] RR $_{Ni\ oxide}$ = 1.5 (1.0–2.2)[d]
Jarup et al. [82]	Cohort	869 (16)	Sweden	Job exposure	General population	SMR = 176
Stomach						
Pang et al. [81]	Cohort	(5)[a]	United Kingdom	Job history	≥1 vs. < 1 yrs. exposed	RR = 2.61 (0.60–11.33)
Karjalainen et al. [80]	Cohort	1,388 (12)	Finland	Job exposure	General population	SIR $_{Employed\ before\ 5/1/60}$ = 1.8 (0.7–3.7) SIR $_{Employed\ after\ 5/1/60}$ = 1.3 (0.4–3.1)
Bladder						
Karjalainen [80]	Cohort	1,388 (3)	Finland	Job exposure	General population	SIR$_{Employed\ before\ 5/1/60}$ = 2.4 (0.5–7.0)
Prostate						
Sorahan et al. [60]	Cohort	3,025 (5)[a]	United Kingdom	Occupational history	General population	SMR = 127 ($p < 0.05$)

[a] Number in parentheses represents number of deaths; [b] SIR = standardized incidence ratio; [c] SMR = standardized mortality ratio; [d] Statistically significant dose–response relationship reported

arsenic levels in nails were outlined by Agahian et al. in 1990 [27], few epidemiologic studies have employed this method. Garland et al. [24], using data from a 6-year reproducibility study, suggests that toenail measures of zinc may be a good indicator of long-term zinc exposure. In contrast, serum and plasma biomarkers of Zn are considered to be poor indicators of whole body Zn status [28, 29] given that plasma levels of zinc are homeostatically regulated and that other common factors that can influence its distribution [29]. A detailed discussion of the validity/reproducibility of biological specimens used for measuring trace element exposure is beyond the scope of the present review—more information can be found in the World Health Organization's (WHO) *Trace Elements in Human Nutrition and Health* [2] and at the United States Department of Health and Human Services ATSDR website (described under the ToxFaq for each trace element) http://www.atsdr.cdc.gov/toxfaq.html.

Results: trace elements and cancer risk—epidemiologic evidence

Arsenic

Although there is some evidence of clinical manifestations resulting from As deficiencies in certain animal species [2, 30, 31], currently there is no known beneficial biological function of As in humans. In contrast,

As has been shown to induce carcinogenesis via a wide range of cellular changes including alterations in cell differentiation and proliferation [7, 32]. In addition, inorganic As has been found to induce chromosomal aberrations and sister chromatid exchange [7]. Cells exposed to As have also been shown to increase cellular tyrosine phosphorylation, which is related to the aberrant cell signaling and uncontrolled cell growth associated with cancer development [33, 34]. A review of the As in drinking water was recently compiled by the State of California [35] and provides information on the association between As and other health conditions, including cancer outcomes not included in this review.

A number of ecologic studies from Taiwan, a location known for its high levels of As in drinking water (average intake > 1 mg/day [36]), have suggested that As may be associated with increased risks of bladder and lung cancer. Given this, studies of lung and bladder cancer risk have been conducted in other areas with known geologic As contamination of drinking water. A summary of the literature regarding high levels of As exposure (≥100 μg/l) and cancer risk is presented in Table 3. Two case–control [37, 38] and two [39, 40] out of three [39–41] cohort studies have found elevated lung cancer risks associated with high levels of exposure to As from drinking water, whereas one cohort study showed an inverse association [41]. In addition, case–control [37, 42] and four [39, 40, 43, 44] out of five [39–41, 43, 44] cohort studies conducted in areas with high As concentrations in drinking water have shown positive associations between As in drinking water and bladder cancer risk. Furthermore, there is some evidence that exposure to high levels of As in drinking water is associated with an increased risk of prostate cancer [41].

While the association between As and cancer, particularly lung and bladder cancers, is established at high levels of exposure, the association at lower levels (< 100 μg/l) is less certain. A summary of the literature regarding lower levels of As exposure (both occupational and from drinking water) and cancer risk is presented in Table 4. In the only study of As and breast cancer risk reported to date, Garland et al. [45] observed no association between levels measured in toenails and risk. With respect to lung cancer, one case–control [46] and two cohort studies [47, 48] have observed positive associations between occupational As exposure and lung cancer risk, while one case–control study by Coggon et al. [49] found no association between occupational As exposure and risk of lung cancer. However, exposure in the latter study was estimated by creating a job matrix where occupational

units were classified according to their likely exposure to As rather than direct measurement of airborne levels, and therefore the levels of exposure cannot be directly compared to those in the other studies included in this review [49]. Both Bates et al. [50] and Steinmaus et al. [51], in analyses of As in drinking water, and Michaud et al. [52], in an analysis of toenail As, found no association between As exposure and bladder cancer risk.

Cadmium

Although there is some evidence that low concentrations of dietary Cd may be beneficial to some animal species [2], currently there is no evidence of a beneficial function in humans. Indeed, on the basis of evidence from experimental and epidemiologic studies, IARC [8] and the US National Toxicology Program [53] have designated Cd as a known human carcinogen. It is thought that Cd acts via genotoxic mechanisms including induction of single-strand DNA breaks [54], and also that it inhibits DNA repair by inactivation of the mismatch repair system [54, 55], activates proto-oncogenes [56, 57] and inhibits apoptosis [58].

Table 5 presents a summary of the literature regarding Cd exposure and cancer risk. To date, most studies of Cd and cancer have focused on lung and prostate cancer. Six of the seven occupational cohort studies that have been reported have found statistically significant increased risks of lung cancer associated with relatively high Cd exposure [59–65].

The relationship between Cd exposure and prostate cancer risk has been examined in one case–control [66], two nested case–control [67, 68], and two cohort analyses [60, 63]. In the only case–control study to date (358 incident cases), West et al. [66] reported a statistically significant positive association with ingested Cd from dietary sources, as assessed by a food frequency questionnaire. The remaining studies differed in that they examined the association between occupational Cd exposure and prostate cancer risk. Armstrong and Kazantzis [68] and Platz et al. [67] each analyzed data from two separate US cohort studies using nested case–control designs (39 and 115 incident cases, respectively) and reported no association between high Cd exposure and prostate cancer risk. Kazantzis et al. [63] likewise found no association between occupational exposure to Cd and prostate cancer mortality in a British cohort, but the study included only 30 cases. In contrast, Sorahan and Waterhouse [60] observed a statistically significant increased risk of prostate cancer mortality among Ni–Cd alloy workers in the United

Table 7 Summary of epidemiologic studies of selenium and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population	Exposure	Comparison	Risk estimate (95% CI)
Breast cancer						
Willett [94]	Case-control	32 (16)	USA	Serum	Mean Se concentration	No difference in mean Se concentration
Schrauzer et al. 1985 [93]	Case-control	104 (79)	Japan	Whole blood[d]	Mean Se concentration	Lower Se concentration for incident breast cancer than control group ($p < 0.001$)
		50 (25)	USA			Lower Se concentration for incident breast cancer than control group ($p < 0.005$)
Meyer et al. [23]	Case-control	154 (38)	USA	Erythrocyte	0.12–0.16 vs. 0.19–0.28 ppm	OR = 0.5 (0.2–1.3)
Van't Veer et al. [85]	Case-control	371 (133)	The Netherlands	Diet / Plasma[a] / Erythrocyte[a] / Toenail[a]	4th vs. 1st quartile	OR = 1.6 (0.8–3.4)[a] / OR = 2.0 (0.9–4.4) / OR = 0.9 (0.4–1.9) / OR = 1.1 (0.6–2.1)
Van't Veer et al. [86]	Case-control	694 (347)	5 European countries	Toenail[a]	> 0.613 vs. < 0.521 µg/g	OR = 0.96 (0.63–1.47)
Strain et al. [91]	Case-control	204 (99)	Northern Ireland	Toenail[a]	> 0.630 vs. ≤ 0.530 µg/g	OR = 1.11 (0.55–2.25)
Ghadirian et al. [87]	Case-control	1,015 (327)	Canada	Toenail[a]	≥ 1 vs. < 0.79 ppm	OR = 0.72 (0.4–1.31)
Coates et al. [92]	Nested case-control	57 (20)	USA	Serum[a]	3rd vs. 1st tertile	RR = 3.4
Van Noord et al. [88]	Cohort	453 (61)	The Netherlands	Toenail[a]	4th vs. 1st quartile	OR = 1.1 (0.5–2.9)
Hunter et al. [89]	Cohort	870 (434)[e]	USA	Toenail[a]	≥ 0.906 vs. < 0.706 µg/g	RR = 1.10 (0.70–1.72)
Van den Brandt et al. [90]	Cohort	1,603 (355)	The Netherlands	Toenail[a]	> 0.645 vs. 0.499 µg/g	RR = 0.84 (0.55–1.27)
Colorectal cancer						
Clark et al. [97]	Cross-sectional	48	USA	Plasma[b]	≥ 128 vs. < 128 µg/l	OR = 3.79 (1.02–15.71)
Fernandez-Banares et al. [98]	Case-control	63 (28)	Spain	Serum[b]	≥ 82.11 vs. < 82.11 µg/l	OR = 0.17 (0.03–0.84)
Ghadirian et al. [87]	Case-control	294 (92)	Canada	Toenail[a]	≥ 1 vs < 0.79 ppm	OR = 0.42 (0.19–0.93)[h]
Mannisto et al. [102]	Case-control	722 (289)	Finland	Toenail[a]	5th vs. 1st quintile	OR premenopausal = 1.1 (0.4–3.2) / OR postmenopausal = 0.7 (0.3–1.5)
Nomura et al. [99]	Nested case-control	375 (82 colon) / 325 (32 rectal)	Hawaii	Serum[a]	< 10.31 vs ≥ 13.3 µg/dl	OR Colon = 1.8 (p_{Trend} = 0.33) / OR Rectum = 1.6 (p_{Trend} = 0.66)
Wallace et al. [100]	Nested case-control	552 (276)	USA	Serum[a]	> 146 vs ≤ 116 µg/l	OR Total Se = 0.76 (0.44–1.30) / OR Bound Se = 0.60 (0.34–1.05)
van den Brandt et al. [103]	Case-cohort	3,500 (313 colon) / 3,500 (166 rectal)	The Netherlands	Toenail[a]	> 0.630 vs. ≤ 0.483 µg/g	RR colon = 0.77 (0.49–1.19) / RR rectum = 1.01 (0.55–1.84)
Garland et al. [101]	Cohort	62,641 (89)	USA	Toenail[a]	3rd vs. 1st tertile	RR rectum = 2.04 (0.88–4.75)
Lung cancer						
Sattar et al. [5]	Case-control	35 (22)	UK	Plasma[c]	Mean Se concentration	No difference in mean Se concentration
Nomura et al. [99]	Nested case-control	364 (71)	Hawaii	Serum[a]	< 10.31 vs ≥ 13.3 µg/dl	OR = 1.1 (p_{Trend} = 0.46)
Kabuto et al. [104]	Nested case-control	197 (77)	Japan	Serum[a]	>128 vs. < 99 ng/ml	OR = 1.8 (0.7–5.0)
Ratnasinghe et al. [105]	Nested case-control	324 (108)	China	Serum[b]	55–121 vs. 20–39 ng/ml	OR = 1.2 (0.6–2.4)

Table 7 (continued)

Reference	Study design	Number of study participants (No. cases)	Population	Exposure	Comparison	Risk estimate (95% CI)
Hartman et al. [107]	Nested case–control	500 (250)	Finland	Toenail[d]	4th versus 1st quartile	OR = 0.20 (0.09–0.44) randomized in earliest trial; OR = 0.61 (0.27–1.41) randomized in 5th yr
Van den Brandt et al. [108]	Cohort	1,388 (370)	The Netherlands	Toenail[a]	> 0.630 vs ≤ 0.483 μg/g	RR = 0.50 (0.30–0.81)[h]
Garland et al. [101]	Cohort	62,641 (47)	USA	Toenail[a]	3rd versus 1st tertile	RR = 4.33 (0.54–34.6)
Reid et al. [106]	Randomized trial	1,250 (60)	USA	200 μ/day Se	Versus placebo	HR $_{1983–1993}$ = 0.56 (0.31–0.76); HR $_{1983–1996}$ = 0.74 (0.44–1.24)
Stomach cancer						
Chen et al. [111]	Cross-sectional	312 (35)	Taiwan	Serum[b]	> 107.2 vs ≤ 107.2 μg/l	OR = 0.84 (0.40–1.76)
Kabuto et al. [104]	Case–control	428 (202)	Japan	Serum[a]	> 128 vs. < 99 ng/ml	OR = 1.0 (0.5–1.9)
Zhang et al. [112]	Nested case–control	609 (88)	US	Serum[a]	3rd versus 1st tertile	OR$_{\text{tertiles}}$ = 0.9 (0.6–1.4)
Nomura et al. [99]	Nested case–control	361 (66)	Hawaii	Serum[a]	< 10.31 vs ≥ 13.3 μg/dl	OR = 0.9 (p_{Trend} = 0.88)
Knekt et al. [113]	Case–cohort	116 (58)	Finland	Serum[b]	4th versus 1st quartile	OR $_{\text{men}}$ = 0.26 (p < 0.01); OR $_{\text{women}}$ = 0.59 (p = ns)
van den Brandt et al. [103]	Case–cohort	3,500 (1550)	The Netherlands	Toenail[a]	> 0.630 vs ≤ 0.483 μg/g	RR = 0.61 (0.33–1.11)
Wei et al. [114]	Case–cohort	1,103 (516)	Linxian, China	Serum[b]	Continuous, unit = 0.15 μmol/l	RR = 0.75 (0.59–0.95)
Mark et al. [115]	Stratified case-cohort	1,551 (402 GC)[f]; 1,551 (82 OG)[g]	Linxian, China	Serum[b]	> 82.1 vs < 59.8 μg/l	RR $_{\text{GC}}$ = 0.47 (0.33–0.65)[h]; RR $_{\text{OC}}$ = 1.07 (0.55–2.08)
Dawsey et al. [116]	Randomized trial	3,318 (58)	China	Combination supplement	Supplement with 50 μg Se vs. placebo	RR $_{1987}$ = 1.91 (0.64–5.68); RR $_{1991}$ = 0.77 (0.38–1.58)
Wang et al. [117]	Randomized trial	29,584 (23 dysplasia or cancer); 29,584 (29,584 (16 cancer)	China	Combination supplement	Vitamin E, Se & β-carotene vs. placebo	RR = 0.83 (0.37–2.92); RR = 1.05 (0.37–2.92)
Bladder cancer						
Nomura et al. [99]	Nested case–control	322 (29)	Hawaii	Serum[a]	< 10.31 vs ≥ 13.3 μg/dl	OR = 1.9 (p_{Trend} = 0.12)
Helzlsouer et al. [118]	Nested case–control	70 (35)	Maryland, USA	Serum[a]	3rd versus 1st tertile	OR = 2.06 (0.67–6.35)[h]
Zeegers et al. [119]	Case–cohort	2,459 (431)	The Netherlands	Toenail[a]	> 0.630 vs ≤ 0.483 μg/g	OR = 0.67 (0.46–0.97)[h]
Michaud et al. [120]	Nested case–control	266 (133)	Finland	Toenail[d]	3rd versus 1st tertile	OR = 0.90 (0.45–1.78)
Prostate cancer						
West et al. [66]	Case–control	1,037 (358)	Utah, USA	Diet	> 183 vs < 106 μg/dl	OR $_{\text{68–74 years old}}$ = 1.6 (1.0–2.8)
Ghadirian et al. [87]	Case–control	285 (83)	Canada	Toenail[a]	> 0.630 vs ≤ 0.483 μg/g	OR = 1.14 (0.46–2.83)
Vogt et al. [121]	Case–control	445 (212)	USA	Serum[a]	> 0.151 vs. < 0.119 μg/ml	OR = 0.71 (0.39–1.28)
Allen et al. [122]	Case–control	600 (300)	UK	Nail[a]	> 0.705 vs. < 0.497 ppm	OR $_{\text{total}}$ = 1.24 (0.73–2.10); OR $_{\text{advanced cancer}}$ = 0.78 (0.27–2.25)
Coates, et al. [92]	Nested case–control	37 (13)	USA	Serum[a]	64–186 vs 24–47 μg/l	RR $_{\text{tertile}}$ = 0.3
Willett et al. [94]	Nested case–control	22 (11)	USA	Serum[a]		Lower Se concentration for prostate cancer than control group (p = 0.12)
Knekt et al. [113]	Nested case–control	92 (46)	Finland	Serum[b]	4th versus 1st quartile	RR $_{\text{quintile}}$ = 1.00 (0.42–2.40)
Li et al. [127]	Nested case–control	1,163 (586)	USA	Plasma[a]	5th versus 1st quintile	RR = 0.52 (0.16–0.97); RR $_{\text{PSA > 4 ng/ml}}$ = 0.49 (0.28–0.86)

Table 7 (continued)

Reference	Study design	Number of study participants (No. cases)	Population	Exposure	Comparison	Risk estimate (95% CI)
Helzlsouer et al. [124]	Nested case-control	350 (117)	Maryland, USA	Toenail[a]	> 0.91 vs < 0.69 ppm	OR = 0.38 (0.17–0.85)
Brooks et al. [123]	Nested case-control	148 (52)	Maryland, USA	Plasma[b]	13.3–18.2 vs 8.2–10.7 μg/dl	OR = 0.24 (0.08–0.77)
Nomura et al. [125]	Nested case-control	498 (249)	Japanese-Americans in USA	Serum[b]	≥ 147.2 vs. < 119.3 μg/ml	OR = 0.5 (0.3–0.9)[h]
Yoshizawa et al. [126]	Nested case-control	362 (181)	USA	Toenail[a]	0.94–7.09 vs 0.53–0.73 ppm	OR = 0.35 (0.16–0.78)
van den Brandt et al. [128]	Case-cohort	1,751 (540)	The Netherlands	Toenail[a]	> 0.616 vs ≤ 0.467 μg/g	RR = 0.69 (0.48–0.99)[h]
Hartman et al. [129]	Trial-based cohort	29,133 (317)	Finland	Diet (including supplements)	> 111.05 vs < 71.52 μg/d	RR No α-tocopherol = 1.27 (0.70–2.20); RR α-tocopherol = 0.84 (0.43–1.67)
				Diet (excluding supplements)	> 105.64 vs < 70.11 μg/d	RR No α-tocopherol = 1.32 (0.70–2.47); RR α-tocopherol = 0.72 (0.33–1.55)
Clark et al. [130]	Randomized trial	974 (48)	USA	200 μg	Versus placebo	RR = 0.37

[a] Se content determined using neutron activation analysis (NAA); [b] Se content determined using atomic emission spectrophotometry (AES); [c] Se content determined using atomic absorption spectrophotometry (AAS); [c] Se content determined using fluorometry; [e] Number in parentheses represents number of deaths; [f] GC = Gastric cardia adenocarcinoma; [g] OG = Non-cardia gastric adenocarcinoma; [h] Statistically significant dose-response relationship reported

Kingdom, although this finding was based on only five prostate cancer cases.

Nickel

In 1996, the World Health Organization classified Ni as a trace element that is 'probably' essential [2], given its role in Ni-containing enzymes found in plants and microorganisms. However, evidence that Ni has similar functions in humans is not currently available. In contrast, Ni compounds can display tumor promoting capability via a number of mechanisms including inhibition of intercellular communication [69], immortalization of fibroblasts and epithelial cells [70–73], the induction of DNA deletions and aberrations [74], production of DNA-protein cross-links, oxidative damage, inhibition of nucleotide excision repair [74–76] and an increase in DNA methylation leading to inactivation of gene expression [77]. In epidemiologic studies of the association between Ni and cancer risk, Ni has been examined either alone or in combination with Cd (in the form of Ni–Cd) (Table 6).

Grimsrud et al. [78], in a nested case–control study of Norwegian Ni-refinery workers, reported no association between lung cancer incidence and occupational sulfidic, oxidic, or metallic Ni exposure. However, in a subsequent study based on the same cohort, Grimsrud et al. [79] analyzed data for workers employed between 1910 and 1989 and who were alive after 1953, and they reported an increased risk of lung cancer associated with both total and water-soluble Ni after controlling for smoking history. Of the six cohort studies of job-related Ni exposure, four observed no association with lung cancer risk [61, 62, 80, 81], and two observed an increased risk [82, 83] (Table 6).

Studies of colorectal, bladder, and gastric cancers [80, 81] and Ni exposure have also been conducted and have reported no association (Table 6). In contrast, Sorahan and Watherhouse [60] reported a statistically significant increased risk of prostate cancer mortality with relatively high occupational Ni exposure. As with results for other cancer sites, the conclusions that can be drawn from these studies are limited by the relatively small number of cases included (Table 6).

Selenium

Selenium is considered an essential trace element because it is the primary component of selenoproteins, which have roles in counteracting oxidative stress and regulating the redox status of other molecules [84]. Not surprisingly, therefore, Se has been studied extensively in relation to cancer risk due to its possible

preventive effects. While there is epidemiologic evidence to support an inverse association between Se and risk of some cancers, the evidence is not consistent. A summary of the current literature regarding Se exposure and risk of breast, colorectal, lung, stomach, bladder, and prostate cancer is presented in Table 7.

The results of case–control and prospective cohort studies conducted to date do not support an association between Se and breast cancer [23, 85–94]. Of the seven case–control studies [23, 85–87, 91, 93, 94], only Schrauzer et al. [93] found a statistically significant inverse association between Se exposure and breast cancer risk. In contrast, larger case–control studies such as those by Van't Veer et al. [85, 86] and Ghadirian et al. [87], both of which examined toenail Se, which is considered more representative of long-term Se exposure [95, 96], found no association with breast cancer risk. In addition, none of the four cohort studies that have examined this relationship [88–90, 92], of which three utilized toenail measures of Se exposure [88–90], have found any association between Se and breast cancer risk. The conclusion that Se is not associated with breast cancer risk is supported by the fact that studies to date have measured exposure using different approaches (including analysis of toenail, whole blood, plasma, and erythrocyte samples, and measurement of dietary Se), and produced mostly null results. In this regard, van't Veer et al. [85] examined the association between Se and breast cancer risk by measuring both dietary Se intake using a FFQ and Se concentrations in plasma, erythrocytes, and toenails. The magnitude of the odds ratios comparing extreme quartile levels ranged from 0.9 (erythrocyte Se) to 2.0 (plasma Se), and none of these associations was statistically significant [85].

In a cross-sectional study of 48 individuals in the United States, Clark et al. [97] observed an almost 4-fold increased risk of colorectal cancer for plasma Se concentrations ≥ 128 μg/l versus those < 128 μg/l (95% CI = 1.02–15.71). However, subsequent case–control and cohort studies of Se and colorectal cancer risk, using either serum [98–100] or toenails [87, 101–103] for Se measurement, have largely reported no association [87, 99–103]. Fernandes-Banares et al. [98] used fasting blood samples and showed an inverse association between serum Se levels and risk, while Nomura et al. [99] used non-fasting samples and showed no association with serum Se levels. However, given that Se levels measured in blood samples represent recent exposure, comparison of the results of studies using fasting blood samples to those using non-fasting blood samples may not be appropriate. Furthermore, long-term measures of Se intake are

more useful. In this regard, Ghadirian et al. [87], Mannisto et al. [102], van den Brandt et al. [103], and Garland et al. [101] measured Se concentrations in toenail samples, each using similar methodologies. However, the results were mixed, with Ghadirian et al. [87] reporting a statistically significant inverse association, Mannisto et al. [102] and van den Brandt et al. [103] observing no association, and Garland et al. [101] reporting a statistically non-significant increased risk of colorectal cancer.

Results from nested case–control studies of Se and lung cancer risk have been mixed. Kabuto et al. [104] conducted a nested case–control study in Japan and reported that cases were more likely to have higher serum Se concentrations than controls, while Nomura et al. [99] and Ratnasinghe et al. [105], in nested case–control analyses of data from Hawaii and China, respectively, reported no association with serum levels. More recently, a randomized trial was conducted in the United States to test the effect of Se supplementation (200 μg/day) on non-melanoma skin cancer recurrence, with lung cancer incidence as a secondary endpoint [106]. Although analysis of data from the first 10 years of the study (1983–1993) revealed a 44% decrease in lung cancer risk (95% CI = 0.31–0.76) in association with the intervention [106], a re-analysis conducted after three years of additional follow-up revealed attenuation of the hazard ratio to 0.74, which was no longer statistically significant (95% CI = 0.44–1.24). A limitation of this study is that it included only 60 incident lung cancer cases [106]. In addition to these studies, which assessed Se exposure using serum samples, toenail Se levels have been investigated in relation to lung cancer risk in a number of studies. Hartman et al. [107], in a nested case–control analysis of data from the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Cohort based on 250 cases, found a statistically significant inverse association between toenail Se and risk. Likewise, van den Brandt et al. [108] reported a 50% decreased risk of lung cancer associated with toenail Se concentrations (p_{trend} = 0.0006). In contrast, Garland et al. [101], in an analysis of data from the Nurses' Health Study (47 incident cases), reported an approximately 4-fold increased risk of lung cancer, although this finding was not statistically significant.

The results of studies of the association between Se and gastric cancer risk have varied somewhat, although most have yielded point estimates at or below unity. Ecologic studies conducted in Japan [109] and China [110] showed statistically significant inverse correlations between Se in drinking water and plasma Se, respectively, and gastric cancer mortality. Chen et al.

[111] in a cross-sectional study and Kabuto et al. [104], in a case–control study, however, observed no association between serum Se and stomach cancer risk. Likewise, both Zhang et al. [112] and Nomura et al. [99] observed no association between serum Se and stomach cancer risk in nested case–control studies in the United States. In contrast, three of four case-cohort studies have reported statistically significant inverse associations [103, 113–115]. Two randomized trials of dietary supplementation have been conducted in Linxian, China [116, 117], a region known for both its high incidence of gastric cancer and a number of nutritional deficiencies [114]. The larger General Population Trial, which included 29,584 adults (16 incident cases) found no association with the vitamin E/β-carotene/Se combination [117]. Dawsey et al. [116] analyzed data from the Dysplasia Trial in Linxian, China, and at the 1987 follow-up they found an increased risk of gastric cancer in association with a multivitamin, multimineral supplement containing Se, but an inverse association in 1991; neither of these findings was statistically significant. However, given that these trials examined the effect of Se in concert with other vitamins/minerals, conclusions about the effect of Se supplementation alone cannot be drawn from them.

With respect to bladder cancer, Nomura et al. [99] and Helzlsouer et al. [118] each examined the association between serum Se and risk and reported elevated odds ratios (1.9 and 2.06, respectively) for the lowest versus the highest tertile of serum Se. While neither of these associations was statistically significant, Helzlsouer et al. [118] did report a statistically significant trend (p_{trend} = 0.03) of increasing risk with decreasing serum Se levels. Similarly, Zeegers et al. [119] reported an inverse association between toenail Se concentration and bladder cancer risk in a case-cohort analysis from the Netherlands Cohort Study. Michaud et al. [120], however, found no association between toenail Se and bladder cancer in a nested case–control analysis of male smokers enrolled in the Alpha-Tocopherol/Beta-Carotene (ATBC) trial. Currently there is insufficient evidence to draw a conclusion regarding the association between Se exposure and bladder cancer risk.

Recently, much attention has been given to the potentially protective effect of Se in relation to prostate cancer. In this regard, although a number of case–control studies, nested [92, 94, 113], and non-nested [87, 121, 122], have suggested that there is no association between Se and prostate cancer risk, several other nested case–control analyses of data from different study populations within the United States [123–127]

and a case-cohort analysis of data from the Netherlands [128] have reported statistically significant inverse associations between Se concentrations (based on measurements in plasma [123, 127], serum [125] and/or toenails [124, 126, 128]) and prostate cancer risk. Hartman et al. [129] analyzed data from the ATBC trial as a cohort study and reported that dietary Se (both including and excluding supplements) was not associated with prostate cancer risk, although there was some evidence for an inverse association with Se among those receiving α-tocopherol supplements. Randomized trials have also been undertaken to further study the potential association between Se and prostate cancer risk. In one such study, Clark et al. [130] examined data from a trial conducted in the United States and reported a 63% decreased risk of prostate cancer for those receiving 200 μg of Se per day versus placebo after 4.5 years of treatment and 6.5 years of follow up (p_{trend} = 0.002). The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a clinical trial with more than 35,000 participants, which will take approximately 12 years to complete, was initiated in order to further investigate this association (http://cancer.gov/select).

Zinc

The effects of Zn deficiency in humans were first reported in the 1960s [131, 132] and include growth retardation, cognitive impairment and immune dysfunction [133]. Zinc is also involved with metallothionine synthesis, which is thought to inhibit free radical production [134]. Furthermore, it has been shown that zinc chloride significantly decreases DNA strand breaks in human cutaneous fibroblasts exposed to UVA1 radiation [135]. Hence, it is conceivable that there might be an inverse association between Zn and cancer risk.

The association between Zn levels and cancer risk has been examined for several anatomic sites (Table 8). Case–control studies by Gupta et al. [136] (35 cases), and more recently by Adzersen et al. [137] (310 cases), both yielded statistically significant inverse associations between Zn exposure, measured in serum and diet, respectively, and breast cancer risk. Garland et al. [45], however, in a nested case–control study, including 433 incident cases, reported no association between toenail Zn and breast cancer risk. Whole blood, and its components, can be tested to measure exposure to a number of trace elements. Plasma and serum measures tend to reflect short-term exposures, while trace element levels in erythrocytes represent long-term exposure [23]. As noted earlier, there is

Table 8 Summary of epidemiologic studies of zinc (Zn) and cancer risk

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Breast						
Gupta et al. [136]	Case–control	90 (35)	India	Serum[b]	Mean Zn concentration	Breast cancer patients had lower Zn concentrations than healthy subjects ($p < 0.01$) & patients with benign breast disease ($p < 0.01$)
Adzersen et al. [137]	Case–control	663 (310)	Germany	Diet	> 13.2 vs. < 9.0 mg/d	OR = 0.35 (0.15–0.78)[h]
Garland et al. [45]	Nested case–control	892 (433)	USA	Toenail[a]	> 0.139 vs. < 0.059 μg/g	OR = 1.09 (0.70–1.70)
Lung						
Sattar et al. [5]	Case–control	35 (22)	UK	Plasma[b]	Mean Zn concentration	Lower Zn conc than control group ($p < 0.05$)
Harris et al. [138]	Case–control	200 (96)	UK	Serum[c]	Mean Zn concentration	No difference in mean serum Zn concentrations between groups
Blot et al. [6]	Case–control	667 (335)	USA	Employment records	Steel workers vs. non-steel workers	OR = 2.2 (1.5–3.3)
Kabuto et al. [104]	Nested case–control	197 (77)	Japan	Serum[a]	> 989 vs < 704 ng/ml	OR = 1.3 (0.4–4.3)
Cocco et al. [139]	Cohort	4,740	Italy	Airborne dust measurement from personal & static sampling devices	General population	SMR[g] = 95 (76–117)
Stomach						
Zhang et al. [140]	Case–control	227 (95)	USA	Diet	5th vs. 1st quintile	OR = 0.7 (0.2–1.8)
Kabuto et al. [104]	Case–control	197 (77)	Japan	Serum[a]	> 989 vs < 704 ng/ml	OR = 1.2 (0.6–2.3)
Zhang et al. [112]	Nested case–control	609 (88)	US	Serum Zn:Cu[d] ratio[a]	High vs. low	OR[tertiles] = 0.6 (0.4–1.0)
Wang et al. [117]	Randomized trial	29,584 (23)[e]	China	Combination supplemental (retinol & Zn)	Versus placebo	RR = 0.58 (0.24–1.39)
Dawsey et al. [116]	Randomized trial	29,584 (16 cancer) 3,318 (210	China	Combination suppl including Zn	Versus placebo	RR = 0.38 (0.13–1.15) RR[1987] = 1.9 (0.64–5.68)
		3,318 (37)				RR[1991] = 0.77 (0.38–1.58)
Prostate						
West et al. [66]	Case–control	1,037 (358)	Utah, USA	Diet	> 16 vs. < 10 mg/day	OR[68–74 years old] = 1.3 (0.8–2.3)
Kristal et al. [144]	Case–control	1,363 (697)	USA	Frequency of supplement use	≥ 7/week vs 0	OR = 0.59 (0.32–1.09)[h]
Vlajinac et al. [145]	Case–control	303 (101)	Yugoslavia	Diet	3rd versus 1st tertile	OR = 0.81 (0.28–2.34)
Kolonel et al. [142]	Case–control	1,351 (452)	Hawaii, USA	Diet	4th vs. 1st quartile	OR (total Zn) ≥ 70 yoa = 1.7 (1.1–2.7)[h] OR (total Zn) < 70 yoa = 1.2 (0.7–2.2) OR (food only) ≥ 70 yoa = 1.1 (0.7–1.7) OR (food only) < 70 yoa = 1.3 (0.7–2.2)

Table 8 continued

Reference	Study design	Number of study participants (No. cases)	Population (source)	Exposure	Comparison	Risk estimate (95% CI)
Platz et al. [67]	Nested case-control	353 (118)	Washington DC, USA	Toenail[b]	5th vs. 1st quintile	OR = 0.63 (0.31–1.29)
Leitzmann et al. [143]	Prospective cohort	46,974 (2,901) 46,974 (434)[f]	USA	Supplemental Zn	1–100 vs. 0 mg/day >100 vs. 0 mg/day	RR = 1.43 (0.95–2.15) RR = 2.91 (1.23–6.90)[h]

[a] Zn content determined using Neutron Activation Analysis (NAA); [b] Zn content determined using atomic absorption spectrophotometry (AAS); [c] Zn content determined using atomic emission spectrophotometry (AES); [d] Cu = Copper; [e] Dysplasia & cancer; [f] Advanced prostate cancer; [g] SMR = Standardized mortality ratio; [h] Statistically significant dose–response relationship reported

evidence that status biomarkers such as blood and plasma tend to be poor indicators of whole body Zn status [28]. Toenails are often preferable to other biological samples (e.g., blood, urine) for the measurement of trace element levels because they tend to reflect longer-term exposure. The use of different status biomarkers in these studies may be an important contributor to the mixed outcome results of competing studies.

The literature regarding the association between Zn exposure and lung cancer differs according to the level of Zn exposure. That is, when compared to those who are Zn sufficient, the effect of Zn deficiency is different from that of Zn overexposure (e.g, through occupational exposure). A case–control study by Sattar et al. [5], which compared individuals who were Zn deficient as a result of inadequate dietary intake to those who were Zn sufficient, suggested that there is an inverse association between plasma Zn levels and lung cancer risk, while in other studies of Zn deficiency, both Harris et al. [138] and Kabuto et al. [104] found no association with lung cancer risk. The results of studies of occupational Zn exposure are mixed. A case–control study by Blot et al. [6], which compared individuals who are Zn sufficient to those who have Zn overload, found a positive association between occupational Zn exposure and risk. In contrast, Cocco et al. [139], in a prospective study of 4,740 lead and Zn smelter workers in Italy, found no association between lung cancer mortality and airborne Zn concentrations as assessed using regular measurements of airborne dust from personal and static sampling devices.

Zinc has also been examined in association with risk of gastric cancer. In a case–control study, Zhang et al. [140] utilized a FFQ to determine dietary Zn intake and reported an inverse trend of borderline statistical significance with increasing consumption ($p_{trend} = 0.07$). In contrast, Kabuto et al. [104] compared serum Zn concentrations in cases of gastric cancer (77 incident cases) and controls in Japan and observed essentially no difference. Zhang et al. [112] likewise observed no difference in the Zn:Cu ratio between cases and controls in a nested case–control study in the United States (88 incident cases). Analyses of data from two randomized trials conducted in China have found no association between a combination of supplements, including Zn (22.5 mg and 45 mg, respectively), and gastric cancer risk [116, 117].

A number of studies have also been undertaken to examine the association of Zn with prostate cancer. Studies comparing Zn levels in malignant to normal prostate tissue have found that Zn is 60–70% lower in malignant prostate tissue [141]. However, thus far,

results from case–control and cohort studies have been mixed. Kolonel et al. [142] studied the association between dietary Zn intake and risk, stratified by age, and reported a statistically significant positive association between total Zn (including Zn from foods and supplements) and prostate cancer risk among Hawaiian men 70 years of age and older, but found no association between either total dietary Zn or non-supplemental Zn and risk among men under 70 years of age, while Leitzmann et al. [143] found a 2.9-fold increased risk of advanced prostate cancer with supplemental Zn use in a prospective cohort study conducted in the United States.. In contrast, Kristal et al. [144] found a borderline inverse association between frequency of Zn supplement use and prostate cancer risk in a case–control study in the United States, and recently, Platz et al. [67] conducted a nested case–control study of prediagnostic toenail Zn and found a statistically non-significant 37% decreased risk of prostate cancer in association with toenail Zn levels. In case–control studies in Utah and Yugoslavia, respectively, neither West et al. [66] nor Vlajinac et al. [145] found an association between dietary Zn and case status.

Discussion

Conclusions

There is now a substantial body of epidemiologic literature on the association between trace element exposure and cancer risk and a summary of the current state of the evidence for the cancer sites of interest here is presented in Table 9. In drawing our conclusions, we considered issues related to exposure measurement, study design, and sample size. Results from cohort studies and randomized trials (when available) were given greater consideration than were results from case–control and cross-sectional studies on the same topic. In addition, studies which utilized objective exposure measures (e.g., biological measures) were given more weight than were those that used subjective measures (e.g., qualitative assessments of high/medium/low exposures).

In brief, the evidence currently available appears to support an inverse association between Se exposure and prostate cancer risk. In contrast, the vast majority of the studies of Se and breast cancer, which have included large case–control and cohort studies utilizing different means of quantifying exposure, do not appear to support an association. Similarly, there do not appear to be associations between Se and risk of colorectal or stomach cancer. With respect to Zn, although there is literature from case–control studies to support an inverse association between Zn and breast cancer risk, the one cohort study to date does not support an association and additional prospective studies are needed. To date, there is essentially no evidence for associations between dietary Zn intake and risk of stomach or prostate cancer, or between occupational Zn exposure and lung cancer risk. There is compelling evidence to support positive associations between As and risk of lung cancer at both high and low exposure levels and between As and bladder cancer risk at high exposure levels [35]. There is also strong evidence of a positive association between occupational Cd exposure and lung cancer risk.

Future directions

Although the association between trace element exposure and cancer risk has been examined in a number of large prospective studies, there is a need for

Table 9 Summary of findings from epidemiological studies

Trace element	Cancer site					
	Breast	Colorectal	Lung	Stomach	Bladder	Prostate
Arsenic						
High level	NA	NA	Positive	More studies needed	Positive	More studies needed
Low level	More studies needed	NA	Positive	NA	More studies needed	NA
Cadmium	NA	NA	Positive	More studies needed	More studies needed	Mixed
Nickel	NA	More studies needed	Mixed	More studies needed	More studies needed	More studies needed
Selenium	No association	No association	Possible inverse	No association	Mixed	Inverse
Zinc	More studies needed	NA	No association	No association	NA	No association

NA = No studies available

a larger studies to be conducted to enable the possibility of effect modification to be examined. For example, it would be of interest to examine the association between Zn and other trace elements and lung cancer risk across strata of smoking history due to the antioxidant role of Zn.

While randomized trials of Se have been conducted with respect to stomach cancer and have been initiated to assess its effect on risk of prostate cancer, randomized trials investigating other trace elements that may also reduce cancer risk (e.g., Zn) have not been conducted as yet. Such trials might focus initially on the effect of the interventions on intermediate end-points such as cancer precursors.

Finally, while there is now a considerable amount of epidemiologic evidence concerning the role of trace elements in influencing cancer risk, additional studies are needed to elucidate further the mechanisms underlying trace element carcinogenesis.

Appendix 1

Search strategy employed for each of the cancers of interest in Medline

Cancer of interest	Search terms
Lung	Exp lung neoplasms
	Lung adj4 cancer$.tw
	Lung adj4 neoplas$.tw
	Lung adj4 carcinoma$.tw
	Lung adj4 tumor$.tw
Colorectal	Exp colorectal neoplasms
	Colorectal adj4 cancer$.tw
	Colorectal adj4 neoplas$.tw
	Colorectal adj4 carcinoma$.tw
	Colorectal adj4 tumor$.tw
Breast	Exp breast neoplasms
	Breast adj4 cancer$.tw
	Breast adj4 neoplas$.tw
	Breast adj4 carcinoma$.tw
	Breast adj4 tumor$.tw
Stomach	Exp stomach neoplasms
	Stomach adj4 cancer$.tw
	Stomach adj4 neoplas$.tw
	Stomach adj4 carcinoma$.tw
	Stomach adj4 tumor$.tw
Bladder	Exp bladder neoplasms
	Bladder adj4 cancer$.tw
	Bladder adj4 neoplas$.tw
	Bladder adj4 carcinoma$.tw
	Bladder adj4 tumor$.tw
Prostate	Exp prostate neoplasms
	Prostate adj4 cancer$.tw
	Prostate adj4 neoplas$.tw
	Prostate adj4 carcinoma$.tw
	Prostate adj4 tumor$.tw

Appendix 2

Search strategy employed for each of the trace elements of interest in Medline

Trace element of interest	Search terms
Selenium	Exp selenium
	Selenium compounds
Zinc	Exp zinc
	Zinc compounds
Arsenic	Exp arsenic
	Arsenic compounds
Cadmium	Exp cadmium
	Cadmium compounds
Nickel	Exp nickel
	Nickel compounds

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