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Selenium, Zinc, and Prostate Cancer

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INTRODUCTION

Specific interest in selenium as a preventive agent for prostate cancer has arisen recently following the publication of a small number of epidemiologic studies, including a large randomized trial and a case-control study nested in a prospective cohort, suggesting a protective effect of selenium intake on prostate cancer incidence. Recent promising findings for constituents of diet and supplements have led to renewed interest in whether zinc, which is important for cell growth regulation and which is found in the highest concentration in the prostate gland, protects against prostate cancer. Given that so few modifiable risk factors for prostate cancer are known, resolving the potential impact of selenium and zinc as preventive agents against prostate carcinogenesis should be a high priority. We review here the evidence for selenium and zinc protecting against prostate cancer and suggest further lines of research for understanding their possible activities.

SELENIUM

Background

Selenium is an essential nonmetal trace element found in grains, meat, poultry, fish, eggs, and dairy products (1). In these foods selenium occurs mostly as organic compounds (1). Food selenium levels are largely dependent on the soil content in the region in which the foodstuff is grown (2). The recommended daily allowance for selenium is 70 μg/day for men and 55 μg/day for women (3). Multiple vitamins that include selenium often contain 20 μg of this element in its inorganic form (4). Selenium supplements containing 50 to 200 μg of the element in its organic form (e.g., yeast or selenomethionine) are available.

Ecologic studies indicate that regions in the United States and internationally with higher soil or plant selenium content or higher per capita selenium intake have a lower age-specific cancer mortality (5–10). In in vitro and in vivo studies, organic and inorganic selenium has been demonstrated to inhibit proliferation of normal and malignant cells and inhibit tumor growth (11) through an accumulation of cells in metaphase and increased apoptosis (12). Apoptosis may result from the competition of selenium for *S*-adenosylmethionine with ornithine decarboxylase (12). The anticancer activity of selenium has also been attributed to its being a component of glutathione peroxidase (GPX), which protects DNA and cell membranes (13) from peroxide damage by catalyzing conversion of peroxides (ROOR) to hydroxy acids (ROH) (1). Other selenium binding proteins have been identified; some protect against oxidative damage (14) and the function of others has not yet been characterized (15).

In vitro and in vivo studies of selenium and prostate carcinogenesis

As for malignant cell lines from other organs, selenium also produces dose-related growth inhibition by apoptosis in prostate-cancer cell lines (16, 17). The apoptotic effect of selenium is greater in androgen-sensitive than in androgen-independent cell lines (17). Apoptosis was induced to a much smaller extent by inorganic selenium and virtually not at all by organic selenium in a primary culture of normal prostate cells (17). Experimental data are not entirely consistent, however. The incidence of prostate tumors (all were in situ) in a carcinogen-induced rat model was not reduced when selenium was administered in the diet for 40 weeks at doses comparable to that in a rodent study showing a beneficial effect on mammary tumors (18). Whether this inconsistency is due to model idiosyncrasies or to differences in the dose of selenium that reaches the prostate versus the mammary gland requires further study.

Whether selenium is especially important for preventing prostate carcinogenesis relative to cancer in general is under study. Androgenic stimulation, which promotes proliferation, increases oxidative burden in prostate cancer cells (19) and, likely, in normal prostate cells. Thus, intraprostatic production or the availability of antioxidant enzymes such as GPX may be essential for preventing mutations in these cells. In the prostate, GPX is found in moderate concentrations in basal cells and in high concentrations in stromal cells, but very little is found in secretory epithelium or in adenocarcinoma (20). This finding possibly indicates protection against mutation in the basal cells that are the precursors for prostate epithelium. These precursor cells are those that retain the

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Abbreviations: CLUE II, a cohort of residents of Washington County, Maryland; GPX, glutathione peroxidase; RR, relative risk; SELECT, Selenium and Vitamin E Cancer Prevention Trial.

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greatest proliferative potential. This finding also suggests that GPX loss may be a step in carcinogenesis.

Both normal and malignant prostate epithelium contain higher selenium levels than stromal tissue (21). The high levels of selenium in prostate epithelium may be incorporated in non-GPX selenium-binding proteins. One such protein of molecular mass 15 kDa, which was present in greater levels in the rat prostate than in other tissues, preferentially incorporates selenium over GPX during selenium deficiency (22). This observation possibly suggests the importance of this selenium-binding protein in the prostate (22). Normal prostate cells and slow-growing androgen-sensitive prostate cancer cells, but not fast-growing androgen-independent prostate cancer cells, express a selenium-binding protein of 56 kDa (SP56). SP56 may modulate epithelial cell growth (15). The gene encoding SP56 is down regulated when androgen is added to cultures of an androgen-sensitive prostate-cancer cell line (15). Further work is needed to define the prostate-specific activities of selenium both in the amelioration of oxidative damage and in the modulation of epithelial cell growth in the presence and absence of androgen.

Epidemiologic studies of selenium and prostate cancer

Findings from epidemiologic studies using a number of designs and with good exposure assessment together generally support that selenium is inversely related to prostate cancer incidence and mortality (table 1). Although limited by lack of individual-specific exposure information and temporal uncertainty, some (7–9), but not all (9, 10) ecologic studies suggest an inverse correlation between selenium and prostate cancer mortality. No association has been observed for dietary selenium intake and prostate cancer in case-control studies (23–26). Because of variability in food selenium content, selenium intake derived from questionnaires, recalls, or histories may be subject to non-differential misclassification (14). This source of error might have accounted for the null results of these dietary studies.

Prospective designs, including trials, with adequate exposure assessment are generally preferred for studying nutrients in relation to disease. A 65 percent reduction in prostate cancer incidence among men randomized to a selenium supplement was found in a secondary analysis of the Nutritional Prevention of Cancer Study (27) (table 1). In this trial, 1,312 patients with non-melanoma skin cancer residing in low selenium regions, of whom 980 were men, were randomized to a brewer's yeast supplement that provided 200 μg of selenium daily (nearly three times the recommended daily allowance) or placebo for 10 years. In a subsequent analysis excluding men who might have had occult prostate cancer at baseline ($n = 974$), the inverse association was even stronger (relative risk (RR) = 0.26, $p = 0.009$) (28). Compared with men who received the placebo, prostate cancer risk was strongly reduced in men receiving the supplement and whose baseline plasma selenium concentration was in the bottom (RR = 0.08) or middle (RR = 0.30) thirds of the distribution (28). Prostate cancer risk was reduced for both local and advanced stage tumors. The beneficial effect of selenium on prostate cancer appeared after only a few years of supplementation. Clark et al. (27) hypothesized that because selenium appears to inhibit promotion and progression of tumors in vitro and in vivo, selenium might rapidly diminish the incidence of, or mortality from cancer. Thus, it is possible that their observation of the rapid decline in incidence is consistent with an effect of selenium, rather than due to bias or chance.

Following the publication of the results of the trial of Clark et al., several controversial issues were raised that potentially influenced the interpretation of the trial's findings. The investigators had not specified that the rates of total or site-specific non-skin cancers would be an outcome prior to the start of the trial. To one editorialist (29), this raised the concern that the decreased rates for total and certain cancer sites that were seen after a midway analysis (1983–1989) might be merely chance observations. Nevertheless, similarly reduced rates of cancer were also observed during the last years (1990–1993) of the trial, including that for prostate cancer (27). The supplement group had reduced rates of some, but not all cancers. Because many comparisons were made, this led to the question of whether the likelihood of detecting chance findings was increased, especially for those sites (such as the prostate) for which at the time there was very little evidence for a benefit of selenium (29). Nevertheless, subsequent studies addressing selenium and prostate cancer have supported the findings of the trial.

Another critique was that several of the site-specific cancer rates in the placebo group of the Nutritional Prevention of Cancer Study were well above the rates reported in the United States Surveillance, Epidemiology, and End Results program, whereas rates in the supplement group were closer to the national rates (30). The authors countered that cancer rates in the population selected for enrollment in this trial were likely higher than the average US rates because participants lived in areas with low soil selenium and each had a prior history of skin cancer (31). Thus, supplementation lowered their rates to background (31). The study did not address the effect of withdrawals due intolerance of the yeast-containing selenium supplement (32). However, it is difficult to construct a scenario whereby those who had yeast intolerance are also those who had a higher risk of cancer. A decrease in the occurrence of cardiovascular disease was not seen in the selenium supplement group, although inorganic selenium increases bleeding time (32). One commentator felt that the lack of an effect on cardiovascular disease called into question whether the dose of selenium given in the trial was biologically effective (32). However, the lack of an effect on cardiovascular disease does not preclude a beneficial effect on cancer risk at this dose because the mechanisms of action for selenium underlying protection are not necessarily the same for these two chronic diseases.

In a secondary cohort analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (33), no association between baseline selenium intake and prostate cancer ($n = 317$) was found during 9 years of follow-up of 29,133 older male smokers. Baseline selenium supplement use, which is not subject to the same degree of non-differential measurement error as exists for dietary selenium, unexpectedly was associated with a slight increased risk of prostate cancer. The

TABLE 1. Epidemiologic studies of selenium and prostate cancer

Author	Study design	Study location and size	Selenium assessment	Results
Shamberger et al. (7), 1976	Ecologic	48 US states	Soil and forage crops	Age-adjusted prostate cancer mortality rate slightly higher in states with lower levels
Schrauzer et al. (9), 1997	Ecologic	27 countries	Per capita intake	Inverse correlation with age-adjusted prostate cancer mortality rate: $r = -0.65$, $p = 0\ 0001$
		22 countries	Whole blood, healthy donors	Inverse correlation with age-adjusted prostate cancer mortality rate: $r = -0.72$, $p = 0.001$
		19 US states	Whole blood, healthy donors	No correlation with age-adjusted prostate cancer mortality rate: $r = -0.10$, $p = 0.67$
Clark et al. (10), 1991	Ecologic	US counties	Forage crops	Age-adjusted prostate cancer mortality rate higher (+0.7/10^5) in adequate vs. low areas
Hardell et al. (46), 1995	Case-control	Sweden: 164 cases, 152 benign prostate hyperplasia (BPH*) controls	Plasma	Prostate cancer risk lower in the highest compared with lowest thirds: odds ratio (OR*) = 0.3, 95% confidence interval (CI*): 0.1, 0.7
Key et al. (24), 1997	Case-control	United Kingdom: 328 cases 328 controls	Diet and supplements	No difference in geometric mean intake between prostate cancer cases and controls ($p = 0.23$)
Lee et al. (25), 1998	Case-control	China: 398 cases, 265 controls	Diet	Risk of prostate cancer did not decrease with increasing intake: OR = 1.00, 95% CI: 0.99, 1 04, $p = 0.75$
West et al. (23), 1991	Population-based case-control	United States: 358 cases, 679 controls	Diet	No difference in prostate cancer risk comparing highest with lowest fourths 45–67 years old: OR = 0.8, 95% CI: 0.5, 1.4, aggressive disease OR = 1.0, 95% CI: 0.3, 3.1 68–74 years old: OR = 1.6, 95% CI: 1.0, 2.8, aggressive disease OR = 1.8, 95% CI: 0.8, 4.4
Jain et al. (26), 1999	Population-based case-control	Canada: 617 cases, 636 controls	Diet	No difference in prostate cancer risk comparing highest with lowest fourths: OR = 0.93, 95% CI: 0.68, 1.28
Ghadirian et al. (47), 2000	Population-based case-control	Canada: 83 cases, 82 controls	Toenails	No difference in prostate cancer risk comparing highest with lowest fourths: OR = 1.14, 95% CI: 0.46, 2.83, p-trend = 0.624
Willett et al. (41), 1983	Nested case-control	United States: 11 cases, 210 controls	Serum	Concentration lower in prostate cancer cases than in controls ($p = 0.12$)
Knekt et al. (43), 1990	Nested case-control	Finland: 51 cases, 2,192 controls	Serum	No difference in prostate cancer risk comparing highest and lowest fifths: OR = 1.15, p-trend = 0.71
Criqui et al. (44), 1991	Nested case-control	North America: 6 cases, 238 controls	Plasma	Concentration lower in prostate cancer cases than in controls ($p < 0.10$)
Coates et al. (42), 1998	Nested case-control	United States: 13 cases, 287 controls	Serum/plasma	Prostate cancer risk lower in the highest compared with lowest thirds: OR = 0.3, p-trend = 0.18
Yoshizawa et al. (39), 1998	Nested case-control	United States: 181 advanced cases, 181 controls	Toenails	Risk of advanced prostate cancer lower in the highest compared with lowest fifths: OR = 0.39, 95% CI: 0.18, 0.84, p-trend = 0.05
Nomura et al. (45), 2000	Nested case-control	Hawaii: 249 cases, 249 controls	Serum	Risk of prostate cancer lower in the highest compared with lowest fourths: OR = 0.5, 95% CI: 0.3, 0.9, p-trend = 0.02; advanced OR = 0.3, 95% CI: 0.1, 0.8, p-trend = 0.01
Helzlsouer et al. (40), 2000	Nested case-control	United States: 117 cases, 233 controls	Toenails	Risk of prostate cancer lower in the highest compared with lowest fifths: OR = 0.38, 95% CI: 0.17, 0.85, p-trend = 0.12
Hartman et al. (33), 1998	Cohort	Finland: 317 cases in 29,133 older male smokers, 9 years of follow-up	Diet and supplements	No difference in prostate cancer risk comparing highest and lowest fourths: randomized to α-tocopherol: relative risk (RR) = 0.84, 95% CI: 0.43, 1.67; randomized to placebo: RR = 1.27, 95% CI: 0.70, 2.20
Clark et al. (27), 1996; (28), 1998	Trial	United States: 48 cases in 974 men with non-melanoma skin cancer, low selenium region, 10 years of follow-up	200 μg/day primarily as seleno-methionine (~3-times the recommended daily allowance) or placebo	Risk of prostate cancer lower in supplement compared with placebo group: RR = 0.35, 95% CI: 0.18, 0.65; Stratified by thirds of baseline plasma selenium level, relative risk for supplement vs. placebo: lowest third, RR = 0.08, $p = 0.002$; middle third, RR = 0.30, $p = 0.03$; highest third, RR = 0.85, $p = 0.75$

* BPH, benign prostatic hyperplasia; OR, odds ratio; CI, confidence interval; RR, relative risk.

authors hypothesized that differences in prostate cancer risk factors associated with the propensity to use supplements, but not accounted for in the analysis, could explain the increased risk (33). Although synergism in activity has been reported between selenium and vitamin E in experimental systems, the results for selenium and prostate cancer were similar between the groups randomized to α-tocopherol or to placebo. The disparity in findings between the Nutritional Prevention of Cancer Trial and the observational component of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study may be due to a notable difference in selenium exposure (33). Prior to the start of the trial, Finland was a country with low soil selenium concentration, although just before the trial began, fertilizer was fortified with selenium (33). Nevertheless, only 2 percent of the participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study had a selenium intake at the level of the treatment dose in the Nutritional Prevention of Cancer Trial (33).

Because assessment of selenium intake from self-reported diet is generally poor due to variability in food content, which depends on geographic source, determining the selenium content of biologic materials may provide a better indicator of selenium intake. In addition, because intestinal absorption and distribution of selenium depend on the presence of metals that compete for uptake (34), selenium content in biologic materials may be a good marker of bioavailable selenium. The representativeness of selenium levels in biologic materials for intake over time has been examined. Plasma/serum selenium concentration is responsive to very recent selenium ingestion (hours) (35), but plasma/selenium levels are also correlated with longer-term selenium intake. In a study with multiple diet records and biologic samples taken over 6 months or 1 year, the correlation coefficients for selenium intake and selenium concentrations in serum and toenails were 0.74 and 0.67, respectively (36). In a 1-year feeding study, toenail selenium concentration roughly reflected the selenium intake in the previous 3 months to 1 year (37). The reliability of toenail measures over several years has been shown to be moderate. One study observed a correlation coefficient of 0.48 for two determinations of toenail selenium concentration taken 6 years apart, although a temporal increase in selenium concentration was seen over the period (38).

Seven prospective studies have examined selenium levels in toenails (39, 40) or in plasma/serum (41–45) in relation to prostate cancer incidence or mortality. A 60 percent reduction in risk of advanced prostate cancer was observed in the Health Professionals Follow-up Study comparing the highest with lowest fifths of prediagnostic toenail selenium (39). Reductions in prostate cancer risk of 60 percent and 50 percent were observed in a cohort of residents of Washington County, Maryland (the CLUE II study—the name CLUE II comes from the slogan "Give us a clue to cancer and heart disease") (40) and a study of Japanese-American men in Hawaii (45) comparing extreme fifths of prediagnostic toenail or serum selenium concentration, respectively. Statistically nonsignificant reductions in prostate cancer incidence or mortality have been observed when comparing high with low circulating baseline selenium levels in three other studies (41, 42, 44). One prospective study conducted in Finland, a country with low selenium intake during the period of follow-up, showed no relation between serum selenium levels and prostate cancer risk (43). In that study, participants had circulating levels almost three times lower (~50 versus ~150 μg/liter) than in the other studies. One hospital-based case-control study also observed an inverse association between plasma selenium and prostate cancer (46), whereas a population-based case-control study observed no association between toenail selenium and prostate cancer (47).

Future directions

Taken together, the epidemiologic studies that have examined the relation of selenium and prostate cancer support a modest to moderate beneficial effect. The consistent findings of a supplementation trial and several prospective studies using biomarkers of selenium lend strong support that it is selenium, rather than other unmeasured dietary constituents, that is responsible for the reduction in risk of prostate cancer (48). The null findings from the studies that evaluated dietary selenium may have resulted from the recognized poor assessment of dietary selenium using reports of foods consumed or to the low intake of dietary and supplemental selenium in some of the study populations. Other explanations for the inconsistent findings include variation in exposure to potential prostate mutagens that are inactivated by selenium-requiring GPX for the prevention of cellular damage, and variation in exposure to other trace elements that by competing with selenium for binding proteins alter the bioavailability of selenium. At this point, additional epidemiologic studies, including cohort studies and trials, are needed to conclude whether selenium reduces the risk of prostate cancer. Especially informative will be studies of large enough size to detect meaningful associations, that use adequate exposure assessment of prediagnostic selenium levels, and that are conducted in demographically diverse populations with a wide range of selenium intake. In future studies employing biomarkers of selenium exposure, investigators should be alert to avoid selenium contamination by laboratory equipment, or for toenails by participant use of selenium-containing shampoos (37).

Future studies must address the optimal selenium status (defined by intake, prostate tissue levels, or levels in other biologic materials) for the prevention of prostate cancer. The Nutritional Prevention of Cancer Study did not examine multiple selenium supplement doses because of logistical issues (31). Whether a benefit of increased selenium intake is achieved may depend on an individual's usual selenium status. In the Nutritional Prevention of Cancer Study, the effect of the intervention was observed mainly among those with lower baseline plasma selenium (28). Given the variability in in vitro activities of forms of selenium, inorganic (e.g., selenite versus selenate) or organic (e.g., selenomethionine versus selenocysteine) (49, 50), the form of selenium that has the greatest protective effect against prostate cancer must also be examined in epidemiologic studies. In both cohort studies and in trials, participants should be monitored for any adverse effects of selenium over the short- and long-term.

In vitro and in vivo studies are needed to define the specific pathways in the prostate that are influenced by selenium at physiologic rather than supra-physiologic doses. Especially important to understand is selenium's role in the synthesis of polyamines, which are essential for cell cycle maintenance (12). Whether selenium acts early or late in the carcinogenic pathway should be explored further in both population studies and the laboratory. Timing of effect has practical implications for when selenium supplements should be started and for how long they should be taken. For example, from the Nutritional Prevention of Cancer Study, a decline in incidence emerged during the first 6 years of the intervention (27), suggesting that selenium may act late in the pathway.

The potentially beneficial role of selenium and prostate cancer prognosis or recurrence also deserves attention. Only one such study, which included four prostate cancer cases, has been published to date (51). Trials of the effect of selenium on markers of progression are on-going at the University of Arizona (50) and the Memorial Sloan-Kettering Cancer Center (52).

The potentially beneficial joint effects of selenium and other dietary constituents should be evaluated. Selenium may antagonize cadmium (53), a possible prostate cancer risk factor in occupational studies (54). Selenium may inhibit the proliferation of prostatic epithelium induced by cadmium in vitro, possibly by the formation of selenium-metal complexes (55). Vitamin E, which may be inversely associated with prostate cancer incidence (56), and selenium act at different points in preventing membrane lipid peroxidation (1). Synergism between selenium and γ-tocopherol was observed in the CLUE II study (40). No synergism was seen for selenium and α-tocopherol in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (33). The Selenium and Vitamin E Cancer Prevention Trial (SELECT) sponsored by the National Cancer Institute will examine the independent and joint effects of selenium and vitamin E (α-tocopherol) supplementation in a trial of 32,000 men over more than 12 years (57).

ZINC

Background

Zinc is a homeostatically regulated essential mineral (58). It is a component of numerous metalloenzymes and is important for cell growth and replication, osteogenesis, and immunity (1). Zinc may also indirectly act as an antioxidant by stabilizing membranes in some cell types (34). The primary dietary sources of zinc are red meat, seafood, poultry, grains, dairy, legumes, and vegetables (1). The recommended daily intake of zinc is 12 mg for women and 15 mg for men (3). Some studies have noted lower zinc levels or intake for patients with certain cancers compared with controls (59–61) while others have observed no association (62–64). Trials that administered nutrient combinations including zinc have observed a reduced incidence of gastric cancer (65, 66). However, the independent effect of zinc on carcinogenesis cannot be determined from these studies.

In vitro and in vivo studies of zinc and prostate carcinogenesis

Circumstantial evidence indicates that zinc may have an important role in the prostate. Total zinc levels in the prostate are 10 times higher than in other soft tissues (67, 68). The concentration of zinc in whole prostate tissue appears to increase with increasing distance from the bladder (69). Others have found the highest concentrations in the lateral lobe of the peripheral zone and the lowest levels in the central zone (70). Zinc is concentrated intracellularly in glandular epithelium and is bound to proteins, such as metalloenzymes (71). Especially high levels are found in the prostate epithelial cell mitochondria, where zinc inhibits mitochondrial aconitase resulting in decreased citrate oxidation (72). Interestingly, malignant prostate cells have a higher rate of citrate oxidation than do normal prostate cells, although it is not currently believed that altered citrate oxidation contributes to prostate carcinogenesis (70).

Adenocarcinoma cells taken from prostate tumors, but not prostate cancer cell lines, lose their ability to amass zinc (71). In response to physiologic testosterone and prolactin levels, prostate epithelial cells rapidly uptake zinc, which is possibly facilitated by a cell membrane transporter (71). In vitro zinc participates in a feedback loop to maintain the intraprostatic balance of testosterone and dihydrotestosterone (73). Physiologic concentrations of zinc inhibit growth of androgen-sensitive and androgen-independent prostate cancer cell lines via cell cycle arrest, programmed cell death, and necrosis (74, 75), which may be initiated in mitochondria (76). Based on these activities of zinc, it could be hypothesized that higher zinc levels would be inversely associated with prostate cancer risk.

Epidemiologic studies of zinc and prostate cancer

Findings for zinc and prostate cancer incidence and mortality have not been consistent (table 2). An ecologic study noted higher prostate cancer mortality in countries with higher per capita zinc intake, although there was essentially no correlation between whole blood zinc concentrations in cancer-free individuals and prostate cancer mortality in several regions in the United States (8). Modest to moderate inverse associations were observed in two case-control studies for dietary zinc (24) or zinc supplement use (77). Other case-control studies have not observed a protective association for dietary (23, 78) or combined dietary and supplemental (79, 80) zinc intake. Differences in findings among these studies may be due to different ranges of zinc intake among the populations studied and misclassification of zinc intake by assessing post-diagnosis diet rather than diet in an etiologically relevant period. Another possible source of misclassification is in the assessment of zinc using food frequency questionnaires or diet records. Although the correlation between zinc intake estimated from food frequency questionnaires and diet records has been observed to be moderate (81), both require linking food intake with estimates of zinc content of foods. The zinc content of certain foods, such as seafood, may be

TABLE 2. Epidemiologic studies of zinc and prostate cancer

Author	Study design	Study location and size	Zinc assessment	Results
Schrauzer et al. (8), 1977	Ecologic	28 countries	Per capita intake	Direct correlation with age-adjusted prostate cancer mortality rate: $r = +0.51$, $p < 0.05$
		19 US states	Whole blood, healthy donors	No correlation with age-adjusted prostate cancer mortality rate: $r = 0.01$
Habib et al. (86), 1976	Case-control	United Kingdom: 9 cases, 23 benign prostatic hyperplasia (BPH*) controls	Prostate tissue	Concentration lower in prostate cancer cases than in normal controls or BPH controls ($p < 0.005$)
Habib et al. (89), 1980	Case-control	United Kingdom: 44 cases, 41 BPH controls, 12 controls	Plasma, leukocytes	No difference in concentrations between prostate cancer cases and controls
Whelan et al. (82), 1983	Case-control	United Kingdom: 19 cases, 27 BPH controls	Serum	Concentration lower in prostate cancer cases than in BPH controls ($p < 0.05$)
Feustel et al. (90), 1986	Case-control	Germany: 17 cases, 21 BPH controls, 45 controls	Plasma, erythrocytes	No difference in concentrations between prostate cancer cases and controls
Feustel et al. (21), 1987	Case-control	Germany: 9 cases, 10 BPH controls, 5 controls	Prostate tissue	Concentration lower in prostate cancer cases than in normal controls or in BPH controls
Ogunlewe et al. (84), 1989	Case-control	Nigeria: 12 cases, 60 BPH controls, 55 controls	Plasma, prostate tissue	Concentration lower in prostate cancer cases than in normal controls ($p < 0.001$) or in BPH controls ($p < 0.001$)
Lekili et al. (85), 1991	Case-control	Turkey: 26 cases, 15 BPH controls	Plasma	Concentration lower in prostate cancer cases than in BPH controls ($p < 0.05$)
Key et al. (24), 1997	Case-control	United Kingdom: 328 cases, 328 controls	Diet and supplements	Risk of prostate cancer lower in the highest compared with lowest thirds: odds ratio (OR*) = 0.73, 95% confidence interval (CI*): 0.49, 1.08, p-trend = 0.13
Vlajinac et al. (80), 1997	Case-control	Serbia: 101 cases, 202 controls	Diet and supplements	No difference in prostate cancer risk comparing highest with lowest tertiles; adjusted for energy: OR = 1.31, 95% CI: 0.81, 2.13, p-trend not statistically significant; adjusted for energy and other nutrients: OR = 0.81, 95% CI: 0.28, 2.34, p-trend not statistically significant
Zaichick et al. (87), 1997	Case-control	Russia: 59 cases, 50 BPH controls, 37 controls	Prostate tissue	Concentration lower in prostate cancer cases than in normal controls or in BPH controls
Brys et al. (88), 1998	Case-control	Poland: 7 cases, 16 BPH controls, 11 controls	Prostate tissue	Concentration lower in prostate cancer cases than in normal controls or in BPH controls
Lee et al. (25), 1998	Case-control	China: 398 cases, 265 controls	Diet	Risk of prostate cancer did not statistically significantly decrease with increasing intake: OR = 0.93, 95% CI: 0.73, 1.19, $p = 0.56$
Kolonel et al. (79), 1988	Population-based case-control	Hawaii: 452 cases, 899 controls	Diet and supplements	No difference in prostate cancer risk comparing highest with lowest fourths ≥70 years old: diet only OR = 1.1, 95% CI: 0.7, 1.7, p-trend = 0.62; diet/supplements OR = 1.7, 95% CI: 1.1, 2.7, p-trend < 0.01; <70 years old: diet only OR = 1.3, 95% CI: 0.7, 2.2, p-trend = 0.71; diet/supplements OR = 1.2, 95% CI: 0.7, 2.2, p-trend = 0.86
West et al. (23), 1991	Population-based case-control	United States: 358 cases, 679 controls	Diet	No difference in prostate cancer risk comparing highest with lowest fourth 45–67 years old: OR = 1.1, 95% CI: 0.6, 1.9; aggressive disease OR = 1.0, 95% CI: 0.3, 3.2; 68–74 years old: OR = 1.3, 95% CI: 0.8, 2.3; aggressive disease OR = 1.0, 95% CI: 0.3, 2.8
Andersson et al. (78), 1996	Population-based case-control	Sweden: 526 cases, 536 controls	Diet	No difference in prostate cancer risk comparing highest with lowest fourths; OR = 1.04, 95% CI: 0.74, 1.46, p-trend = 0.50; advanced OR = 1.14, 95% CI: 0.77, 1.70, p-trend = 0.37
Kristal et al. (77), 1999	Population-based case-control	United States: 697 cases, 666 controls	Supplements	Risk of prostate cancer lower among those using supplements ≥7 days/week compared with never: OR = 0.55, 95% CI: 0.30, 1.00, p-trend = 0.04

* BPH, benign prostatic hyperplasia; OR, odds ratio; CI, confidence interval.

highly variable (1). Also, some studies did not consider in their estimation of zinc intake the use of zinc-containing multiple vitamins and supplements.

Use of biomarkers of zinc exposure may minimize some of the misclassification of zinc associated with estimating intake from food frequency questionnaires or diet records. Absorption of zinc varies by dietary source. For example, zinc is more bioavailable in red meat and less bioavailable in vegetables (1). It also varies by the presence of other dietary constituents that bind zinc to increase (e.g., citric acid and the amino acids histidine and cysteine) or decrease (e.g., phytate and oxalate) its uptake (1). Thus, use of biomarkers may better reflect absorbed zinc. Because the prostate amasses zinc, the relevance of prostate tissue levels to zinc intake, circulating zinc levels, or toenail zinc concentration is unknown.

Some small case-control studies indicate lower concentrations of zinc in plasma/serum (82–85) or total prostate tissue (21, 84, 86–88) in men with prostate cancer compared with men without prostate disease or with benign prostatic hyperplasia, although other small case-control studies observed no differences (89, 90) (table 2). Several of the epidemiologic studies of zinc and prostate cancer used zinc biomarkers, but none of the studies was conducted prospectively and, thus, the possible influence of disease pathology on zinc levels limits the interpretability of the findings.

Future directions

The epidemiologic evidence for zinc protecting against prostate cancer is equivocal and is based mainly on studies of retrospective design. The disparity in findings among epidemiologic studies may result from several sources. Firstly, the accuracy of assessment of zinc exposure differed; some used self report of diet, others measured zinc content in biologic specimens. Secondly, zinc levels were assessed at different points in the natural history of the disease and in different biologic tissues. Thirdly, the ranges of exposure to zinc may have varied among studies. Finally, control for other dietary factors that are both associated with zinc and with prostate cancer may have differed. The bioavailability of zinc and other trace elements, such as cadmium and selenium, is controlled by binding proteins called metallothioneins (53, 91). Thus, the inconsistent findings for zinc and prostate cancer might reflect the variability between populations in exposure to other metals that compete with zinc for binding proteins, rendering zinc more or less bioavailable than would be indicated by measures of total zinc content of serum/plasma or prostate tissue.

At this time, the evidence for a beneficial effect of zinc on prostate cancer incidence is insufficient to warrant undertaking randomized chemoprevention trials. Prospective studies that employ adequate assessment of exposure to zinc and other elements conducted in populations with wide ranges of zinc exposure are needed to uncover whether zinc protects against prostate cancer. At present no single biologic indicator is thought to adequately reflect zinc exposure (92). Among individuals who are not zinc deficient, the interrelations of zinc intake and zinc concentrations in biologic materials, including serum/plasma, toenails, and prostate tissue, require further characterization. The usual methods for zinc determination in serum/plasma (59, 82, 90), toenails (60), and prostate tissue (88) have been flame atomic absorption spectrometry or instrumental neutron activation analysis. For determination of zinc in toenails, the toenails must first be cleaned to remove skin and surface contamination and then digested. Investigators should avoid contamination of biologic materials by zinc in laboratory supplies, including blood collection tubes with zinc-containing anticoagulants and stoppers (92). When analyzing and interpreting data, investigators should also be aware of attributing effects to zinc if other correlated metals are present in the diet or in biologic materials.

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