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Selenium and the Prevention of Prostate and Colorectal Cancer

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Abstract

Prostate and colorectal cancers are among the most common cancers and identifying modifiable risk factors are important steps to reduce the burden of these severe diseases. Results from several but mostly small observational studies as well as the secondary analysis of an intervention trial provide support for a chemopreventive effect of selenium on prostate and colorectal cancers. Results suggest effect modification by gender and smoking, but this interpretation is limited by the statistical power of previous studies. Several cancer preventive mechanisms have been described and it is likely that selenium acts through multiple pathways. In particular, the anti-oxidative and anti-inflammatory effects mediated through activity of selenoenzymes are discussed given the relevance of oxidative stress and inflammation in these cancers. Genetic variation in selenoenzymes may modify the potential chemopreventive effect of selenium and need to be further investigated. Additional large observational studies using biomarkers of selenium intake and intervention trials, such as the Selenium and Vitamin E Cancer Prevention Trial, will be important to further evaluate the potential chemopreventive effect of selenium. Furthermore, characterization of functional effects of polymorphisms in selenoenzymes is needed.

Keywords

biomarker; colorectal cancer; selenoenzyme; prostate cancer; selenium

Introduction

Prostate and colorectal cancers are among the most commonly diagnosed cancers and leading cause of cancer deaths in the United States; lifetime risk for prostate and colorectal cancers is estimated to be 16.7% and 5.4%, respectively [1,2]. Identifying modifiable risk factors will be important in improving preventive strategies in addition to available screening methods for these common cancers.

Supplemental Selenium in Randomized Intervention Trials

Interest in selenium as potential preventive agent was particularly stirred by findings from the Nutritional Prevention of Cancer Trial, providing support for its preventive effect [3]. In this trial, 1,312 patients with a history of skin cancer were randomly assigned to receive either 200 µg selenium per day or placebo. Although the trial found no significant association between selenium supplementation and skin cancer recurrence (primary endpoint), significantly reduced risks were noted for all four secondary outcomes: overall cancer death and incidence of lung, prostate, and colorectal cancers [3]. In the initial report,

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including an intervention period of up to 10 years (average 4.5 years), a total of 35 prostate cancer cases were reported in the placebo arm and 13 cases in the selenium arm resulting in a 65% reduced prostate cancer risk ($p=0.001$; Table 1). During the same period 19 cases of colorectal cancer were diagnosed in the placebo group but only 8 cases in the selenium group—a 61% risk reduction ($p=0.03$; Table 2) [3]. Two additional years of follow-up up to the end of blinded treatment further support these findings although results for colorectal cancer were marginally non-significant [prostate cancer hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.28–0.80, $p=0.005$; colorectal cancer HR 0.46, 95% CI 0.21–1.02, $p=0.06$] [4,5].

These findings as well as results from observational and experimental studies (details see below) have lead to one of the largest intervention trials currently ongoing in North America, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [6]. Between 2001 and 2004 more than 35,000 men have been recruited by the Southwest Oncology Group at over 400 study sites throughout the US, including all 50 states, District of Columbia, and Puerto Rico, and Canada. Men are randomized to one of the four groups: selenium (200 μg), vitamin E, selenium + vitamin E, or placebo. Results from the SELECT trial are expected in 2013. The primary outcome of the trial is prostate cancer and colorectal cancer is among the secondary outcomes. Besides SELECT, two other randomized trials are currently investigating the preventive effect of selenium supplementation. One trial is studying the impact of 200 $\mu\text{g/day}$ of selenium supplementation in the form of selenomethionine for 3 years on the prostate cancer incidence among men with high-grade prostatic intraepithelial neoplasia (HGPIN). The trial targets to include a total of 466 men in the US and is expected to complete in 2009 [7]. The second ongoing trial conducted at the Arizona Cancer Center is currently investigating the recurrence of colorectal adenomas, a precursor of colorectal cancer [8]. Because the likelihood of recurrence of an adenoma in patients who were previously diagnosed with an adenoma is rather high, the size and timeline of this trial can be substantially smaller/shorter than trials in healthy individuals: 1,600 patients are randomized to 200 μg selenium or placebo and followed up for 3 to 5 years. Initially, this trial was set up as a 2×2 factorial design to also test the effect of cyclooxygenase-2 inhibitor, Celebrex[®]. However, adverse effects for cardiovascular diseases reported in other trials resulted in an early termination of the Celebrex[®] component of the trial, while the selenium component was maintained. The recruitment of this trial has been completed in 2008 and results are expected about three years after completion of recruitment.

Selenium and Prostate Cancer: Evidence from Observational Studies

In the following we will focus on observational studies assessing selenium in biological samples or those reporting supplemental use, because the assessment of selenium intake by dietary questionnaire is not accurate due to the large variation in the selenium content of the same food [9–12]. Blood, toenails, and urine have shown to be good surrogates for selenium intake because they are an integrative measure of selenium intake from various foods and selenium supplement [13]. While urinary and serum levels reflect more short-term intake of selenium, selenium measured in erythrocyte and toenail reflect more long-term intake [14,15]. Results from population-based case-control studies [16–18] provide overall limited support for a beneficial effect of selenium (Table 1). Only one study [17] found a non-significant inverse association between serum selenium levels and prostate cancer. In contrast, most [19–24] but not all [25–27] case-control studies nested within prospective cohorts showed a protective association between selenium levels and prostate cancer risk. More recent analyses of cohort studies included sufficient number of prostate cancer cases to investigate advanced cases separately (predominately defined as regional or distant stage). These studies showed consistently slightly stronger protective associations between

selenium and risk of advanced prostate cancer [19–21,23,25,27], however, risk estimates for advanced diseases are less precise. This finding for advanced diseases underlines a potential importance of selenium in prostate cancer prevention given the known higher mortality from advanced diseases, while the relevance of local stage and low grade diseases is less clear. In a recent cohort study long-term selenium supplementation was not associated with prostate cancer, however, the dose of supplemental selenium was very low (average of 26.6 µg/day for the past 10 years) [27]. Similarly, a meta-analysis summarized that dietary selenium intake was inversely associated with prostate cancer [28].

Subgroup analysis within the Nutritional Prevention of Cancer Trial further indicated that significant inverse associations were limited to men with low baseline selenium concentrations [RR 0.08 in the first tertile (<106 ng/ml) and RR 0.30 in the second tertile (106–121 ng/ml) of baseline serum selenium] [29]. This finding that selenium supplementation might be most effective in populations with low selenium intake is supported by the observation that circulating enzyme activity of some selenoenzymes, such as the glutathione peroxidases, tend to plateau at greater serum selenium concentrations [30,31]. While this finding is intriguing, in observational studies an inverse selenium-prostate cancer association is not limited to studies with lower mean serum selenium concentrations (Table 1).

Some observational studies further suggest an interaction between selenium and smoking; strongest inverse selenium-prostate cancer associations were observed among smokers [17,20,21,27]. Such interaction may be biologically plausible given that smoking results in increased exposure to reactive oxygen species (ROS) [32–35], while several selenium-dependent selenoenzymes inhibit the damaging effect of ROS on DNA. In addition, smoking as oxidative stress may increase the transcription of some selenoenzymes, such as glutathione peroxidases, which have an oxidative-response element in their promoter region [36–39]. Taken together, results from observational studies suggest that selenium prevents prostate cancer over a wide range of selenium intake and that smoking and selenium status may modify the selenium-prostate cancer association.

Epidemiological Studies on Selenium and Colorectal Tumors

As mentioned above our review focuses on biomarker and supplement use studies to assess selenium intake. Perhaps as a consequence of the complexity and cost of determining selenium in biological specimens, most earlier studies entailed relatively small numbers of cases, with fewer than 100 cases in some studies [18,26,40,41] and fewer than 50 cases in many others [42–51]. Several of these studies generally supported a protective association between selenium and colorectal cancer [18,40,41,43,44,46–49,52,53] and adenoma [40,42,45], although most results were not statistically significant (Table 2). Relatively few of these smaller observational studies found either no association [50,51,54]—including the largest prospective study on colorectal cancer [54]—or a non-significant positive association (Table 2) [55,56]. Additionally, a cohort study found a non-significant lower risk of colon cancer among selenium supplement users than non-users (dose not provided) [57].

More recently four larger studies investigating precursor lesions of colorectal cancer (adenoma or adenoma recurrence) have been published, providing additional support for a protective effect of selenium on colorectal carcinogenesis (Table 2) [58–60]. Three studies, which include 247 to 403 recurrent adenoma cases per study, showed a 25% to 40% risk reduction associated with higher serum selenium [58,59], and a pooled analysis of these three studies resulted in a significant inverse association with a highly significant linear trend ($p_{\text{trend}} = 0.006$) [59]. We investigated the association between serum selenium and advanced adenoma in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening

Trial [60]. Among 758 advanced adenoma cases and 767 sigmoidoscopy-negative controls we observed an inverse association with serum selenium ($p_{\text{trend}} = 0.01$) although the odds ratio (OR) was not significant [60]. This large study was the first study to investigate an interaction with smoking and reported significant effect modification; the respective OR comparing the third tertile to the first tertile are 1.27 (95% CI 0.79–2.03, $p_{\text{trend}} = 0.82$) for nonsmokers, 0.84 (95% CI 0.53–1.33, $p_{\text{trend}} = 0.23$) for former smokers and 0.53 (95% CI 0.27–1.01, $p_{\text{trend}} = 0.008$) for recent smokers. Similar to results for prostate cancer the inverse association was strongest within smokers.

So far limited data also suggest a differential effect of selenium on colorectal tumors by gender. The Nutritional Prevention of Cancer Trial [4,5] found that the inverse association between selenium supplementation and overall cancer incidence was limited to men (results for colorectal cancer separately were not provided). Effect modification by gender may be plausible due to potential gender differences in selenium metabolism; women have been reported to have higher excretion rates than men [5,61,62]. Within the PLCO Trial, the inverse selenium-adenoma association was restricted to men [60]. Similarly, one earlier observational study [26] reported an inverse association in men only and another that included only women found a positive association [55] while two studies reported inverse associations in both men and women [18,59]. Given the small number of studies reporting gender-specific associations and the small percentage of women in the PLCO study [60] and in the Nutritional Prevention of Cancer Trial [3]—30% and 25%, respectively—these findings of possible gender-specific differences may reflect a chance finding. Accordingly, larger studies with sufficient numbers of women are needed to address this question. In this respect, SELECT [63], which will investigate colorectal cancer as secondary outcome, only includes men will not shed further light on this relevant question. In summary, several but mainly small observational studies reported inverse associations between selenium and colorectal adenoma and cancer risk. Results may also suggest interactions with smoking and gender (inverse associations limited to smokers and men); however, further large studies using biospecimens to assess selenium intake are needed.

Potential Mechanisms That Underlie an Effect of Selenium on Cancer

A large body of experimental data supports a role for selenium in cancer prevention [64–66]. In virtually every animal tumor model tested supra-nutritional doses of selenium has reduced cancer, including cancer in the prostate colon, and rectum (see reviews [65,67]). Both direct effects and indirect effects (through selenoproteins) of selenium on cancer prevention have been observed and it is likely that selenium acts through multiple pathways. Molecular targets for these direct effects include p53, caspase-8, p21, nuclear factor- κ B (NF- κ B), protein kinase C, and androgen receptors [68–73]. In cell lines, selenomethionine was shown to activate p53 tumor suppressor gene along with related increases in p53-dependent DNA repair [74] and methyl selenic acid induced apoptosis via caspase-8 [70]. NF- κ B promotes expression of anti-apoptotic genes and an *in vivo* study showed a reduced activation of NF- κ B by selenium supplementation [75]. Selenite supplementation in human prostate cancer cells induced cell cycle arrest and apoptosis via an increased expression of a cyclin-dependent kinase inhibitor p21 [73]. Selenometabolites are involved in selective inactivation of protein kinase C, which leads to inhibition of tumor promotion and cell growth [76]. Androgen receptor transcription was inhibited by methylselenic acid supplementation [68]. Methylated forms of selenium, which are produced to excrete selenium, are particularly active and directly affect cell cycle control and apoptosis [70,77–79].

Furthermore, important biological activities of selenium are mediated through selenoenzymes, which incorporate selenocysteine (Sec) into their active center [80].

Compared with other amino acids, Sec occurs infrequently in a small number of proteins (about 25) [81]. Incorporation of Sec into selenoenzymes is highly complex and evolves several unique features, such as a hairpin loop, known as a Sec insertion sequence located in the 3' untranslated region and several specific trans-acting factors [69,81,82]. Synthesis of selenoproteins is highly selenium-dependent [30,83–87] and replacement of Sec by cysteine results in very poor enzyme activity [82]. Several selenoproteins, such as glutathione peroxidases (GPXs), thioredoxin reductases (TXNRDs), selenoprotein P (SEPP1) and selenoprotein 15 (SEP15) are expressed in the prostate, colon and rectum [88,89]. Their preventive effects on oxidative stress and inflammation (for details see below) may impact prostate and colorectal cancers.

Antioxidative Effects of Selenium

Several animal and human studies have shown that selenium supplementation or high blood concentrations of selenium are inversely associated with markers of oxidative stress and DNA damage and that these effects are related to the activity of selenoenzymes [65,90–96]. Oxidative stress occurs through excessive production of ROS, including hydrogen peroxide, hydroxyl radicals and superoxide radicals, and/or decreased antioxidant defenses by antioxidative nutrients and enzymes [97,98]. ROS can damage important biomolecules such as DNA, RNA, lipids, proteins, and membranes and ROS-induced DNA damage can subsequently promote tumor progression [99–105]. The prostate, as androgen-sensitive organ, may be particularly susceptible to oxidative damage because androgens increase oxidative stress, potentially in part by increased mitochondrial activity and decrease in glutathione [106–108]. Furthermore, prostate cancer risk is an age-related disease and oxidative stress increases with age [101,109], through increased generation of ROS and reduced activity of antioxidative enzymes. Because of the direct contact of the colonic epithelial cells with microbial- and food-derived ROS, the colorectal tract may also be particularly susceptible to oxidative damage [110–114]. In summary, the antioxidative properties of selenoenzymes may reduce cancer risk and are potentially particularly important for prostate and colorectal cancer due to increased ROS exposure induced by androgens, ageing and microbial gut flora.

Selenium and Inflammation

Selenium supplementation and high selenium levels are associated with lower risk of diseases related to inflammation, such as asthma, pancreatitis, or arthritis [115–117], and a recent cross-sectional study found an inverse association between selenium levels and C-reactive protein, a marker of inflammation [118]. Inflammation appears to contribute importantly to prostate cancer [119,120] and colorectal carcinogenesis [121–123]. These effects are possibly mediated through increase in hydroperoxides [124,125]. Hydroperoxides can activate lipoxygenase and cyclooxygenase, and reduction of hydroperoxides by selenoenzyme activity may thus decrease the production of inflammatory prostaglandins and leukotrienes [126,127]. Specifically, in colon cancer cell lines and in colon tissue of rats, selenomethionine and organoselenium compounds have been found to reduce cyclooxygenase activity, with a related inhibition of cell and tumor growth [128–130]. As mentioned above also activity of selenoenzymes reduces adverse effects of inflammation by reducing ROS, which are produced during inflammatory processes [131]. Interestingly, the promoter of the selenoenzyme SEPP1 is cytokine responsive, suggesting that it may play an important role in moderating inflammation [132,133].

Results from mouse studies with targeted disruption of *GPX* genes provide intriguing support for the impact of selenium on inflammation and colorectal carcinogenesis: disruption for both *GPX1* and *GPX2* genes in mice results in a high susceptibility to

bacteria-induced inflammation and colon cancer [131,134] and this observation is accompanied by accumulation of lipid hydroperoxides [135]. A link between prostate cancer and inflammation has been postulated [136,137]. Chronic inflammation, initiated by infection such as sexually-transmitted infections, can facilitate ROS-induced DNA damage, cell injury and genetic instability. These cellular and DNA changes can lead to prostate carcinogenesis mediated through proliferative inflammatory atrophy and prostatic intraepithelial neoplasia [136,137]. In human prostate tissues, gene expression of antioxidant enzymes (i.e., copper-zinc superoxide dismutase, manganese superoxide dismutase and catalase) was lower in prostatic intraepithelial neoplasia and prostate carcinoma than benign epithelium [138], which corroborates the importance of antioxidants in carcinogenesis and inflammation in the prostate. In summary, because increasing evidence suggests the involvement of inflammatory processes in the development of prostate and colorectal cancer, anti-inflammatory effects of selenoenzyme activity may in part explain the preventive effect of selenium for these cancers [120,139–141].

Selenoproteins: Activity and Genetic Variation

Several studies [142–148] have shown that selenium intake increases the activity of circulating selenoenzymes and that the activity plateaus at the level of selenium intake commonly found in the United States. However, very little is known about selenoenzyme activity at tissue levels, such as in the colon and prostate, where several selenoenzymes compete for selenium and where exposure to oxidative stress is potentially high. Furthermore, it is to a large extent unknown whether genetic polymorphisms affect enzyme activity. Rayman [125] pointed out that selenium requirements differ among individuals, as shown by the substantial variation in selenoenzyme activity in response to selenium supplementation [149]. These individual differences may be at least in part explained by genetic variation in selenoenzymes [150,151]. We recently resequenced several selenoenzymes relevant for prostate and colorectal cancer (*GPX1-4*, *SEPP1*, and *TXNRD1*) and identified numerous genetic variants [152], which we genotyped in a nested case-control study for colorectal adenoma [153]. While this study supports an impact of some of the genetic variants in these selenoenzymes on colorectal carcinogenesis, these findings need to be replicated in large independent study populations, ideally those with available data on serum selenium concentrations and smoking to further explore potential interactions. Further information about the genetic susceptibility may be provided by currently ongoing genome-wide association studies. Although initial genome-wide scans have not pointed towards the involvement of selenoenzymes in prostate and colorectal cancer [154–161] it is possible that further analyses in larger scans, powered to identify weaker associations, will. Incorporating information on the genetic background into the ongoing selenium prevention trials may allow identifying subgroups that are particularly susceptible to the potential chemopreventive effect of selenium supplementation.

Dietary Intake of Selenium

Dietary selenium is mainly found in grains, dairy products, eggs, meat, poultry, and fish [162]. The selenium content of the same foods varies up to 10-fold because of differences in the selenium concentration of the soil where the crops are grown [9,11,12]. Geographical areas with high selenium soil content include Nebraska, the Dakotas, and Texas. Soil selenium content is lower in Florida and the Northeast and Northwest regions of the United States [163,164]. These regional differences contribute to a substantial variation in dietary selenium intake within the United States, which is estimated to range between about 50 to 500 µg/day [165–170]. Despite this wide range, dietary selenium intake is considered to be adequate for the U.S. population because the recommended dietary allowance (RDA) for selenium is 55 µg/day [171]. The RDA does not, however, reflect the higher selenium intake

that has been associated with reduced risk for cancer because the evidence for this effect was deemed insufficient [3,65,171–173].

Summary

Findings from several observational and a small intervention trial support a potential preventive role of selenium in prostate and colorectal cancer development. However, as several studies are limited in sample size and intervention trials were based on a secondary analysis, additional large studies using biomarkers of selenium intake and intervention trials, such as SELECT, will be important to further evaluate the potential chemopreventive effect of selenium. Consistent with this the most recent report from the World Cancer Research Fund and American Institute for Cancer Research concluded that limited suggestive evidence exists on the protective effect of selenium on colorectal cancer and that selenium probably decreases the risk of prostate cancer [174]. Thus, future studies will also need to be powered to further explore suggestive interaction with smoking and gender and to evaluate genetic variations in selenoenzymes.

Abbreviations used

CI	confidence interval
GPX	glutathione peroxidase
HR	hazard ratio
PLCO Trial	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
RDA	recommended dietary allowance
Sec	selenocysteine
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SEP15	selenoprotein 15
SEPP1	selenoprotein P
TXNRDs	thioredoxin reductases
ROS	reactive oxygen species

References

1. Ries, LAG.; Melbert, D.; Krapcho, M.; Mariotto, A.; Miller, BA.; Feuer, EJ., et al. SEER Cancer Statistics Review, 1975–2004. Bethesda, MD: National Cancer Institute; 2007.
2. American Cancer Society. Cancer Facts & Figures 2007. Atlanta, GA: American Cancer Society; 2007.
3. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA. 1996; 276:1957–1963. [PubMed: 8971064]
4. Combs GF Jr. Status of selenium in prostate cancer prevention. Br J Cancer. 2004; 91:195–199. [PubMed: 15213714]
5. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev. 2002; 11:630–639. [PubMed: 12101110]

6. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM Jr, Kristal AR, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst.* 2005; 97:94–102. [PubMed: 15657339]
7. Marshall JR, Sakr W, Wood D, Berry D, Tangen C, Parker F, et al. Design and progress of a trial of selenium to prevent prostate cancer among men with high-grade prostatic intraepithelial neoplasia. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:1479–1484. [PubMed: 16896036]
8. Nelson MA, Goulet AC, Jacobs ET, Lance P. Studies into the anticancer effects of selenomethionine against human colon cancer. *Ann N Y Acad Sci.* 2005; 1059:26–32. [PubMed: 16382040]
9. Levander OA. Considerations on the assessment of selenium status. *Fed Proc.* 1985; 44:2579–2583. [PubMed: 3996613]
10. Chen J, Peters U, Foster C, Chatterjee N. A haplotype-based test of association using data from cohort and nested case-control epidemiologic studies. *Human heredity.* 2004; 58:18–29. [PubMed: 15604561]
11. Finley J, Matthys L, Shuler T, Kotynty E. Selenium content of foods purchased in North Dakota. *Nutr Res.* 1996; 16:865–871.
12. Holden J, Gebhardt R, Davis C, Lurie D. A nationwide study of the selenium content and variability in white bread. *Journal Food Composition Analysis.* 1991; 4:183–195.
13. Longnecker MP, Stram DO, Taylor PR, Levander OA, Howe M, Veillon C, et al. Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. *Epidemiology.* 1996; 7:384–390. [PubMed: 8793364]
14. Willett, WC. *Nutritional Epidemiology.* 2. New York Oxford: OXFORD UNIVERSITY PRESS; 1998.
15. Longnecker MP, Stampfer MJ, Morris JS, Spate V, Baskett C, Mason M, et al. A 1-y trial of the effect of high-selenium bread on selenium concentrations in blood and toenails. *Am J Clin Nutr.* 1993; 57:408–413. [PubMed: 8438776]
16. Allen NE, Morris JS, Ngwenyama RA, Key TJ. A case-control study of selenium in nails and prostate cancer risk in British men. *Br J Cancer.* 2004; 90:1392–1396. [PubMed: 15054461]
17. Vogt TM, Ziegler RG, Graubard BI, Swanson CA, Greenberg RS, Schoenberg JB, et al. Serum selenium and risk of prostate cancer in U.S. blacks and whites. *Int J Cancer.* 2003; 103:664–670. [PubMed: 12494476]
18. Ghadirian P, Maisonneuve P, Perret C, Kennedy G, Boyle P, Krewski D, et al. A case-control study of toenail selenium and cancer of the breast, colon, and prostate. *Cancer Detect Prev.* 2000; 24:305–313. [PubMed: 11059562]
19. Li H, Stampfer MJ, Giovannucci EL, Morris JS, Willett WC, Gaziano JM, et al. A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst.* 2004; 96:696–703. [PubMed: 15126606]
20. Van den Brandt PA, Zeegers MP, Bode P, Goldbohm RA. Toenail selenium levels and the subsequent risk of prostate cancer: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev.* 2003; 12:866–871. [PubMed: 14504196]
21. Nomura AM, Lee J, Stemmermann GN, Combs GF Jr. Serum selenium and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2000; 9:883–887. [PubMed: 11008904]
22. Helzlsouer KJ, Huang HY, Alberg AJ, Hoffman S, Burke A, Norkus EP, et al. Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. *J Natl Cancer Inst.* 2000; 92:2018–2023. [PubMed: 11121464]
23. Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst.* 1998; 90:1219–1224. [PubMed: 9719083]
24. Brooks JD, Metter EJ, Chan DW, Sokoll LJ, Landis P, Nelson WG, et al. Plasma selenium level before diagnosis and the risk of prostate cancer development. *J Urol.* 2001; 166:2034–2038. [PubMed: 11696701]
25. Goodman GE, Schaffer S, Bankson DD, Hughes MP, Omenn GS. Predictors of serum selenium in cigarette smokers and the lack of association with lung and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:1069–1076. [PubMed: 11588133]

26. Knekt P, Aromaa A, Maatela J, Alfthan G, Aaran RK, Hakama M, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst.* 1990; 82:864–868. [PubMed: 2332904]
27. Peters U, Foster CB, Chatterjee N, Schatzkin A, Reding D, Andriole GL, et al. Serum selenium and risk of prostate cancer—a nested case-control study. *Am J Clin Nutr.* 2007; 85:209–217. [PubMed: 17209198]
28. Etminan M, FitzGerald JM, Gleave M, Chambers K. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control.* 2005; 16:1125–1131. [PubMed: 16184479]
29. Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol.* 1998; 81:730–734. [PubMed: 9634050]
30. Hill KE, Xia Y, Akesson B, Boeglin ME, Burk RF. Selenoprotein P concentration in plasma is an index of selenium status in selenium-deficient and selenium-supplemented Chinese subjects. *J Nutr.* 1996; 126:138–145. [PubMed: 8558294]
31. Neve J. Human selenium supplementation as assessed by changes in blood selenium concentration and glutathione peroxidase activity. *J Trace Elem Med Biol.* 1995; 9:65–73. [PubMed: 8825978]
32. Frei B, Forte TM, Ames BN, Cross CE. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. Protective effects of ascorbic acid. *Biochem J.* 1991; 277 (Pt 1):133–138. [PubMed: 1854329]
33. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ Health Perspect.* 1985; 64:111–126. [PubMed: 3007083]
34. Pryor WA, Hales BJ, Premovic PI, Church DF. The radicals in cigarette tar: their nature and suggested physiological implications. *Science.* 1983; 220:425–427. [PubMed: 6301009]
35. Pryor WA, Stone K, Zang LY, Bermudez E. Fractionation of aqueous cigarette tar extracts: fractions that contain the tar radical cause DNA damage. *Chem Res Toxicol.* 1998; 11:441–448. [PubMed: 9585474]
36. Cowan DB, Weisel RD, Williams WG, Mickle DA. Identification of oxygen responsive elements in the 5'-flanking region of the human glutathione peroxidase gene. *J Biol Chem.* 1993; 268:26904–26910. [PubMed: 8262924]
37. de Haan JB, Bladier C, Griffiths P, Kelner M, O'Shea RD, Cheung NS, et al. Mice with a homozygous null mutation for the most abundant glutathione peroxidase, Gpx1, show increased susceptibility to the oxidative stress-inducing agents paraquat and hydrogen peroxide. *J Biol Chem.* 1998; 273:22528–22536. [PubMed: 9712879]
38. Fuchs O. Effects of intracellular chelatable iron and oxidative stress on transcription of classical cellular glutathione peroxidase gene in murine erythroleukemia cells. *Neoplasma.* 1997; 44:184–191. [PubMed: 9372861]
39. Jornot L, Junod AF. Hyperoxia, unlike phorbol ester, induces glutathione peroxidase through a protein kinase C-independent mechanism. *Biochem J.* 1997; 326 (Pt 1):117–123. [PubMed: 9337858]
40. Fernandez-Banares F, Cabre E, Esteve M, Mingorance MD, bad-Lacruz A, Lachica M, et al. Serum selenium and risk of large size colorectal adenomas in a geographical area with a low selenium status. *Am J Gastroenterol.* 2002; 97:2103–2108. [PubMed: 12190184]
41. Schober SE, Comstock GW, Helsing KJ, Salkeld RM, Morris JS, Rider AA, et al. Serologic precursors of cancer. I. Prediagnostic serum nutrients and colon cancer risk. *Am J Epidemiol.* 1987; 126:1033–1041. [PubMed: 3687915]
42. Clark LC, Hixson LJ, Combs GF Jr, Reid ME, Turnbull BW, Sampliner RE. Plasma selenium concentration predicts the prevalence of colorectal adenomatous polyps. *Cancer Epidemiol Biomarkers Prev.* 1993; 2:41–46. [PubMed: 8420611]
43. Criqui MH, Bangdiwala S, Goodman DS, Blaner WS, Morris JS, Kritchevsky S, et al. Selenium, retinol, retinol-binding protein, and uric acid. Associations with cancer mortality in a population-based prospective case-control study. *Ann Epidemiol.* 1991; 1:385–393. [PubMed: 1669519]
44. Ringstad J, Jacobsen BK, Tretli S, Thomassen Y. Serum selenium concentration associated with risk of cancer. *J Clin Pathol.* 1988; 41:454–457. [PubMed: 3366933]

45. Russo MW, Murray SC, Wurzelmann JI, Woosley JT, Sandler RS. Plasma selenium levels and the risk of colorectal adenomas. *Nutr Cancer*. 1997; 28:125–129. [PubMed: 9290116]
46. Salonen JT, Alfthan G, Huttunen JK, Puska P. Association between serum selenium and the risk of cancer. *Am J Epidemiol*. 1984; 120:342–349. [PubMed: 6475911]
47. Salonen JT, Salonen R, Lappetelainen R, Maenpaa PH, Alfthan G, Puska P. Risk of cancer in relation to serum concentrations of selenium and vitamins A and E: matched case-control analysis of prospective data. *Br Med J (Clin Res Ed)*. 1985; 290:417–420.
48. Scieszka M, Danch A, Machalski M, Drozd M. Plasma selenium concentration in patients with stomach and colon cancer in the Upper Silesia. *Neoplasma*. 1997; 44:395–397. [PubMed: 9605014]
49. Willett WC, Polk BF, Morris JS, Stampfer MJ, Pressel S, Rosner B, et al. Prediagnostic serum selenium and risk of cancer. *Lancet*. 1983; 2:130–134. [PubMed: 6134981]
50. Peleg I, Morris S, Hames CG. Is serum selenium a risk factor for cancer? *Med Oncol Tumor Pharmacother*. 1985; 2:157–163. [PubMed: 4068802]
51. Coates RJ, Weiss NS, Daling JR, Morris JS, Labbe RF. Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol*. 1988; 128:515–523. [PubMed: 3046338]
52. Nomura A, Heilbrun LK, Morris JS, Stemmermann GN. Serum selenium and the risk of cancer, by specific sites: case-control analysis of prospective data. *J Natl Cancer Inst*. 1987; 79:103–108. [PubMed: 3474437]
53. Zhao N. A case-control study of risk factors of colorectal cancer in Shanxi Province. *Zhonghua Liu Xing Bing Xue Za Zhi*. 1990; 11:295–298. [PubMed: 2261619]
54. Van den Brandt PA, Goldbohm RA, van' V, Bode P, Dorant E, Hermus RJ, et al. A prospective cohort study on toenail selenium levels and risk of gastrointestinal cancer. *J Natl Cancer Inst*. 1993; 85:224–229. [PubMed: 8423627]
55. Garland M, Morris JS, Stampfer MJ, Colditz GA, Spate VL, Baskett CK, et al. Prospective study of toenail selenium levels and cancer among women. *J Natl Cancer Inst*. 1995; 87:497–505. [PubMed: 7707436]
56. Nelson RL, Davis FG, Sutter E, Kikendall JW, Sobin LH, Milner JA, et al. Serum selenium and colonic neoplastic risk. *Dis Colon Rectum*. 1995; 38:1306–1310. [PubMed: 7497844]
57. Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, et al. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res*. 1993; 53:4230–4237. [PubMed: 8364919]
58. Wallace K, Byers T, Morris JS, Cole BF, Greenberg ER, Baron JA, et al. Prediagnostic serum selenium concentration and the risk of recurrent colorectal adenoma: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*. 2003; 12:464–467. [PubMed: 12750244]
59. Jacobs ET, Jiang R, Alberts DS, Greenberg ER, Gunter EW, Karagas MR, et al. Selenium and colorectal adenoma: results of a pooled analysis. *J Natl Cancer Inst*. 2004; 96:1669–1675. [PubMed: 15547179]
60. Peters, U.; Hayes, RB.; Chatterjee, N.; Church, TR.; Mayo, C.; Sturup, S., et al. Serum selenium and genetic variation in the selenoprotein GPX1 and risk of colorectal adenoma. 95th Annual meeting of the AACR March 27th–31st; Orlando, FL. 2004. AACR LB-231
61. Rodriguez Rodriguez EM, Sanz Alaejos MT, Diaz RC. Urinary selenium status of healthy people. *Eur J Clin Chem Clin Biochem*. 1995; 33:127–133. [PubMed: 7605824]
62. Waters DJ, Chiang EC, Cooley DM, Morris JS. Making sense of sex and supplements: differences in the anticarcinogenic effects of selenium in men and women. *Mutat Res*. 2004; 551:91–107. [PubMed: 15225584]
63. Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, Taylor PR, et al. SELECT: the next prostate cancer prevention trial. Selenium and Vitamin E Cancer Prevention Trial. *J Urol*. 2001; 166:1311–1315. [PubMed: 11547064]
64. El Bayoumy K, Upadhyaya P, Date V, Sohn OS, Fiala ES, Reddy B. Metabolism of [14C]benzyl selenocyanate in the F344 rat. *Chem Res Toxicol*. 1991; 4:560–565. [PubMed: 1793806]
65. Combs GF Jr, Gray WP. Chemopreventive agents: selenium. *Pharmacol Ther*. 1998; 79:179–192. [PubMed: 9776375]

66. Combs, GF.; Clark, LC. Nutritional Oncology. Academic Press; 1999. Selenium and Cancer; p. 215-222.
67. Combs GF Jr. Chemopreventive mechanisms of selenium. *Med Klin.* 1999; 94 (Suppl 3):18–24.
68. Dong Y, Lee SO, Zhang H, Marshall J, Gao AC, Ip C. Prostate specific antigen expression is down-regulated by selenium through disruption of androgen receptor signaling. *Cancer Res.* 2004; 64:19–22. [PubMed: 14729601]
69. Driscoll DM, Copeland PR. Mechanism and regulation of selenoprotein synthesis. *Annu Rev Nutr.* 2003; 23:17–40. [PubMed: 12524431]
70. Jiang C, Wang Z, Ganther H, Lu J. Caspases as key executors of methyl selenium-induced apoptosis (anoikis) of DU-145 prostate cancer cells. *Cancer Res.* 2001; 61:3062–3070. [PubMed: 11306488]
71. Menter DG, Sabichi AL, Lippman SM. Selenium effects on prostate cell growth. *Cancer Epidemiol Biomarkers Prev.* 2000; 9:1171–1182. [PubMed: 11097224]
72. Venkateswaran V, Klotz LH, Fleshner NE. Selenium modulation of cell proliferation and cell cycle biomarkers in human prostate carcinoma cell lines. *Cancer Res.* 2002; 62:2540–2545. [PubMed: 11980647]
73. Zhong W, Oberley TD. Redox-mediated effects of selenium on apoptosis and cell cycle in the LNCaP human prostate cancer cell line. *Cancer Res.* 2001; 61:7071–7078. [PubMed: 11585738]
74. Seo YR, Kelley MR, Smith ML. Selenomethionine regulation of p53 by a ref1-dependent redox mechanism. *Proc Natl Acad Sci U S A.* 2002; 99:14548–14553. [PubMed: 12357032]
75. Christensen MJ, Nartey ET, Hada AL, Legg RL, Barzee BR. High selenium reduces NF-kappaB-regulated gene expression in uninduced human prostate cancer cells. *Nutr Cancer.* 2007; 58:197–204. [PubMed: 17640166]
76. Rayman MP. Selenium in cancer prevention: a review of the evidence and mechanism of action. *Proc Nutr Soc.* 2005; 64:527–542. [PubMed: 16313696]
77. Dong Y, Zhang H, Hawthorn L, Ganther HE, Ip C. Delineation of the molecular basis for selenium-induced growth arrest in human prostate cancer cells by oligonucleotide array. *Cancer Res.* 2003; 63:52–59. [PubMed: 12517777]
78. Ip C, Thompson HJ, Zhu Z, Ganther HE. In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. *Cancer Res.* 2000; 60:2882–2886. [PubMed: 10850432]
79. Zhao H, Whitfield ML, Xu T, Botstein D, Brooks JD. Diverse effects of methylseleninic acid on the transcriptional program of human prostate cancer cells. *Mol Biol Cell.* 2004; 15:506–519. [PubMed: 14617803]
80. Leinfelder W, Zehelein E, Mandrand-Berthelot MA, Bock A. Gene for a novel tRNA species that accepts L-serine and cotranslationally inserts selenocysteine. *Nature.* 1988; 331:723–725. [PubMed: 2963963]
81. Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zettab O, Guigo R, et al. Characterization of mammalian selenoproteomes. *Science.* 2003; 300:1439–1443. [PubMed: 12775843]
82. Hatfield DL, Gladyshev VN. How selenium has altered our understanding of the genetic code. *Mol Cell Biol.* 2002; 22:3565–3576. [PubMed: 11997494]
83. Low SC, Harney JW, Berry MJ. Cloning and functional characterization of human selenophosphate synthetase, an essential component of selenoprotein synthesis. *J Biol Chem.* 1995; 270:21659–21664. [PubMed: 7665581]
84. Allan CB, Lacourciere GM, Stadtman TC. Responsiveness of selenoproteins to dietary selenium. *Annu Rev Nutr.* 1999; 19:1–16. [PubMed: 10448514]
85. Hill KE, Chittum HS, Lyons PR, Boeglin ME, Burk RF. Effect of selenium on selenoprotein P expression in cultured liver cells. *Biochim Biophys Acta.* 1996; 1313:29–34. [PubMed: 8781546]
86. Sunde RA, Thompson BM, Palm MD, Weiss SL, Thompson KM, Evenson JK. Selenium regulation of selenium-dependent glutathione peroxidases in animals and transfected CHO cells. *Biomed Environ Sci.* 1997; 10:346–355. [PubMed: 9315329]
87. Brigelius-Flohe R. Tissue-specific functions of individual glutathione peroxidases. *Free Radic Biol Med.* 1999; 27:951–965. [PubMed: 10569628]

88. Mork H, Lex B, Scheurlen M, Dreher I, Schutze N, Kohrle J, et al. Expression pattern of gastrointestinal selenoproteins--targets for selenium supplementation. *Nutr Cancer*. 1998; 32:64–70. [PubMed: 9919613]
89. Winkler K, Bocher M, Flohe L, Kollmus H, Brigelius-Flohe R. mRNA stability and selenocysteine insertion sequence efficiency rank gastrointestinal glutathione peroxidase high in the hierarchy of selenoproteins. *Eur J Biochem*. 1999; 259:149–157. [PubMed: 9914487]
90. Jozanov-Stankov O, Demajo M, Djubic I, Mandic M. Selenium intake as a modulator of responsiveness to oxidative stress. *J Environ Pathol Toxicol Oncol*. 1998; 17:251–257. [PubMed: 9726798]
91. Karunasinghe N, Ryan J, Tuckey J, Masters J, Jamieson M, Clarke LC, et al. DNA stability and serum selenium levels in a high-risk group for prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:391–397. [PubMed: 15006914]
92. Sobajic SS, Mihailovic MB, Miric MO. The effects of selenium deficiency, dietary selenium, and vitamin E supplementation on the oxidative status of pig liver. *J Environ Pathol Toxicol Oncol*. 1998; 17:265–270. [PubMed: 9726800]
93. Thirunavukkarasu C, Sakthisekaran D. Effect of selenium on N-nitrosodiethylamine-induced multistage hepatocarcinogenesis with reference to lipid peroxidation and enzymic antioxidants. *Cell Biochem Funct*. 2001; 19:27–35. [PubMed: 11223868]
94. Thirunavukkarasu C, Sakthisekaran D. Sodium selenite, dietary micronutrient, prevents the lymphocyte DNA damage induced by N-nitrosodiethylamine and phenobarbital promoted experimental hepatocarcinogenesis. *J Cell Biochem*. 2003; 88:578–588. [PubMed: 12532333]
95. Rao L, Puschner B, Prolla TA. Gene expression profiling of low selenium status in the mouse intestine: transcriptional activation of genes linked to DNA damage, cell cycle control and oxidative stress. *J Nutr*. 2001; 131:3175–3181. [PubMed: 11739862]
96. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: biochemical role as a component of glutathione peroxidase. *Science*. 1973; 179:588–590. [PubMed: 4686466]
97. Frei B, Stocker R, Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma. *Proc Natl Acad Sci U S A*. 1988; 85:9748–9752. [PubMed: 3200852]
98. Hayes JD, McLellan LI. Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. *Free Radic Res*. 1999; 31:273–300. [PubMed: 10517533]
99. Emerit I. Reactive oxygen species, chromosome mutation, and cancer: possible role of clastogenic factors in carcinogenesis. *Free Radic Biol Med*. 1994; 16:99–109. [PubMed: 8300000]
100. Schwartz JL, Antoniadis DZ, Zhao S. Molecular and biochemical reprogramming of oncogenesis through the activity of prooxidants and antioxidants. *Ann N Y Acad Sci*. 1993; 686:262–278. [PubMed: 8512252]
101. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. *J Mol Med*. 1996; 74:297–312. [PubMed: 8862511]
102. Gate L, Paul J, Ba GN, Tew KD, Tapiero H. Oxidative stress induced in pathologies: the role of antioxidants. *Biomed Pharmacother*. 1999; 53:169–180. [PubMed: 10392289]
103. Jackson AL, Loeb LA. The contribution of endogenous sources of DNA damage to the multiple mutations in cancer. *Mutat Res*. 2001; 477:7–21. [PubMed: 11376682]
104. Dreher D, Junod AF. Role of oxygen free radicals in cancer development. *Eur J Cancer*. 1996; 32A:30–38. [PubMed: 8695238]
105. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci USA*. 1993; 90:7915–7922. [PubMed: 8367443]
106. Ripple MO, Henry WF, Rago RP, Wilding G. Prooxidant-antioxidant shift induced by androgen treatment of human prostate carcinoma cells. *J Natl Cancer Inst*. 1997; 89:40–48. [PubMed: 8978405]
107. Iynem AH, Alademir AZ, Obek C, Kural AR, Konukoglu D, Akcay T. The effect of prostate cancer and antiandrogenic therapy on lipid peroxidation and antioxidant systems. *Int Urol Nephrol*. 2004; 36:57–62. [PubMed: 15338676]

108. Tam NN, Gao Y, Leung YK, Ho SM. Androgenic regulation of oxidative stress in the rat prostate: involvement of NAD(P)H oxidases and antioxidant defense machinery during prostatic involution and regrowth. *Am J Pathol.* 2003; 163:2513–2522. [PubMed: 14633623]
109. Tapiero H, Townsend DM, Tew KD. The antioxidant role of selenium and seleno-compounds. *Biomed Pharmacother.* 2003; 57:134–144. [PubMed: 12818475]
110. Sanders LM, Henderson CE, Hong MY, Barhoumi R, Burghardt RC, Carroll RJ, et al. Pro-oxidant environment of the colon compared to the small intestine may contribute to greater cancer susceptibility. *Cancer Lett.* 2004; 208:155–161. [PubMed: 15142673]
111. Babbs CF. Free radicals and the etiology of colon cancer. *Free Radic Biol Med.* 1990; 8:191–200. [PubMed: 2185144]
112. Erhardt JG, Lim SS, Bode JC, Bode C. A diet rich in fat and poor in dietary fiber increases the in vitro formation of reactive oxygen species in human feces. *J Nutr.* 1997; 127:706–709. [PubMed: 9164990]
113. Huycke MM, Abrams V, Moore DR. Enterococcus faecalis produces extracellular superoxide and hydrogen peroxide that damages colonic epithelial cell DNA. *Carcinogenesis.* 2002; 23:529–536. [PubMed: 11895869]
114. Wang X, Huycke MM. Extracellular superoxide production by Enterococcus faecalis promotes chromosomal instability in mammalian cells. *Gastroenterology.* 2007; 132:551–561. [PubMed: 17258726]
115. McCloy R. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. *Digestion.* 1998; 59 (Suppl 4):36–48. [PubMed: 9832634]
116. Peretz A, Neve J, Duchateau J, Famaey JP. Adjuvant treatment of recent onset rheumatoid arthritis by selenium supplementation: preliminary observations. *Br J Rheumatol.* 1992; 31:281–282. [PubMed: 1555045]
117. Shaheen SO, Sterne JA, Thompson RL, Songhurst CE, Margetts BM, Burney PG. Dietary antioxidants and asthma in adults: population-based case-control study. *Am J Respir Crit Care Med.* 2001; 164:1823–1828. [PubMed: 11734430]
118. Ford ES, Liu S, Mannino DM, Giles WH, Smith SJ. C-reactive protein concentration and concentrations of blood vitamins, carotenoids, and selenium among United States adults. *Eur J Clin Nutr.* 2003; 57:1157–1163. [PubMed: 12947436]
119. Chung TD, Yu JJ, Spiotto MT, Bartkowski M, Simons JW. Characterization of the role of IL-6 in the progression of prostate cancer. *Prostate.* 1999; 38:199–207. [PubMed: 10068344]
120. De Marzo AM, Marchi VL, Epstein JI, Nelson WG. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. *Am J Pathol.* 1999; 155:1985–1992. [PubMed: 10595928]
121. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol.* 2004; 287:G7–17. [PubMed: 15194558]
122. Clevers H. At the crossroads of inflammation and cancer. *Cell.* 2004; 118:671–674. [PubMed: 15369667]
123. Sinicrope FA, Gill S. Role of cyclooxygenase-2 in colorectal cancer. *Cancer Metastasis Rev.* 2004; 23:63–75. [PubMed: 15000150]
124. Imai H, Nakagawa Y. Biological significance of phospholipid hydroperoxide glutathione peroxidase (PHGPx, GPx4) in mammalian cells. *Free Radic Biol Med.* 2003; 34:145–169. [PubMed: 12521597]
125. Rayman MP. The importance of selenium to human health. *Lancet.* 2000; 356:233–241. [PubMed: 10963212]
126. Villette S, Kyle JA, Brown KM, Pickard K, Milne JS, Nicol F, et al. A novel single nucleotide polymorphism in the 3' untranslated region of human glutathione peroxidase 4 influences lipoxigenase metabolism. *Blood Cells Mol Dis.* 2002; 29:174–178. [PubMed: 12490284]
127. Spallholz JE, Boylan LM, Larsen HS. Advances in understanding selenium's role in the immune system. *Ann N Y Acad Sci.* 1990; 587:123–139. [PubMed: 2193564]

128. Baines A, Taylor-Parker M, Goulet AC, Renaud C, Gerner EW, Nelson MA. Selenomethionine inhibits growth and suppresses cyclooxygenase-2 (COX-2) protein expression in human colon cancer cell lines. *Cancer Biol Ther.* 2002; 1:370–374. [PubMed: 12432249]
129. Rao CV, Cooma I, Rodriguez JG, Simi B, El Bayoumy K, Reddy BS. Chemoprevention of familial adenomatous polyposis development in the APC(min) mouse model by 1,4-phenylene bis(methylene)selenocyanate. *Carcinogenesis.* 2000; 21:617–621. [PubMed: 10753194]
130. Rao CV, Wang CQ, Simi B, Rodriguez JG, Cooma I, El Bayoumy K, et al. Chemoprevention of colon cancer by a glutathione conjugate of 1,4-phenylenebis(methylene)selenocyanate, a novel organoselenium compound with low toxicity. *Cancer Res.* 2001; 61:3647–3652. [PubMed: 11325834]
131. Chu FF, Esworthy RS, Doroshow JH. Role of Se-dependent glutathione peroxidases in gastrointestinal inflammation and cancer. *Free Radic Biol Med.* 2004; 36:1481–1495. [PubMed: 15182851]
132. Dreher I, Jakobs TC, Kohrle J. Cloning and characterization of the human selenoprotein P promoter. Response of selenoprotein P expression to cytokines in liver cells. *J Biol Chem.* 1997; 272:29364–29371. [PubMed: 9361018]
133. Mostert V, Wolff S, Dreher I, Kohrle J, Abel J. Identification of an element within the promoter of human selenoprotein P responsive to transforming growth factor-beta. *Eur J Biochem.* 2001; 268:6176–6181. [PubMed: 11733012]
134. Chu FF, Esworthy RS, Chu PG, Longmate JA, Huycke MM, Wilczynski S, et al. Bacteria-induced intestinal cancer in mice with disrupted Gpx1 and Gpx2 genes. *Cancer Res.* 2004; 64:962–968. [PubMed: 14871826]
135. Esworthy RS, Aranda R, Martin MG, Doroshow JH, Binder SW, Chu FF. Mice with combined disruption of Gpx1 and Gpx2 genes have colitis. *Am J Physiol Gastrointest Liver Physiol.* 2001; 281:G848–G855. [PubMed: 11518697]
136. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, et al. Inflammation in prostate carcinogenesis. *Nat Rev Cancer.* 2007; 7:256–269. [PubMed: 17384581]
137. Klein EA, Silverman R. Inflammation, infection, and prostate cancer. *Curr Opin Urol.* 2008; 18:315–319. [PubMed: 18382242]
138. Bostwick DG, Alexander EE, Singh R, Shan A, Qian J, Santella RM, et al. Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. *Cancer.* 2000; 89:123–134. [PubMed: 10897009]
139. Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. *J Urol.* 2004; 172:S6–11. [PubMed: 15535435]
140. Palapattu GS, Sutcliffe S, Bastian PJ, Platz EA, De Marzo AM, Isaacs WB, et al. Prostate carcinogenesis and inflammation: emerging insights. *Carcinogenesis.* 2004
141. Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer. *J Urol.* 2004; 171:S36–S40. [PubMed: 14713751]
142. Xia Y, Zhao X, Zhu L, Whanger PD. Metabolism of selenate and selenomethionine by a selenium-deficient population of men in China. *J Nutr Biochem.* 1992; 3:202–210.
143. Lassen KO, Horder M. Selenium status and the effect of organic and inorganic selenium supplementation in a group of elderly people in Denmark. *Scand J Clin Lab Invest.* 1994; 54:585–590. [PubMed: 7709159]
144. Persson-Moschos M, Alfthan G, Akesson B. Plasma selenoprotein P levels of healthy males in different selenium status after oral supplementation with different forms of selenium. *Eur J Clin Nutr.* 1998; 52:363–367. [PubMed: 9630388]
145. Thomson CD, Robinson MF, Butler JA, Whanger PD. Long-term supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1. 9) in blood components of New Zealand women. *Br J Nutr.* 1993; 69:577–588. [PubMed: 8490010]
146. Alfthan G, Xu GL, Tan WH, Aro A, Wu J, Yang YX, et al. Selenium supplementation of children in a selenium-deficient area in China: blood selenium levels and glutathione peroxidase activities. *Biol Trace Elem Res.* 2000; 73:113–125. [PubMed: 11049204]

147. Yang, GQ.; Zhu, LZ.; Liu, SJ.; Gu, LZ.; Qian, PC.; Huang, JH., et al. Human selenium requirements in China. In: Combs, G.; Levander, OA.; Spallholz, JE.; Oldfield, JE., editors. *Selenium in Biology and Medicine*. New York: Avi; 1987. p. 589-607.
148. Duffield AJ, Thomson CD, Hill KE, Williams S. An estimation of selenium requirements for New Zealanders. *Am J Clin Nutr*. 1999; 70:896–903. [PubMed: 10539752]
149. Brown KM, Pickard K, Nicol F, Beckett GJ, Duthie GG, Arthur JR. Effects of organic and inorganic selenium supplementation on selenoenzyme activity in blood lymphocytes, granulocytes, platelets and erythrocytes. *Clin Sci (Lond)*. 2000; 98:593–599. [PubMed: 10781391]
150. Taylor PR, Parnes HL, Lippman SM. Science peels the onion of selenium effects on prostate carcinogenesis. *J Natl Cancer Inst*. 2004; 96:645–647. [PubMed: 15126594]
151. Diwadkar-Navsariwala V, Diamond AM. The link between selenium and chemoprevention: a case for selenoproteins. *J Nutr*. 2004; 134:2899–2902. [PubMed: 15514248]
152. Foster CB, Aswath K, Chanock SJ, McKay HF, Peters U. Polymorphism analysis of six selenoprotein genes: support for a selective sweep at the glutathione peroxidase 1 locus (3p21) in Asian populations. *BMC Genet*. 2006; 7:56. [PubMed: 17156480]
153. Peters U, Chatterjee N, Hayes RB, Schoen RE, Chanock SJ, Foster CB. Variation in the selenoenzyme genes and risk of advanced distal colorectal adenoma. *Cancer Epidemiology Biomarkers and Prevention*. 2008 in press.
154. Broderick P, Carvajal-Carmona L, Pittman AM, Webb E, Howarth K, Rowan A, et al. A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. *Nat Genet*. 2007; 39:1315–1317. [PubMed: 17934461]
155. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, et al. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet*. 2008; 40:316–321. [PubMed: 18264097]
156. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet*. 2007; 39:631–637. [PubMed: 17401366]
157. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, et al. Common sequence variants on 2p15 and Xp11. 22 confer susceptibility to prostate cancer. *Nat Genet*. 2008; 40:281–283. [PubMed: 18264098]
158. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet*. 2008; 40:310–315. [PubMed: 18264096]
159. Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, et al. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24. 21. *Nat Genet*. 2007; 39:984–988. [PubMed: 17618284]
160. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet*. 2007; 39:645–649. [PubMed: 17401363]
161. Zanke BW, Greenwood CM, Rangrej J, Kustra R, Tenesa A, Farrington SM, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat Genet*. 2007; 39:989–994. [PubMed: 17618283]
162. Schwarz K, Foltz C. *J Am Chem Soc*. 1957; 79:3292.
163. Grossman, JN.; Grosz, AE.; Schweitzer, PN.; Schruben, PN. The National Geochemical Survey Team. The National Geochemical Survey - Database and Documentation. U.S. Geological Survey Open-File Report 2004-1001. 2005.
<http://tin.er.usgs.gov/geochem/doc/averages/se/usa.html>
164. Kubota J, Allaway WH, Carter DL, Cary EE, Lazar VA, et al. Selenium in crops in the United States in relation to selenium-responsive diseases of animals. *J Agric Food Chem*. 1967; 15:448.
165. Longnecker MP, Taylor PR, Levander OA, Howe M, Veillon C, McAdam PA, et al. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. *Am J Clin Nutr*. 1991; 53:1288–1294. [PubMed: 2021136]

166. Hunter DJ, Morris JS, Chute CG, Kushner E, Colditz GA, Stampfer MJ, et al. Predictors of selenium concentration in human toenails. *Am J Epidemiol.* 1990; 132:114–122. [PubMed: 2356804]
167. Pennington JA, Wilson DB, Newell RF, Harland BF, Johnson RD, Vanderveen JE. Selected minerals in foods surveys, 1974 to 1981/82. *J Am Diet Assoc.* 1984; 84:771–780. [PubMed: 6736504]
168. Pennington JA, Young BE, Wilson DB. Nutritional elements in U.S. diets: results from the Total Diet Study, 1982 to 1986. *J Am Diet Assoc.* 1989; 89:659–664. [PubMed: 2723289]
169. Giovannucci E. Selenium and risk of prostate cancer. *Lancet.* 1998; 352:755–756. [PubMed: 9737275]
170. Combs GF Jr, Clark LC, Turnbull BW. An analysis of cancer prevention by selenium. *Biofactors.* 2001; 14:153–159. [PubMed: 11568452]
171. Panel on Dietary Antioxidants and Related Components. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Beta-Carotene and other Carotenoids. Washington, DC: National Academy Press; 2000.
172. Thomson CD. Assessment of requirements for selenium and adequacy of selenium status: a review. *Eur J Clin Nutr.* 2004; 58:391–402. [PubMed: 14985676]
173. Rayman MP. The argument for increasing selenium intake. *Proc Nutr Soc.* 2002; 61:203–215. [PubMed: 12133202]
174. World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR; 2007.
175. Peters U, Chatterjee N, Church TR, Mayo C, Sturup S, Foster CB, et al. High serum selenium and reduced risk of advanced colorectal adenoma in a colorectal cancer early detection program. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:315–320. [PubMed: 16492922]

Table 1

Epidemiological Studies on Selenium and Prostate Cancer^a

—ordered by study design and publication year

1 st Author, pub. Year, reference	Country	Cases/Controls	Results (RR comparing highest to lowest quantile)				Selenium assessment				
			All cancer		Advanced cancer		All cancer		Advanced cancer		
			OR	95%CI	p-trend	OR	95%CI	p-trend	Specimen	Mean/median ^b	
Randomized Clinical Trial											
Clark 1996[3]	United States	13/35 ^c	0.37	0.18–0.71	0.002					Plasma (at baseline)	114
Nested Case-Control, Case-Cohort Studies or Cohort											
Peters 2008	United States	830/34412	0.90	0.62–0.13	0.97	0.46	0.17–1.3	0.31		Supplement	26.6 µg in users
Peters 2007[27]	United States	724/879	0.84	0.62–1.14	0.70	0.62	0.30–1.29	0.57		Serum	141
Li 2004[19]	United States	586/577	0.78	0.54–1.13	0.16	0.52	0.28–0.98	0.05		Plasma	108
van den Brandt 2003[20]	Netherlands	540/1211	0.69	0.48–0.99	0.008	0.62	0.37–1.05	0.02		Toenails	0.55
Brooks 2001[24]	United States	52/996	0.24	0.08–0.77	0.01					Serum	120
Goodman 2001[25]	United States	235/456	1.02	0.65–1.60	0.69	0.76	0.34–1.71	0.35		Serum	114
Nomura 2000[21]	United States	249/249	0.5	0.3–0.9	0.02	0.3	0.1–0.8	0.01		Serum	132
Helzlsouer 2000[22]	United States	117/233	0.38	0.17–0.85	0.12					Toenails	0.79
Yoshizawa 1998[23]	United States	181/181				0.35	0.16–0.78	0.03		Toenails	0.96
Criqui 1991[43]	North America	6/12	Selenium levels lower in prostate cancer cases than controls by 20 ng/ml (p<0.1)							Plasma	149
Knekt 1990[26]	Finland	51/102	1.15	Not reported	0.71					Serum	58
Coates 1988[51]	United States	13/22	0.3	Not reported	0.18					Serum Plasma	162 148
Peleg 1985[50]	United States	14/28	Selenium levels not-significant higher in prostate cancer cases (0.120 µg/ml) than controls (0.117 µg/ml)							Serum	117
Willett 1983[49]	United States	11/22	Selenium levels lower in prostate cancer cases (0.128 µg/ml) than controls (0.139 µg/ml) (p=0.12)							Serum	139
Population-based Case-Control Studies											
Allen 2004[16]	United Kingdom	300/300	1.24	0.73–2.10	0.58	0.78	0.27–2.25	0.48		Nails	0.61
Vogt 2003[17]	United States	212/233	0.71	0.39–1.28	0.11	0.75	0.32–1.80	0.49		Serum	137
Ghadirian 2000[18]	Canada	83/82	1.14	0.46–2.83	0.62					Toenails	0.91

Ecologic studies and observational studies using dietary questionnaire data to assess selenium intake or patients with benign hyperplasia as controls were excluded
Mean/median selenium levels in controls only, serum and plasma selenium levels in ng/ml and toenail selenium levels in ng/mg
Number of prostate cancer cases in selenium supplementation group/placebo group

Table 2
Epidemiological Studies on Selenium and Colorectal Cancer and Adenoma^a
 —ordered by study design and publication year

1 st Author, pub. Year, reference	Country	Cases/controls	Outcome ^b	Results (OR for highest vs. lowest quantile)			Selenium assessment		
				OR	95% CI	p-trend	Specimen	Mean/median ^c	
Randomized Trials									
Clark 1996[3]	United States	8/19 ^d	CR	0.39	0.17–0.90	0.03	Plasma (at baseline)	114	
Nested Case-Control and Case-Cohort Studies or Cohort									
Peters 2006[175]	United States	758/767	A	0.76	0.53–1.10	0.01	Serum	134	
Jacobs 2004[59]	United States	403/310	AR	0.67	0.43–1.05	0.21	Serum	131	
		247/251	AR	0.66	0.40–1.10	0.13	Plasma	134	
		362/190	AR	0.57	0.34–0.95	0.04	Serum	131	
		pooled		0.66	0.50–0.87	0.006		132	
Garland 1995[55]	United States	89/89	CR	2.04	0.88–4.75	0.12	Toenails	0.843	
van den Brandt 1993[54]	The Netherlands	105 ^e /2569	C	1.07	0.61–1.88	0.55	Toenails	0.535 in men; 0.560 in women	
Bostick 1993[57]	United States	76 ^e /2569 212/35004	R CR	1.12 0.60	0.49–2.55 0.27–1.32	0.89	Supplement	-	
Criqui 1991[43]	United States	30/55	GI	Mean selenium levels lower in GI cases than controls by 9 ng/ml (p<0.1)			Plasma	149	
Knekt 1990[26]	Finland	32/64 59/118	CR-men CR-women	0.69 1.26	Not reported Not reported	ns ns	Serum	64 65	
Ringstad 1988[44]	Norway	11/11	GI	Mean selenium levels lower in CR cases (124 ng/ml) than controls (129 ng/ml) (p=0.3)			Serum	130 ng/ml	
Schober 1987[41]	United States	72/143	C	0.71	0.29–1.67		Serum	115	
Coates 1988[51]	United States	28/51	GI	1.00	Not reported	0.89	Ser./Plas.	162/148	
Nomura 1987[52]	Hawaii Japanese	82/293 32/293	C R	0.56 0.63	Not reported	0.33 0.66	Serum	123	
Peleg 1985[50]	United States	19/38	GI	Mean selenium levels not different between GI cases (115 ng/ml) and controls (116 ng/ml)			Serum	116	
Salonen 1985[47]	Finland	18/18	GI	Mean selenium levels lower in GI cases (54.9 ng/ml) than controls (60.1 ng/ml) (p>0.05)			Serum	61	

1 st Author, pub. Year, reference	Country	Cases/controls	Outcome ^b	Results (OR for highest vs. lowest quantile)			Selenium assessment	
				OR	95% CI	p-trend	Specimen	Mean/median ^c
Salonen 1984[46]	Finland	21/21	GI	Mean selenium levels lower in GI cases (48.6±3.2 ng/ml) than controls (54.3±3.4 ng/ml) (p not provided)			Serum	54
Willett 1983[49]	United States	13/26	GI	Mean selenium levels lower in GI cases (114 ng/ml) than controls (134 ng/ml) (p=0.01)			Serum	134
Case-Control Studies								
Fernandez-Banares 2002[40]	Spain	24/35	CR	Mean selenium levels lower in CR cases (41.9±4.3 ng/ml) than controls (64.9±6.3 ng/ml) (p=0.006)			Serum	89 in ≤60y 45 in >60y
	Spain	28/35	A	In subjects ≤60 years (n=30): Mean selenium levels lower in adenoma cases (57.9±4.3 ng/ml) than controls (88.9±8.0 ng/ml) (p=0.002)				
Ghadirian 2000[18]	Canada	92/202	CR	0.42	0.19–0.93	0.009	Toenails	0.91 ng/mg
Scieszka 1997[48]	Poland	25/25	CR	Mean selenium levels lower in CR cases (51.4±14.1 ng/ml) than controls (38.4±12.6 ng/ml) (p=0.0018)			Plasma	51
Russo 1997[45]	United States	37/36	A	0.24	0.06–1.04	0.09	Plasma	120
Nelson 1995[56]	United States	139/138	A	1.8	0.9–4.0		Serum	123
		25/138	CR	1.7	0.5–5.9			
Clark 1993[42]	United States	28/20	A	0.24	0.07–0.80	0.04	Plasma	128
Zhao 1990[53]	China	202/404	CR	Selenium levels lower in CR cases (135 ng/ml) than controls (150 ng/ml) (p<0.01)			Blood	150

^a Ecologic studies and observational studies using dietary questionnaires to assess selenium intake were excluded

^b A=adenoma, AR=adenoma recurrence, C=colon cancer, CR=colorectal cancer, GI=gastrointestinal cancer, R=rectal cancer

^c Mean (or median) selenium levels in controls only, serum and plasma selenium levels in ng/ml and toenail selenium levels in ng/mg

^d Number of colorectal cancer cases in selenium supplementation group/placebo group

^e Cases diagnosed during 1st year of follow-up were excluded. Results including all cases are for colon cancer (n = 216): OR, 0.79; 95% CI, 0.50–1.25; rectal cancer (n = 102): OR, 1.05; 95% CI, 0.57–1.94 for highest versus lowest quintile.