Review

Selenium and the prevention of prostate and colorectal cancer

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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 / Prostate cancer / Selenium / Selenoenzyme

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1 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.

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Abbreviations: CI, confidence interval; **GPX,** glutathione peroxidase; **OR,** odds ratio; **PLCO Trial,** Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; **ROS,** reactive oxygen species; **Sec,** selenocysteine; **SELECT,** Selenium and Vitamin E Cancer Prevention Trial; **SEPP1,** selenoprotein P

2 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, 1312 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, 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 resulting in 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

Table 1. Epidemiological studies on selenium and prostate cancer[a] – ordered by study design and publication year

1st Author, pub. Year, reference	Country	Cases/ controls	Results (RR comparing highest to lowest quantile)						Selenium assessment	
			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/ 34 412	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-significantly 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

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

results for colorectal cancer were marginally nonsignificant (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 led 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 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 μg/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: 1600 patients are randomized to 200 μg selenium or placebo and followed up for 3 – 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

Table 2. Epidemiological studies on selenium and colorectal cancer and adenoma[a] – ordered by study design and publication year

1st 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]	Netherlands	105[e]/ 2569	C	1.07	0.61 – 1.88	0.55	Toenails	0.535 in men;
		76[e]/ 2569	R	1.12	0.49 – 2.55	0.89		0.560 in women
Bostick 1993 [57]	United States	212/35 004	CR	0.60	0.27 – 1.32		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	CR- men	0.69	Not reported	ns	Serum	64
		59/118	CR- women	1.26	Not reported	ns		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	Serum/Plasma	162/148
Nomura 1987 [52]	Hawaii Japanese	82/293	C	0.56	Not reported	0.33	Serum	123
		32/293	R	0.63		0.66		
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
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 ≤ 60 y 45 in < 60 y
	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 first 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.

component was maintained. The recruitment of this trial has been completed in 2008 and results are expected about 3 years after the completion of recruitment.

3 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 nonsignificant 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 (GPXs), 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 GPXs, 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.

4 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 number 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 nonsignificant positive association (Table 2) [55, 56]. Additionally, a cohort study found a nonsignificant lower risk of colon cancer among selenium supplement users than nonusers (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 247–403 recurrent adenoma cases *per* study, showed a 25–40% 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 ($p_{trend} = 0.006$) [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 ($p_{trend} = 0.01$)

although the odds ratio (OR) was not significant [60]. This large study was the first 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, $p_{trend} = 0.82$) for nonsmokers, 0.84 (95% CI 0.53 – 1.33, $p_{trend} = 0.23$) for former smokers, and 0.53 (95% CI 0.27 – 1.01, $p_{trend} = 0.008$) 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.

5 Potential mechanisms that underlie an effect of selenium on cancer

A large body of experimental data support 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-κB (NF-κB), 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-κB promotes expression of anti-apoptotic genes and an *in vivo* study showed a reduced activation of NF-κB 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 involves several unique features, such as a hairpin loop, known as a Sec insertion sequence located in the 3′ untranslated region and several specific transacting 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 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 have an impact on prostate and colorectal cancers.

6 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, aging, and microbial gut flora.

7 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].

8 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 toward 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.

9 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 types of food varies up to ten-fold because of dif-

ferences 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 and 500 μg/day [165 – 170]. Despite this wide range, dietary selenium intake is considered to be adequate for the US 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].

10 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.

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