Review

Prostate cancer and vegetable consumption

Ruth Chan, Kris Lok and Jean Woo

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR

Epidemiological studies have shown marked variations in prostate cancer incidence and mortality across different geographic regions, leading to the rising interest in the role of nutrition in prostate cancer risk. There is also a large body of evidence that a diverse diet, rich in vegetables, can reduce the risk of prostate cancer. In this review, the role of various kinds of vegetables and their bioactive compounds associated with prostate cancer risk, and the underlying mechanisms of these associations are summarized. There is accumulating evidence to support the consumption of lycopene, in particular tomato and tomato-based products, as protective factors against prostate cancer. Evidence on the protective role of β-carotene was inconsistent from cohort and case–control studies. Evidence on the effect of pulses or soy consumption on prostate cancer risk was limited but suggestive of decreased risk with increased pulses or soy consumption. However, the role of vitamin C, vitamin E, allium vegetables, and cruciferous vegetables on prostate cancer risk remains to be determined due to limited evidence. Although the impact on prostate cancer risk differs among various vegetables and their constituent nutrients, the overall benefits of plant based diet on cancer prevention and other diet-related diseases should be promoted.

Keywords: Allium vegetable / Carotenoids / Cruciferous vegetable / Prostate cancer / Vitamins

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1 Introduction

Prostate cancer is the fifth most common cancer in the world (in the number of new cases) and the second most common cancer in men [1]. In 2002, the number of new cases of prostate cancer was estimated at 679 000 worldwide, and this disease accounts for 11.7% of all cancers in men (19% in developed countries and 5.3% in developing countries) [1]. Epidemiological studies have shown marked variations in prostate cancer incidence and mortality across different geographic regions [2, 3], leading to the rising interest in the role of nutrition in prostate cancer risk. Around the world, age-adjusted incidence rates range from more than 100 *per* 100 000 men in North America, parts of the Caribbean, and Oceania, to less than 10 *per* 100 000 in Melanesia and much of Asia (International Agency for Research on Cancer, Globocan 2002, http://www-dep.iarc.fr/). There is also a large body of evidence that a diverse diet, rich in vegetables, can reduce the risk of prostate cancer. Tomatoes and tomato products, cruciferous vegetables, legumes, and other plant-based nutrients may be beneficial for prostate cancer prevention [4]. Studies have linked the association of vegetable consumption with prostate cancer risk. However, results are inconclusive and vary with the study design [5], the types of vegetables consumed [6, 7], and the different criteria in categorizing vegetable groups [5]. A commonly cited mechanism for the beneficial effects of increased vegetable consumption on prostate cancer is antioxidant protection against deoxyribonucleic acid (DNA) and cell damage [8].

A comprehensive report on food, nutrition, physical activity, and prostate cancer has been recently published by the World Cancer Research Fund and the American Institute for Cancer Research titled Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective (Global Report) [8]. This review will examine (i) the evidence on the association between vegetable consumption and prostate cancer risk, and (ii) describe the underlying

Correspondence: Dr. Ruth Chan, Rm 426, School of Public Health, Prince of Wales Hospital, Shatin, N.T., Hong Kong SAR
E-mail: ruthchansm@cuhk.edu.hk
Fax: +852-2606-3500

Abbreviations: CI, confidence interval; **DNA,** deoxyribonucleic acid; **OR,** odds ratio; **PSA,** prostate-specific antigen; **RCTs,** randomized controlled trials; **RR,** relative risk

mechanisms for these associations, based on the 2007 Global Report [8] and other reviews [4, 9–20] or studies [21–33] not mentioned in the 2007 Global Report.

2 Methods

Published papers in the Global Report related to prostate cancer were retrieved from OVID Medline/Pubmed using the University library system. Details of selection criteria of studies and methods of assessment have been described in the Global Report [8]. In brief, the Global Report included references published between 1966 and 2006, which were searched from databases including OVID Medline, OVID Embase, Cochrane Databases (DARE, CDSR, and HTA), ISI Web of Science (including Science Citation Index), CAB abstracts, Lilacs, BIOSIS, Pascal, and Metaregister. Both epidemiological studies and experimental studies were included. Epidemiological studies covered descriptive studies, ecological studies, migrant studies, case–control studies, cohort studies, randomized controlled trials (RCTs) and meta-analysis. Experimental studies included human feeding studies and live animal models. *In vitro* studies were excluded for review in the Global Report. This review included evidence from epidemiological studies, which only limited to cohort studies, case–control (nested or true) studies and RCTs published in English or Chinese.

Further literature search from OVID Medline was performed to check for cohort studies, case–control studies and RCTs published between 2006 and 2008. The following key words were used in the primary search strategy: "prostate cancer," "prostatic neoplasms," "vegetables or vegetable," "tomato," "lycopene," "β-carotene," "legumes," "soy," "soy milk," "soy foods," "vitamin C," "ascorbic acid," "vitamin E," "allium," and "cruciferous." Only studies with dietary intake measured by questionnaires or interviews, and blood biomarkers were included. Dietary factors described in this review included tomato, tomato-based products, lycopene, β-carotene, legumes, soy and soy products, vitamin C, vitamin E, α-tocopherol, γ-tocopherol, allium vegetables, and cruciferous vegetables. Data on the association of serum/plasma level of lycopene, β-carotene, vitamin C, vitamin E, α-tocopherol, and γ-tocopherol, and prostate cancer risk were also presented.

Multivariate risk ratios adjusted for age and other risk factors were available in most publications, and were used in this review. Dietary factors are considered to be positively or negatively associated with prostate cancer risk when the relative risk (RR) or odds ratio (OR) estimate for the highest *versus* lowest exposure category was <1 (significantly decreased risk) or >1 (significantly increased risk) when $p< 0.05$. Association was defined as nonsignificant when the risk estimate $= 1$ or when the decreased or increased risk did not reach statistical significance.

3 Results and discussions

3.1 Characteristics of studies

Eighty-eight papers were retrieved based on the Global Report and 14 additional papers were included from further literature search. The 14 additional papers included results from 3 studies [23, 31, 32] that have also been mentioned in the Global Report and 10 studies [21, 22, 24–30, 33] that have not been included in the Global Report. Of the 102 papers reviewed, 29 were from cohort studies, 69 from case–control studies, and 4 from RCTs. Detailed references will be discussed in the later sections.

For cohort studies, baseline measurement was performed after 1980 with most studies. Cohort size varied from 189 to 673 706 men and the length of follow up years ranged from 4 to 33 years. Most studies included all stages of prostate cancer cases, except one by Giovannucci which excluded stage A1 cases [31, 34–36]. Most studies included symptomatic prostate cancer cases. To minimize bias in the adoption of prostate-specific antigen (PSA) screening [37], some studies repeated the analysis by excluding the PSA cases [27–29, 31, 34–36]. Similar results were reported in most studies after excluding the PSA cases [27, 31, 34–36].

For case–control studies (nested or true), the studies were conducted between 1957 and 2001. Most studies included all the stages of prostate cancer cases, except some with cases with specific staging [38–40]. Most studies included symptomatic prostate cancer cases. To minimize result bias from the adoption of PSA screening [37], some studies repeated the analysis by excluding the PSA cases or controlling for the screening practice [6, 25, 38, 39, 41–43]. Similar risk estimates of prostate cancer risk were reported in most studies after excluding the PSA cases [6, 38, 39, 41, 43] or adjusting for screening practice [25].

Among the four RCTs, two were conducted in USA [44, 45] and the other two were reported from Finland [46, 47]. The following supplements were studied in these trials: β-carotene [44], β-carotene with/without vitamin E [46, 47], and β-carotene with retinol [45]. All these studies included symptomatic prostate cancer cases.

3.2 Tomato products, lycopene, and prostate cancer

Lycopene is the most potent carotenoid antioxidant and the predominant carotenoid in plasma [48], various tissues [49], and the prostate gland [50]. The presence of lycopene in human plasma and tissues primarily results from the consumption of a variety of tomato products, such as tomatoes, spaghetti sauce, salsa, tomato soup, and ketchup [11].

Epidemiological studies have suggested the beneficial role of tomatoes on prostate cancer risk (Table 1). The Global Report summarized five cohort studies [34, 35, 51–53] and nine case–control studies [49, 54–61] on tomato

Table 1. Risk estimate of tomatoes, tomato based products, lycopene, and prostate cancer risk using dietary questionnaires or interviews and blood biomarkers to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Tomatoes									
Cohort studies	0.74	0.03	[34, 35]	NST		[51]	1.05	NS	[52]
	0.60	0.02	[53]						
	0.99 (total tomato servings)	0.36	[62]						
Case – control studies	0.64	0.04	[55]	1	0.29	[57]	1.01	0.30	[54]
	0.16	<0.01	[58]	NST	NS	[61]	1.07/1.08[b)]	0.85/ 0.78	[56]
	0.86	0.87	[59]						
	0.9[c)]	*0.35*	*[60]*				*1.10[d)]*	*0.57*	*[60]*
Tomato based products									
Cohort studies	0.65	0.01	[34]				1.12	NS	[52]
	0.77/0.72[e)]/0.65[b)]	<0.01/<0.001/0.02	[35]						
	0.75[e)]/0.64[f)]/0.66[b)]	≤0.05/NS/NS	[31]						
Case – control studies	0.8	0.03	[39]	1	0.29	[57]			
	0.82	0.93	[54]	NST	NS	[61]			
Dietary lycopene									
Cohort studies	0.6	NS	[63]						
	0.84	<0.01	[35]						
	0.98/0.92[b)]	0.58/0.98	[64]						
	0.82	0.06	[72]						
	0.95/0.82[g)]	*0.33/0.08*	*[28, 62]*				*1.11[b)]*	*0.80*	*[28, 62]*
Case – control studies	0.76	0.30	[54]				1.73	0.21	[41]
	0.18	<0.01	[58]				1.01	NS	[55]
	0.69	0.47	[66]				1.2	0.90	[71]
	0.17	<0.05	[32]				1.04	0.13	[73]
	CL[h)]	0.02	[67]						
	0.89	0.96	[6]						
	0.8	0.30	[39]						
	0.87	0.95	[65]						
	0.94	0.93	[68]						
	0.99	0.88	[70]						
	0.89	0.53	[26]						
	0.9[c)]	*0.35*	*[60]*				*1.1[d)]*	*0.57*	*[60]*
Serum/plasma lycopene									
Cohort studies	*0.97/0.40[b)]*	*0.41/0.05*	*[30]*				*1.40[j)]*	*0.50*	*[30]*
Case – control studies	0.75/0.56[b)]	0.12/0.05	[74]				1.04	0.83	[75]
	0.83 (CLUE I)/ 0.79 (CLUE II)	0.72/0.49	[43]				1.1	0.86	[76]
	0.67	0.01	[66]						
	0.65/0.79[g)]/0.37[b)]	0.09/0.36/0.04	[69]						
	0.66	0.33	[38]						
	0.46	0.08	[21]						
	0.96[b)]	*0.62*	*[25]*				*1.14*	*0.28*	*[25]*

NST, no significant trend; NS, not significant; NA, not available.

a) RR for cohort study, OR for case – control study, RR or OR without superscript refers to risk estimate of all cases in the study, italic row refers to contrast risk estimates reported in same study.
b) For advanced/aggressive cases.
c) For men of younger age.
d) For men of older age.
e) For organ-confined cases.
f) For minimally extraprostatic cases.
g) For nonadvanced/nonaggressive cases.
h) Cases with lower intake or level than controls.
i) For localized cases.
j) Cases with higher intake or level than controls.
k) Cases with similar intake or level to controls.

and tomato based products consumption and prostate cancer risk. Further literature search added two recent studies in this review [31, 62]. For tomato consumption, two cohort studies reported significantly decreased risk [34, 53] and three cohort studies reported nonsignificant association [51, 52, 62]. For case–control studies, two showed significantly decreased risk [55, 58] and five showed nonsignificant association [54, 56, 57, 59, 61]. The effect of subjects' age on prostate cancer risk was also estimated in one case–control study [60]. Le Marchand *et al.* (1991) reported different OR for subjects aged <70 years and 70 years or above (0.9 *vs*. 1.1) for increasing quartiles of tomato consumption. For tomato based products consumption, three cohort studies reported significantly decreased risk [31, 34, 35] and one reported no association [52]. The protective risk was more pronounced in advanced stage of prostate cancer as compared with organ-confined prostate cancer [31, 35]. Of the four case–control studies, only one showed significantly decreased risk [39] and three reported no association [54, 57, 61].

Although tomatoes and tomato products contain many nutrients and phytochemicals that are proposed to inhibit carcinogenesis, lycopene has received the most intense focus. The Global Report summarized three cohort studies [35, 63, 64] and 14 case–control studies [6, 39, 41, 54, 55, 58, 60, 65–71] on dietary lycopene intake and prostate cancer risk. Further literature search added two more recent cohort studies [28, 72] and three more case–control studies [26, 32, 73] in this review (Table 1). All five cohort studies showed decreased risk for the highest intake groups of lycopene when compared to the lowest [28, 35, 63, 64, 72], but only one reached statistical significance [35]. Of the 17 case–control studies, 3 reported significantly decreased risk for increasing intake [32, 58, 67], 12 showed nonsignificant association [6, 26, 39, 41, 54, 55, 65, 66, 68, 70, 71, 73], 1 did not report the OR [69], and 1 reported different OR (0.9 *vs*. 1.1) for the two age groups (<70 years *vs*. ≥70 years) [60].

In view of the inaccurate estimation of dietary intake of lycopene (*i.e*., incomplete lycopene content in food database, varied lycopene concentrations in different brands of tomato sauce), it is proposed that the measurement of lycopene concentration in blood may provide a useful link between dietary lycopene intake and risk assessment in epidemiological studies [11]. The Global Report summarized seven case–control studies on serum or plasma lycopene concentration and prostate cancer risk [38, 43, 66, 69, 74–76]. One cohort study [30] and two case–control studies [21, 25] were available from further literature search (Table 1). The cohort study failed to show significant association of increasing blood level of lycopene with prostate cancer risk and results were different for localized and advanced prostate cancer cases [30]. Only one of the nine case–control studies significantly showed a reduced risk with increasing blood level of lycopene [66]. The protective risk was more pronounced in advanced stage of prostate cancer as compared with organ-confined prostate cancer [69].

The underlying mechanism of tomato/tomato-based product consumption or lycopene on prostate cancer development and treatment can be shown by *in vitro* cell line studies. *In vitro* cell line studies have shown that lycopene inhibits the growth of prostate cancer cells through pathways that affect growth factor signaling and cell-to-cell communication *via* gap junctions [77, 78]. Lycopene is the most potent antioxidant in quenching singlet oxygen *in vitro*, as compared with other carotenoids [79]. The anticancer effect of lycopene is suggested to be due to its ability to interact with reactive oxygen species produced during metabolism of cells and inflammatory infiltrates [11]. Lycopene also induces apoptosis along with modulations in several biomarkers associated with prostate carcinogenesis [12, 80]. However, a study has shown that consumption of tomato powder but not lycopene inhibited prostate carcinogenesis, suggesting that tomato products contain other compounds that modify prostate carcinogenesis [81].

In conclusion, cohort and case–control studies showed inconsistent results for tomatoes or tomato-based products on prostate cancer risk. The protective effects of tomatoes or tomato-based products on prostate cancer risk were mainly supported by cohort studies but not case–control studies. For lycopene, there was some evidence mainly from case–control studies to support the protective role of increased dietary intake of lycopene or increased lycopene level in blood against prostate cancer, especially for advanced prostate cancer cases. These findings supported the conclusion from the Global Report, which stated that foods containing lycopene probably protected against prostate cancer.

3.3 β-Carotene and prostate cancer

Other than lycopene, β-carotene is another carotenoid being extensively studied for the possible roles in prostate cancer prevention. β-Carotene acts as an antioxidant and its chemopreventive effect has been proposed to be due to its ability in increasing resistance of LDL to oxidant stress [82]. Yellow orange vegetables including carrot, pumpkin, sweet potato, and some dark leafy vegetables, such as kale, spinach, and collards, are the main sources of β-carotene [83].

The Global Report reviewed five cohort studies [34, 51, 64, 84, 85] and 23 case–control studies [6, 39, 41, 54, 55, 58, 65–68, 71, 86–97] on dietary β-carotene and prostate cancer risk. One cohort study [29] and one case–control study [73] was available from further literature search (Table 2). None of the six cohort studies showed significant effect with increasing dietary β-carotene intake on prostate cancer risk [29, 34, 51, 64, 84, 85]. Of the 24 case–control studies, four reported significantly decreased risk for increasing intake [68, 93, 96, 97] and most reported no significant association (Table 2). One other study reported

Table 2. Risk estimate of β-carotene and prostate cancer risk using dietary questionnaires or interviews and blood biomarkers to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Dietary β-carotene									
Cohort studies	0.96	0.40	[29]	NST	NS	[51]	1.09	NS	[84]
							1.05	0.70	[34]
							1.03	0.88	[85]
	0.97[b)]	*0.54*	*[64]*				*1.09*	*0.79*	*[64]*
Case – control studies	0.80	0.40	[39]	1	0.79	[71]	CH[j)]	0.83	[91]
	0.34	0.25	[58]	1	0.05	[92]	1.09	0.54	[54]
	0.72	0.40	[65]				1.06	NS	[55]
	0.72	0.13	[6]				1.04	0.75	[90]
	0.44	0.35	[66]				1.02[c)]/1.52[d)]	0.94/0.20	[89]
	CL[h)]	0.52	[67]						
	0.72	0.02	[68]						
	0.97	0.72	[41]						
	0.28	<0.01	[97]						
	0.47	<0.05	[96]						
	0.90/0.82[b)]	0.55/0.38	[95]						
	0.94	0.50	[94]						
	0.60/0.30[c)]/0.96[d)]	<0.05/<0.05/NS	[93]						
	0.91	0.63	[73]						
	0.80[c)]/0.60[b+c)]	*NS/NS*	*[88]*	*1[b+d)]*	*NS*	*[88]*	*1.40[d)]*	*NS*	*[88]*
				1[c)]	*0.55*	*[87]*	*1.5[d)]*	*0.09*	*[87]*
	0.6 (Blacks)	*NS*	*[86]*	*1 (Whites)*	*NS*	*[86]*			
Serum/plasma β-carotene									
Cohort studies	0.96	NS	[98]						
	0.92	0.24	[30]						
Case – control studies	0.85	0.69	[75]	CS[k)]	NS	[104]	1.60	0.33	[76]
	0.78/0.36[c)]/0.99[d)]	0.49/0.03/0.69	[38]				CH	0.13	[91]
	0.91	0.94	[99]				1.64/1.54[g)]/1.61[b)]	0.22/0.20/0.41	[69]
	0.69/0.75[g)]/0.62[b)]	0.09/0.33/0.24	[100]				1.30/3.16[b)]	0.16/0.02	[25]
	0.60	NS	[101]				1.48	0.64	[21]
	0.43	0.45	[66]						
	0.77	0.47	[102]						
	CL	0.30	[103]						
	CL	0.40	[61]						
	0.94 (CLUE I)	*0.59*	[43]				*1.47 (CLUE II)*	*0.60*	*[43]*
β-Carotene supplement									
RCTs				1	0.62	[44]	1.01	0.95	[45]
							1.23	NA	[46, 47]
Cohort studies							1.33	0.14	[100]

NST, no significant trend; NS, not significant; NA, not available.
For definitions see footnote to Table 1.

different OR (0.6 *vs*. 1.0) for the Blacks and the Whites [86]. Two other studies reported different OR for different age groups [87, 88], with lower prostate cancer risk among younger subjects. Both cohort studies and case – control studies showed a more pronounced decreased risk in cases of advanced/aggressive stage [64, 88, 95].

For serum or plasma β-carotene, the Global Report reviewed 1 cohort study [98] and 14 case – control studies [38, 43, 61, 66, 69, 75, 76, 91, 99 – 104] on dietary β-carotene and prostate cancer risk. One cohort study [30] and two case – control studies [21, 25] were available from recent literature search (Table 2). All cohort studies showed nonsignificant effect of increasing blood level of β carotene [30, 98] on prostate cancer risk. Of the 16 case – control studies, 1 reported significantly decreased risk for younger men [38] and another reported significantly increased risk for advanced cases [25]. The remaining studies reported no association (Table 2).

Table 3. Risk estimate of flavonoids and prostate cancer risk using dietary questionnaires or interviews to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Dietary pulses/legumes									
Cohort studies	0.71 (pulses)	0.01	[52]	NST	NS	[51]			
	0.53 (beans, lentils, peas)	0.01	[53]						
	Higher consumption of soy-based products, beans, lentils and peas was associated with lower risk	<0.05	[106]						
Case–control studies	0.86 (beans)	0.88	[6]	NST	NS	[61]	1.1 (legumes)	0.85	[71]
	0.80 (legumes)	0.08	[39]	NST	0.50	[107]	CH[j)]	NS	[108]
	0.69 (beans, lentils, nuts, seeds)	0.03	[55]	1 (lentils, baked beans)	0.41	[57]	1.06 (legumes)	0.93	[24]
	0.62 (legumes)/ 0.74 (legumes)[b)]	<0.001/ 0.04	[56]						
	0.83 (total legumes)	0.09	[70]						
Dietary soy/soy products									
Cohort studies	0.79 (total soy intake)	0.23	[109]	NST	NA	[112]			
	0.88 (tofu)	0.51							
	0.94 (miso soup)	0.64							
	0.30 (soy milk)	0.02	[110]						
	0.35 (tofu)	*0.05*	*[111]*				*1.24 (miso soup)*	*NS*	*[111]*
	0.82 (soy food)	*0.18*	*[27]*				*1.04 (miso soup)*	*0.94*	*[27]*
Case–control studies	0.62/0.59[b)]	0.06/0.13	[56]				2.02	<0.01	[115]
	0.53 (all soy products)	0.11	[59]						
	0.47 (tofu)	0.16							
	0.25 (natto)	0.03							
	0.58 (tofu)	0.03	[113]						
	0.51 (combined soy foods)	0.06							
	0.95 (soy milk)	NS	[114]						
	0.8 (tofu or soy bean)	0.29	[57]						
	0.48 (isoflavones)	0.02	[26]						
	0.68 (genistein)	0.19							
	0.64 (daidzein)	0.12							
	0.52 (soy food)	0.34	[33]						

NST, no significant trend; NS, not significant; NA, not available.
For definitions see footnotes to Table 1.

Both cohort and case–control studies showed inconsistent results for dietary or serum/plasma β-carotene on prostate cancer risk, the effect of β-carotene on prostate cancer risk remains inconclusive. Evidence from supplementation trials also failed to demonstrate decreased risk with supplemental use of β-carotene [44–47, 100] (Table 2). A randomized trial of β-carotene (50 mg, alternate days) and aspirin in primary prevention of cancer and cardiovascular disease among 22 071 US male physicians was conducted in 1982 [44]. During the 13 years follow-up period, 1117 prostate cancers were detected. There were no significant differences with supplementation in prostate cancer risk (RR = 1.0, 95% confidence interval (CI) = 0.9–1.1).

In conclusion, evidence on the role of β-carotene from diet or blood biomarkers on prostate cancer risk was limited from cohort studies and mainly from case–control studies. Results from the cohort studies and case–control studies were inconclusive. There was no evidence to show a protective effect of supplemental use of β-carotene on prostate cancer risk based on supplementation trials. These findings were consistent with the conclusion of the Global Report. The Global Report documents that the existing evidence

fails to demonstrate a protective effect of β-carotene on prostate cancer risk, and it is unlikely that β-carotene supplements or foods containing it have a substantial effect on the risk of prostate cancer.

3.4 Flavonoids and prostate cancer

Flavonoids are polyphenolic compounds presenting a basic structure of 15 carbon atoms, comprising 2 aromatic rings bound through a 3 carbon chain (C6–C3–C6). This type of carbon skeleton, as well as the conformation of the central chain, is responsible for the chemical diversity of these compounds [13]. In nature, flavonoids are ubiquitously present in foods of plant origins [9]. Flavonoids are mainly classified into flavanols (catechins), flavonols, flavones, isoflavones, and anthocyanins [13]. The dietary flavonoids possess antioxidative and anti-inflammatory effects, and possibly some anticancer properties including suppression of angiogenesis, induction of apoptosis and down-regulation of hormone receptors expression [9, 13, 14].

Among the flavonoids, soy isoflavones, specifically genistein and daidzein, and equol have been identified as an important dietary component in reducing prostate cancer risk [4]. However, genistein has been studied more extensively for its role in prostate cancer prevention as compared to daidzein and equol. Genistein has been shown to inhibit growth of cancer cells through modulation of genes involved in homeostatic control of cell cycle and apoptosis [105]. Genistein could also inhibit activation of nuclear transcription factor, P13K/Akt and NF-κB signaling pathway, and regulate estrogen- and androgen-mediated signaling pathways in prostate carcinogenesis [15].

The Global Report reviewed four cohort studies [51–53, 106] and ten case–control studies [6, 39, 55–57, 61, 70, 71, 107, 108] on pulses (legumes) consumption and prostate cancer risk (Table 3). One case–control study was available from further literature search [24] (Table 3). For the four cohort studies, three reported significantly decreased prostate cancer risk for the increasing consumption of pulses/legumes [52, 53, 106] and one showed no association [51]. Of the 11 case–control studies, 2 reported significantly decreased risk [55, 56] and most did not find significant association [6, 24, 39, 57, 61, 70, 71, 107, 108] with prostate cancer risk.

For soy and soy product consumption, the Global Report reviewed four cohort studies [109–112] and six case–control studies [56, 57, 59, 113–115] on soy and soy product consumption and prostate cancer risk (Table 3). One cohort study [27] and two case–control studies [26, 33] were available from further literature search (Table 3). For the five cohort studies, one showed significantly decreased risk for the increasing consumption of soy and soy products [110], two showed nonsignificant association [109, 112], two reported different prostate cancer risk for different soy products [27, 111]. Three of the case–cohort studies reported significantly decreased risk [26, 59, 113], one showed significantly increased risk [115], and four studies reported nonsignificant association [33, 56, 57, 114].

In conclusion, although there were limited studies to examine the effect of pulses or soy consumption on prostate cancer risk, the evidence was suggestive of decreased prostate cancer risk with increasing consumption of pulses or soy consumption. The findings supported the conclusion of the Global Report that there was some evidence suggesting consumption of pulses (legumes) including soy and soy products, protected against prostate cancer.

3.5 Vitamins and prostate cancer

3.5.1 Vitamin C

Vitamin C is a potent antioxidant that scavenges reactive oxygen species and other free radicals capable of causing damage to lipids and DNA [116]. Well-known sources include citrus fruit and tomatoes. Other good sources include white potatoes, sweet potatoes, cabbage, broccoli, and other green and yellow vegetables, and fruits [83].

In animal studies, vitamin C has been shown to inhibit prostate tumor growth and viability in nude mice transplanted with both androgen-sensitive and -insensitive human prostate cancer cells [117]. Vitamin C, together with other vitamins, such as vitamins E and K_3 (a synthetic derivative of vitamin K_1) also inhibit surviving protein, a promoter of prostate cancer cell growth [118], and inhibit DNA synthesis [119]. Other proposed mechanisms of vitamin C on prostate cancer prevention include inducing apoptosis and reducing membrane lipid peroxidation by recycling of α-tocopherol radicals to α-tocopherol [16].

Results of epidemiological studies on the role of vitamin C and prostate cancer are, however, limited and inconclusive (Table 4). The Global Report reviewed 4 cohort studies [63, 64, 84, 85] and 12 case–control studies [40, 41, 65, 67, 90, 91, 96, 108, 120–123] on dietary vitamin C intake and prostate cancer risk. Further literature search added two cohort studies [29, 72] and one case–control study [73] on this aspect. Of the six cohort studies, all reported nonsignificant association between increasing consumption of vitamin C and prostate cancer risk [29, 63, 64, 72, 84, 85]. Of the 13 case–control studies, the results were inconsistent, with some reported significantly decreased risk [65, 121], and other studies showed significantly increased risk [40, 123] with increasing vitamin C intake.

Studies examining the association of serum/plasma vitamin C or the supplemental use of vitamin C on prostate cancer are also limited and inconclusive (Table 4). Two cohort studies [98, 124] and two case–control studies [40, 43] were reviewed in the Global Report for the association of serum/plasma vitamin C with prostate cancer risk. All these studies showed nonsignificant association of increasing level of vitamin C in blood with prostate cancer risk [40, 43, 98, 124]. For supplemental use of vitamin C, two cohort

Table 4. Risk estimate of vitamin C and prostate cancer risk using dietary questionnaires or interviews and blood biomarkers to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Dietary vitamin C									
Cohort studies	0.96	NS	[84]	1	0.65	[29]	1.15/1.24[b)]	0.19/0.32	[64]
							2.3	NA	[63]
							1.27	0.67	[85]
							1.02	0.90	[72]
Case – control studies	CL[h)]	0.29	[67]	CS[k)]	0.84	[91]	1.14	0.87	[41]
	0.99	0.56	[108]	NST	NS	[122]	1.20	NS	[90]
	0.92	0.56	[120]				CH[j)]	<0.05	[40]
	0.89	NS	[96]				2.32/1.77[e)]/3.41[d)]	<0.01/NS/<0.05	[123]
	0.63	0.02	[65]						
	0.61	<0.001	[121]						
	0.87	0.33	[73]						
Serum/plasma vitamin C									
Cohort studies	0.93	NS	[124]				1.34	NS	[98]
Case – control studies							1.02	0.76	[43]
							CH	NS	[40]
Vitamin C supplement									
Cohort studies	0.80/0.64[b)]	NS/NS	[64]	1	NS	[84]	1.01	0.98	[29]
Case – control studies	0.77	0.07	[42]	NST	NS	[125]			

NST, no significant trend; NS, not significant; NA, not available.
For definitions see footnotes to Table 1.

studies [64, 84] and two case – controls [42, 125] were reviewed in the Global Report whereas one additional cohort study [29] was available from further literature search. None of the five studies demonstrated significant effect of supplemental use of vitamin C on prostate cancer risk [29, 42, 64, 84, 125].

In conclusion, there was limited evidence to examine the role of vitamin C on prostate cancer risk. Most of the cohort studies and case – control studies failed to show the protective role of vitamin C on prostate cancer risk. The findings were consistent with the conclusion of the Global Report, stating that the role of vitamin C on prostate cancer risk remains to be determined due to limited evidence.

3.5.2 Vitamin E

Vitamin E is a family of naturally occurring fat-soluble vitamin compounds that include eight compounds with similar chemical and biological properties distributed between two major groups: the tocopherols and the tocotrienols [16]. Vitamin E is predominantly found in plant foods and certain animal foods. Plant foods, such as vegetable oils, nuts and nuts oil, green leafy vegetables, sweet potatoes, carrots, and tomatoes are good sources of vitamin E [83]. Vitamin E functions as the major lipid-soluble antioxidant in cell membranes. Several mechanisms have been proposed for vitamin E on prostate cancer prevention and treatment, including scavenging free radicals, inducing apoptosis, decreasing production of vascular endothelial growth factor by prostate cancer cells, inhibiting expression of PSA and androgen receptor mRNA, and inhibiting protein kinase C activity [16, 17].

However, epidemiological studies showed inconsistent results of the role of dietary vitamin E in prostate cancer (Table 5). The Global Report reviewed two cohort studies [64, 126] and 16 case – control studies [39 – 41, 55, 65 – 67, 70, 71, 95, 104, 107 – 109, 127, 128] on the role of dietary vitamin E in prostate cancer risk. Two additional cohort studies [22, 29] and one case – control study [73] were available from further literature search. None of the four cohort studies [22, 29, 64, 126] showed significant association of increased dietary vitamin E intake with prostate cancer risk. Results from the case – control studies were less consistent. Of the 17 case – control studies, three reported significantly decreased risk [71, 104, 107], one showed significantly increased risk [67], and other studies showed non-significant association [39 – 41, 55, 65, 66, 70, 95, 108, 109, 128] with increasing dietary vitamin E intake. One other study showed decreased risk for younger subjects [127] and another study reported decreased risk for dietary α-tocopherol but not for dietary γ-tocopherol intake [73].

Further studies relating serum/plasma vitamin E, α-tocopherol, and γ-tocopherol to prostate cancer risk also failed

to support the role of vitamin E in prostate cancer. Only six studies [40, 76, 99, 124, 129, 130] were retrieved from the Global Report and no recent study has been conducted in relation serum/plasma vitamin E and prostate cancer risk. All studies failed to show significant association between serum/plasma vitamin E and prostate cancer risk (Table 5), but it was shown that smokers with low plasma vitamin E level had significantly higher prostate cancer risk as compared to those with normal plasma vitamin E level or nonsmoker [124].

For serum/plasma α-tocopherol, four cohort studies [98, 126, 131, 132] and ten case–control studies [43, 66, 74–

Table 5. Risk estimate of vitamin E on prostate cancer risk using dietary questionnaires or interviews and blood biomarkers to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Dietary vitamin E									
Cohort studies	0.94/0.96[b)]	0.42/0.57	[64]				1.26	0.17	[126]
	α-Tocopherol		[22]						
	0.97/0.98[i)]/0.93[b)]	0.29/0.53/0.21							
	γ-Tocopherol								
	0.93/0.97[i)]/0.68[b)]	0.14/0.78/<0.01							
	α-Tocopherol		[29]						
	0.92	0.63							
	γ-Tocopherol								
	0.87	0.34							
Case–control studies	0.93	0.89	[70]	1	0.90	[39]	1.12	NS	[55]
	0.53	0.03	[107]				1.08	0.82	[65]
	0.38	0.06	[66]				2.40	0.04	[67]
	0.60	0.03	[71]				1.46	0.43	[41]
	0.91/0.89[b)]	0.74/0.52	[95]				1.30	0.09	[128]
	CL[h)]	0.04	[104]				CH[j)]	0.14	[108]
	0.85	NS	[109]				CH	NS	[40]
	0.48[c)]	*0.15*	*[127]*				*1.02[d)]*	*0.25*	*[127]*
	0.96 (α-tocopherol)	*0.15*	*[73]*				*1.06 (γ-tocopherol)*	*0.46*	*[73]*
Serum/plasma vitamin E									
Cohort studies									
	0.76 (nonsmoker with low plasma vitamin E level)	*NS*	*[124]*				*1.28 (smoker with normal plasma vitamin E level)*	*NS*	*[124]*
							3.26 (smoker with low plasma vitamin E level)	*<0.05*	
Case–control studies	0.90	0.64	[76]	1	0.90	[99]	1.20	0.87	[130]
	CL	NS	[40]	1	0.90	[129]			
Serum/plasma α-tocopherol									
Cohort studies	0.86	NS	[98]						
	0.98	0.80	[126]						
	0.43	0.58	[131]						
	Serum level was inversely associated with incidence of prostate cancer	<0.01	[132]						
	0.82	0.48	[30]						
	0.80/0.95[g)]/0.56[b)]	0.03/0.84/<0.01	[23]						
Case–control studies	0.59	0.04	[75]	CS[k)]	0.88	[91]	1.02	0.12	[66]
	0.58 (CLUE I)	0.11	[43]	1	NS	[129]	1.40	0.71	[76]
	0.78 (CLUE II)	0.46							
	0.49	0.05	[104]						
	0.67/0.59[b)]	0.11/0.09	[102]						
	0.64	0.37	[133]						
	0.64[b)]	*0.11*	*[74]*				*1.06*	*0.70*	*[74]*

Table 5. Continued

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Serum/plasma γ-tocopherol									
Cohort studies				NST	NS	[23]	1.33	0.34	[30]
Case – control studies	0.86	0.57	[75]				1.17	NS	[129]
	0.66	0.41	[66]						
	0.77 (CLUE I)	0.30	[43]						
	0.21 (CLUE II)	<0.01							
	0.70	0.27	[76]						
	0.57	0.08	[104]						
	0.25	0.01	[133]						
	0.98	*0.89*	*[74]*	*1*[b]	*0.96*	*[74]*			
Vitamin E supplement									
RCTs	0.66	NS	[46, 47]						
Cohort studies	0.97/0.99[i]/0.86[b]	0.90/0.61/0.11	[22]						
	0.97/0.91[b]	*0.81/0.61*	*[29]*						

NST, no significant trend; NS, not significant.
For definitions see footnotes to Table 1.

76, 91, 102, 104, 129, 133] were retrieved from the Global Report, and two additional cohort studies [23, 30] were available from further literature search (Table 5). Two of the six cohort studies reported significantly decreased prostate cancer risk with increasing serum/plasma α-tocopherol level [23, 132] whereas other studies showed nonsignificant association [30, 98, 126, 131]. Results from the case – control studies were similar, with one reported significantly decreased risk [75] and most showed no association [43, 66, 74, 76, 91, 102, 104, 129, 133]. The protective effect was more pronounced in advanced prostate cancer cases [74, 102].

Results relating serum/plasma γ-tocopherol to prostate cancer risk were slightly different from those of serum/plasma α-tocopherol level. Cohort studies showed nonsignificant association of increasing serum/plasma γ-tocopherol level with prostate cancer risk [23, 30]. Two of the eight case – control studies reported significantly decreased prostate cancer risk [43, 133] with increasing serum/plasma γ-tocopherol level and most showed nonsignificant association [66, 74 – 76, 104, 129] (Table 5).

The possible synergy between vitamin E and other antioxidants has also been investigated in supplementation trial. The effect of vitamin E on prostate cancer prevention has been examined in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial [46, 47]. The study enrolled 29 133 male smokers aged 50 – 69 years. For those receiving 50 mg α-tocopherol supplements over a mean period of 6.1 years, the prostate cancer incidence was 34% lower (95% CI = –48 to –14%) than those not receiving the supplements. However, nearly all subjects in this trial were current or past smokers, so it is unknown whether the results are applicable to nonsmokers [47]. Two cohort studies have been recently published to examine the effect of supplemental use of vitamin E on prostate cancer risk. Both studies failed to show the use of vitamin E supplements for reducing prostate cancer risk [22, 29] (Table 5).

Based on the inconclusive results of vitamin E from foods or supplements, the protective role of vitamin E against prostate cancer remains to be investigated. The findings supported the conclusion of the Global Report. The Global Report documented that evidence on vitamin E and prostate cancer risk was inconsistent and there was limited evidence suggesting that foods containing vitamin E protected against prostate cancer.

3.6 Allium vegetables and prostate cancer

Allium vegetables, including garlic, onions, leeks, chives, scallions, and shallots, are rich in flavonols and organosulfur compounds. Among allium vegetables, garlic has been most extensively studied in the past few decades. The main sulfur-containing constituents in garlic are the S-allylcysteines (SAC) [10]. When garlic is cut, chopped, or crushed, the clove's membrane disrupts and SAC sulfoxide is transformed enzymatically into allicin by allinase. The main component of the volatile oil are sulfur compounds including allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, and ajoene [18]. Several mechanisms have been reported to explain the chemopreventive effects of garlic-derived products on prostate cancer. These include apoptosis induction, carcinogens detoxification, cell cycle arrest, Akt inactivation, and reduction of PSA secretion [18, 134, 135].

Table 6. Risk estimate of allium and cruciferous vegetable consumption on prostate cancer risk using dietary questionnaires or interviews to measure exposure[a)]

Exposure	Effect estimate (RR or OR)								
	<1 (decreased risk)	*p*	Reference	=1 (no association)	*p*	Reference	>1 (increased risk)	*p*	Reference
Allium vegetables									
Cohort studies	0.95 (alliums)	0.90	[52]						
Case – control studies	0.70 (alliums)	<0.01	[39]						
	0.85 (onion)	0.65	[70]						
	0.64 (garlic)	0.13							
	0.29 (onion)	0.05	[136]						
	0.81 (garlic)	0.05							
	0.51 (alliums)	*<0.001*	*[7]*				*1.09 (leeks)*	*0.22*	*[7]*
	0.71 (onion)	*0.12*							
	0.47 (garlic)	*<0.001*							
	0.30 (scallions)	*<0.001*							
	0.83 (Chinese chives)	*0.44*							
Cruciferous vegetables									
Cohort studies	0.82	0.06	[52]	NST	NS	[51]	1.05 (broccoli) 1.09 (kale, mustard, chard)	0.17 0.54	[34]
	0.91/0.92[e)]	*0.13/0.13*	*[36]*	*1[f)]*	*0.76*	*[36]*			
Case – control studies	0.78/0.61[b)]	0.02/<0.001	[56]				1.06	NS	[123]
	0.59	0.02	[6]						
	0.90	0.57	[57]						
	0.85	NS	[55]						
	CL[h)]	NS	[108]						
	CL	<0.001	[58]						
	0.58 (cruciferous vegetables)	<0.01	[140]						
	0.72 (broccoli)	<0.01							

NST, no significant trend; NS, not significant.
For definitions see footnotes to Table 1.

A few population studies have been done to investigate the association between allium vegetables and prostate cancer risk (Table 6). The Global Report reviewed one cohort study [52] and four case – control studies [7, 39, 70, 136] on allium vegetable consumption and prostate cancer risk. No recent study was available from further literature search. Results from two case – control studies showed a significantly decreased prostate cancer risk with increasing allium vegetable consumption [7, 39]. One study was conducted in China to investigate the association of allium vegetables and prostate cancer risk [7]. The study showed that men with more than 10 g/day of allium vegetables had a reduced risk of prostate cancer compare with those who consumed less than 2.2 g/day (OR = 0.51, 95% CI = 0.34 – 0.76, p for trend <0.001). The effect of risk reduction was most pronounced for garlic and scallions, and for patients with localized prostate cancer than for those with advanced cancer.

Although animal and laboratory studies suggested the protective role of allium vegetables on prostate cancer risk, there were only few population studies to relate the intake of allium vegetables to prostate cancer risk. This review was consistent with the conclusion of the Global Report that the role of allium vegetables on prostate cancer risk remained to be determined due to limited evidence.

3.7 Cruciferous vegetables and prostate cancer

Cruciferous or *Brassica* vegetables, such as broccoli, cauliflower, Brussels sprouts, cabbage, bok choy, collard greens, and kale, are rich in sulforaphane and indole-3 carbinol (I3C) [19]. These phytochemicals possess anticarcinogenic properties, such as induction of cell cycle arrest, inhibition of tumor invasion and angiogenesis, anti-inflammatory activity, inhibition of extracellular signal-regulated kinases, proteasome degradation, and alteration of phase I and phase II biotransformation enzyme expression [10, 19, 20]. Sulforaphane has also been shown to have proapoptotic properties in prostate cancer cells *in vitro* and *in vivo* [137, 138], and I3C has antiproliferative and antimetastic properties in animal models of prostate cancer [139].

Several epidemiological studies have been done to examine the associations of cruciferous vegetables and prostate cancer risk (Table 6). The Global Report reviewed four cohort studies [34, 36, 51, 52] and eight case – control stud-

ies [6, 55 – 58, 108, 123, 140] on cruciferous vegetable consumption and prostate cancer risk. No recent study was available from further literature search. Results from the cohort studies failed to show the protective effect of cruciferous vegetable consumption on prostate cancer risk (Table 6). Results of case – control studies suggested a protective role of cruciferous vegetables on prostate cancer risk. Four of the eight case – control studies showed significantly decreased prostate cancer risk with increasing cruciferous vegetable intake [6, 56, 58, 140] (Table 6).

Cohen *et al*. [6] studied the associations of fruit and vegetable intakes with prostate cancer risk in a population-based, case – control study of men under 65 years of age from Seattle area, United States. Six hundred twenty-eight cases newly diagnosed with prostate cancer and 602 controls were included. Self-administered food frequency questionnaire were used to assess diet over the 3 – 5-year period before diagnosis or recruitment. The OR (95%CI) for comparison of cruciferous vegetable consumption of ≥3 servings *per* week with <1 serving *per* week was 0.59 (0.39 – 0.90), p for trend = 0.02. The results suggested that high consumption of vegetables, particularly cruciferous vegetables, was associated with a reduced prostate cancer risk.

Kolonel *et al.* [56], in a multiethnic case – control study completed in United States and Canada, compared diet of 1618 cases <85 years of age identified from population-based tumor registries with 1618 controls. The OR (95% CI) comparing lowest with higher quintiles of cruciferous vegetable intake were 1, 1.10 (95% CI = 0.88 – 1.37), 0.90 (95% CI = 0.72 – 1.13), 1.04 (95% CI = 0.83 – 1.31), and 0.78 (95% CI = 0.61 – 1.00), p for trend = 0.02. The contrast was evidently greater when restricted to men with advanced diseases with lowest to highest quintile of cruciferous vegetable intake, with OR of 0.61 (95% CI = 0.42 – 0.88), p for trend = 0.0006.

In conclusion, cohort studies provided little evidence on the protective role of cruciferous vegetable consumption on prostate cancer risk whereas there was limited evidence from case – control studies to show the beneficial role of cruciferous vegetable consumption on prostate cancer risk. This review supported the conclusion of the Global Report that the role of cruciferous vegetables on prostate cancer risk remained to be determined due to limited evidence.

3.8 Considerations for data interpretation

Several biological and methodological issues should be considered in relating vegetable intake and prostate cancer risk in this review. First, some factors may be important in the context of other exposures, such as smokers *versus* non-smokers. Second, different techniques of prostate cancer diagnosis and screening have been used across the studies. The impact of vegetables and associated nutrients may vary for different stages of prostate cancer development. Most studies did not differentiate the associations between dietary factors and prostate cancer risk between latent and clinically apparent or advanced/aggressive prostate cancer. Therefore, the biological heterogeneity in prostate cancer across studies may limit comparisons. Third, variations in length of study, study design, and classification of vegetables, the completeness of questionnaires for dietary assessment, and the confounding factors may limit comparison of results across studies.

4 Concluding remarks

Increasing knowledge of prostate cancer has led to a view that prostate cancer is a preventable disease. Because of the long latency period of this disease, the role of diet has gained considerable attention. Over the past decades, there is accumulating body of evidence from epidemiological studies supporting the role of tomato products and lycopene on prostate cancer risk. As with the Global Report, this review supports that there is probably decreased prostate cancer risk with the increased consumption of lycopene, in particular tomato and tomato-based products. Although there are limited studies to examine the effect of pulses or soy consumption on prostate cancer risk, both the Global Report and this review show a suggestive of decreased risk with increased pulses or soy consumption. However, the role of vitamin C, vitamin E, allium vegetables, and cruciferous vegetables on prostate cancer risk remains to be determined due to limited evidence. Few RCTs have been conducted to relate vegetables and their constitute nutrients to prostate cancer risk, and these trials focused on limited nutrients, such as β-carotene and vitamin E. Diet is a complex composite and it is likely that various vegetables and their constituent nutrients act in synergy in the context of a whole diet. This review shows that the impact on prostate cancer risk differs among various vegetables and their constituent nutrients. Diet recommendation therefore should not be targeted at increasing or decreasing consumption of a specific vegetable or nutrient. Instead, the overall benefits of plant based diet on cancer prevention and other diet-related diseases should be promoted. As with diet recommendations for general health promotion from various advisory groups, a balanced diet with daily intake of at least 240 g (~2.5 cups) of a variety of vegetables (dark green, orange, legumes, starchy vegetables, and other vegetables) is recommended. Further studies are needed to investigate the underlying molecular pathways by which vegetables and their constituent nutrients may prevent the development of prostate cancer. More efforts are required to identify appropriate surrogate biomarkers for prostate cancer. Information on PSA screening, tumor stage and grade should also be incorporated in analyses for future studies.

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