COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Third draft statement on vitamin E and the risk of prostate cancer

1. The Committee considered a review of the literature on vitamin E and the risk of prostate cancer at their meeting in July 2012. Members agreed that a draft statement should be produced which was reviewed at their meeting in September 2013 and July 2014. Minutes from the meeting held in July 2014 can be found in Annex 1. Following comments from the Committee, a revised draft statement is presented in Annex 2.

2. Members are invited to comment on the third draft statement on vitamin E and the risk of prostate cancer in Annex 2. This is followed by a draft Executive Summary at Annex 3 and a draft Lay Summary at Annex 4, as requested at the last meeting.

Secretariat
October 2014

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Third draft statement on vitamin E and the risk of prostate cancer

Minutes from the meeting held on the 17th July 2014

"Second draft statement on vitamin E and the risk of prostate cancer (CC/2014/09)

7. The Committee considered a review of the literature on vitamin E and the risk of prostate cancer at their meeting in July 2012. This was prompted by the publication of the SELECT study[1] that found a positive relationship between supplementation with vitamin E and the incidence of prostate cancer. A draft statement on the topic was reviewed at the COC meeting in September 2013. This paper was a revised draft statement incorporating the comments and changes suggested at the September 2013 meeting. An updated literature search had been carried out for years 2013 and 2014 to identify any new publications since the previous draft statement was seen by the Committee and these studies were included in the paper. Members were asked to consider a new annex containing a table summarising the studies on vitamin E and risk of prostate cancer described in the statement. Three forest plots of the epidemiological studies (randomised controlled trials, prospective cohort and case-control studies) were tabled at the meeting to illustrate the spread of the data.

8. The review was commended by Members and it was suggested that the paper should be published in the peer-review literature. Members provided a number of general comments on the current draft, including the need for an executive summary and a lay summary. It was also noted that there was a need for a clear introduction to the topic explaining why this review was undertaken.

9. Members discussed the incidence of prostate cancer and how it had increased over the last 30 years due to both more screening, the aging population and greater awareness. It was noted that, despite the fact that the incidence of prostate cancer is much higher in the US, where regular screening occurs, compared to the UK, the mortality rate is the same in the two countries.

10. For the observational studies, it was not clear if the risk estimates had been adjusted for possible confounders. It was agreed that either an additional paragraph on confounders would be included in the statement or the tables would be amended to include a column stating the adjustment factors used for each risk estimate. It was noted that the uncertainties in the etiology of prostate cancer made it difficult to accurately control for variables.

[1] Klein EA et al. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 306(14):1549-56.

11. The tabled forest plots were discussed and it was suggested that the data on the different forms of Vitamin E be presented separately. Similarly the data on smokers and non-smokers should be presented separately. It was agreed that the forest plots were presented as illustrative diagrams and a pooled analysis would not be performed on the data.

12. The Committee suggested that the statement should clearly indicate what form of vitamin E was being referred to when the term was used. Similarly the doses used should be reported consistently, and information on the level of Vitamin E should be provided where it acts as a pro-oxidant in humans as opposed to an antioxidant. With respect to the animal studies, Members were concerned that the doses of Vitamin E used were very high, and clarity was needed on the relevance of these high doses to human exposures and what the effective dose would be in animals compared to in humans.

13. It was agreed that a revised draft statement would be brought back to the Committee at a later date."

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Third draft statement on vitamin E and the risk of prostate cancer

COC/2014/xx – November 2014

Introduction

1. The Food Standards Agency requested that the Committee review the information available on vitamin E and the risk of prostate cancer, including epidemiological, animal and *in vitro* studies on this topic in the light of the results from the SELECT study.

2. Vitamin E is an antioxidant and may help control cell damage that can lead to cancer. While some *in vitro* studies, animal experiments as well as some observational and intervention studies in humans had indicated that vitamin E could prevent and reduce the risk of prostate cancer; other studies have shown no significant association. Results from the selenium and vitamin E cancer prevention trial (SELECT), which investigated the hypothesised chemoprotective effects of selenium and vitamin E, suggested that vitamin E supplementation in the general population of healthy men significantly increased the risk of prostate cancer (Klein *et al* 2011). SELECT is the first study that has reported an increased risk of prostate cancer with vitamin E supplementation (Klein *et al* 2011).

3. Prostate cancer is the most common cancer in men in the UK, accounting for a quarter of all new cases of cancer in males. Prostate cancer incidence is strongly related to age, family history of prostate cancer and racial background (more common in black Caribbean, black African, and mixed race men than it is in white or Asian men). Other factors that influence the incidence are genetic susceptibility and androgen metabolism as well as lifestyle factors such as smoking, exercise and body size. The incidence of prostate cancer in the UK has increased in recent years but much of this increase may be attributed to improved detection as a result of screening and increased awareness (Cancer Research UK, 2012). Previously many asymptomatic prostate cancer cases would have remained undetected. Longer lifespan and a stable mortality rate may also contribute to this apparent increase in incidence.

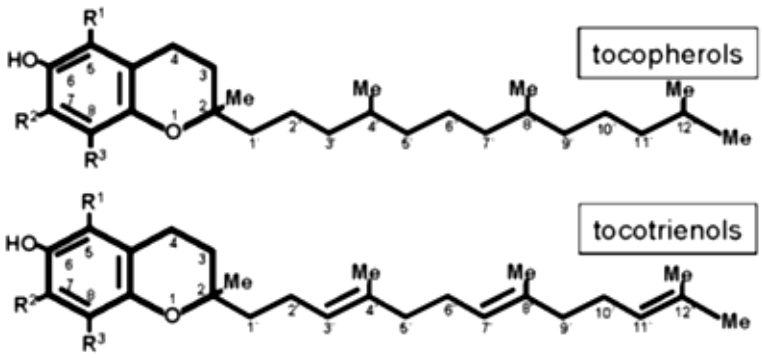
4. Studies have shown that dietary factors such as fat, protein and fibre intake could affect the aetiology of prostate cancer; dietary fat for instance has been associated with increased prostate cancer risk (Dagnelie *et al*, 2004). Consumption of plant-based foods such as tomatoes, soy, cruciferous vegetables such as broccoli, cauliflower and Brussels sprouts have shown an inverse association with risk of developing prostate cancer. Epidemiological studies have also indicated that vitamins and other nutrients may have roles in preventing and inhibiting growth of prostate cancer. Soy, isoflavones, polyphenols, lycopene and antioxidant vitamins

(A, C and E) as well as minerals like calcium, iron and selenium have been studied for their potential in preventing and reducing the risk of prostate cancer (Crawford, 2003 and Grönberg, 2003).

Vitamin E - sources, structure and stereoisomers

5. Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds. Vegetable oils and vegetable oil-containing products such as margarine, mayonnaise and shortening are the richest sources of natural vitamin E in the diet, followed by whole-wheat products and nuts. Vitamin E is also present in small quantities in a wide range of foods including vegetables, milk, animal fat and egg yolk.

6. At least eight different tocopherols and tocotrienols have vitamin E biological activity; all sharing a common 6-hydroxychroman ring and a long, saturated phytyl side chain structure (see Figure 1). The tocopherols (α-, β-, γ- and δ-) differ in the number of methyl groups on the chroman moiety and are characterized by a fully saturated phytyl chain, while the tocotrienols represent the same α-, β-, γ- and δ - moieties but with three unsaturated chain bonds in the hydrocarbon tail.



	R1	R2	R3
α-	-Me	-Me	-Me
β-	-Me	-H	-Me
γ-	-H	-Me	-Me
δ-	-H	-H	-Me

Figure 1: Structure of vitamin E (tocopherols and tocotrienols)

7. Tocopherols are most commonly found in nuts and vegetable oils, whereas tocotrienols are primarily derived from palm oil, oat, rye, wheat germ, barley and rice bran. α-Tocopherol is the predominant tocopherol in European diets, whereas a standard American diet contains larger amounts of γ-tocopherol due to high intake of soybeans and corn oil (Barve *et al*, 2009 and Key *et al* 2007).

8. Tocopherols have three chiral centres, and in nature, exist as the *RRR* stereoisomers (*RRR*-α, *RRR*-β, *RRR*-γ and *RRR*-δ tocopherols[2]. The corresponding tocotrienols have one chiral centre, occurring in nature as the *R* stereoisomers. The most active and bioavailable form is *RRR*-α-tocopherol (formerly called *d-α-*

[2] The eight possible stereoisomers for each tocopherol are the *RRR, SRR, RRS, RSS, RSR, SSR, SRS* and *SSS* forms.

tocopherol); it is also among the most abundant and is widely distributed in nature and is the predominant form in human tissues.

9. Vitamin E activity is expressed as *RRR*- α-tocopherol equivalents, which accounts for about 90% of the activity in human tissue; the relative potency of α-, β-, γ-, and δ-tocopherol is reported to be approximately 100:50:25:1 (IOM, 2000).

10. The nutritional requirement for vitamin E is met by the naturally occurring form (*RRR*) and the other three synthetic 2*R*-stereoisomer forms (*RRS*, *RSR* and *SRR*) of α-tocopherol. The other naturally occurring forms of vitamin E (β-, γ- and δ-tocopherols and the tocotrienols) do not contribute towards the vitamin E requirement because (although absorbed) they are not converted to α-tocopherol by humans and are recognized poorly by the α-tocopherol transfer protein (α-TTP) in the liver.

11. Synthetic α-tocopherol is the form of vitamin E that is present in most nutritional supplements. It is designated *all-racemic*-α-tocopherol (all-rac-α-tocopherol; formerly referred to as *dl*-α-tocopherol) and is an equimolar mixture of the 8 stereoisomers. All eight stereoisomers of α-tocopherol have an identical chromanol group and similar antioxidant properties, yet only four of them are retained in the body. Synthetic α-tocopherol has one-half the activity of *RRR*-α-tocopherol found in foods or present with the other 2*R* stereoisomeric forms (*RRS*-, *RSR*- and *SRR*-) of α-tocopherol in fortified foods and supplements. α-Tocopherol is often esterified to prolong its shelf life while protecting its antioxidant properties. In healthy humans, the body hydrolyses and absorbs these esters (α-tocopheryl acetate and succinate) as efficiently as α-tocopherol. The commercially available synthetic *all-rac*-α-tocopheryl acetate has the activity of 0.67 x *RRR*-α-tocopherol. For practical purposes, 1 International Unit (IU) of vitamin E is referred to as 1 mg of *all-rac*-α-tocopheryl acetate (IOM, 2000).

Vitamin E – intakes and reference values

12. The Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that daily intakes of 4 mg and 3 mg of α-tocopherol equivalents could be adequate for men and women respectively (COMA, 1991). Intakes of 3.8 - 6.2 mg/day appeared to be satisfactory for pregnant and lactating women.

13. The daily average and high-level (97.5th percentile) intake of vitamin E from food and supplements by men aged 19-64 years in the UK as estimated from the National Diet and Nutrition Survey (NDNS)[3] is 10.2 mg and 18.6 mg respectively (PHE, 2014). Plasma α-tocopherol concentrations can be used as a measure of vitamin E status. It has been suggested that 14 μmol/L (6 mg/L) is an adequate plasma α-tocopherol concentration (IOM, 2000). In the NDNS, the mean plasma α-

[3] The National Diet and Nutrition Survey (NDNS) is a continuous cross-sectional survey, designed to assess the diet, nutrient intake and nutritional status of the general population aged 18 months upwards living in private households in the UK.

tocopherol concentration of 19 - 64 year old men was 32.8 (± 11.5) µmol/L (14.1 ± 4.9 mg/L) (PHE, 2014).

14. Vitamin E supplements are widely available both individually and as a part of multivitamin supplements. Single dose capsules with varying amounts of vitamin E up to 670 mg are available and multivitamin supplements contain from 2 mg to 83.9 mg all-rac-α-tocopherol.

15. The Expert Group on Vitamins and Minerals (EVM) established a safe upper level of consumption of 540 mg RRR-α-tocopherol equivalents/day over a lifetime, based on the absence of adverse effects in human volunteers taking 536 – 1072 mg of vitamin E per day (EVM, 2003). The EU Scientific Committee on Food (SCF) derived a Tolerable Upper Level (TUL) of 300 mg based on the same data (no observed adverse effects at 540 mg) incorporating an uncertainty factor of two, and rounded to 300 mg/day (EFSA, 2006).

16. The Department of Health advises that the best way for most people to get the required vitamin E is by eating a balanced, varied diet.

Absorption, distribution, metabolism and excretion of vitamin E

17. Tocopherols and tocotrienols are absorbed equally well in the intestine via a nonsaturable, non-carrier-mediated passive diffusion process and are secreted with chylomicrons into the lymph. In the liver, α-TTP selects α-tocopherol from the available tocopherols for incorporation into VLDL (very-low-density-lipoprotein). α-Tocopherol-enriched lipoproteins are then secreted into the circulation and delivered to peripheral tissues.

18. α-TTP exhibits little affinity for the other vitamin E isomers and they are metabolized to a large extent and excreted through bile and urine. (Brigelius-Flohé *et al* 1999, 2002; Blatt *et al*, 2001, 2004)

19. Thus, the bioavailability and bioequivalence of the different forms of vitamin E differ. For example even where the amount of γ-tocopherol in the diet is higher than that of α-tocopherol, the plasma γ-tocopherol concentration is only ≈ 10% of that of α-tocopherol, which is the most abundant in plasma. There are also various differences in uptake between the different chemical forms of tocopherol with, for example, synthetic *all-rac*-α-tocopherol increasing plasma α-tocopherol concentrations only half as much as the equivalent dose of *RRR*-α-tocopherol (Brigelius-Flohé *et al*, 2002).

20. Tocopherol uptake varies between individuals. The underlying reasons are unknown but may include variations in α-TTP activity, metabolic rate, dietary lipid content and composition, the status of other micronutrients that recycle α-tocopherol and environmental conditions (Brigelius-Flohé *et al*, 2002).

21. Single doses (364 – 1092 mg) of all-rac-α-tocopherol resulted in peak plasma concentrations at 12 - 24 hours, repeated administration (28 days) resulted in a steady state by days 4 - 5 of supplementation (Dimitrov *et al*, 1991). The plasma

concentrations returned to baseline values 12 - 20 days after supplementation ceased. The plasma elevation of α-tocopherol was affected by dietary fat intake, with significantly higher levels in individuals consuming a high-fat diet.

22. Vitamin E is extensively metabolised before excretion. After supplementation with *RRR*-α-tocopherol, 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (α-CEHC) was the major urinary metabolite (Schultz *et al* 1995, Brigelius-Flohé *et al* 1999, 2002). This metabolite is analogous to the metabolite of δ-tocopherol found previously in rats and that of γ-tocopherol in human urine. The total degradation of *all-rac*-α-tocopherol to α-CEHC is 3-4 times that of *RRR*-α-tocopherol. Identification of the immediate precursors of CEHC led to the proposed pathway of side-chain degradation via ω- and β- oxidation shown in Figure 2.

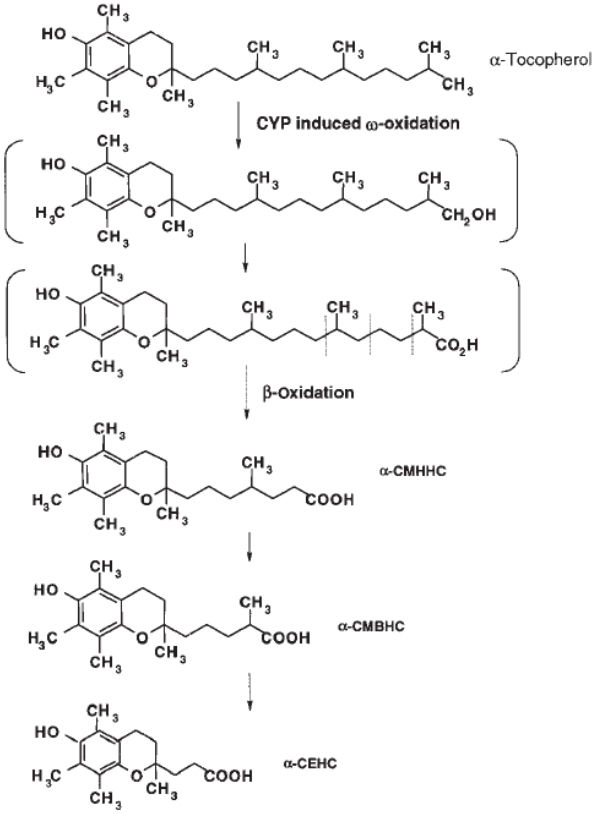


Figure 2: Proposed pathway of side-chain degradation of α-tocopherol via ω- and β-oxidation (from Brigelius-Flohé *et al* 2002)

23. α-Tocopherol can be oxidized to the tocopheroxyl radical-one-electron oxidation product, which can be reduced back to the unoxidised form by reducing agents such as vitamin C. Further oxidation of the tocopheroxyl radical forms tocopheryl quinone, the two-electron oxidation product. The tocopheryl quinone is not converted in any physiologically significant amounts back to tocopherol. Other oxidation products, including dimers and trimers as well as adducts, are formed during in vitro oxidation; their importance in vivo is unknown (Traber and Stevens, 2011).

Anti-cancer activity of Vitamin E

24. The possible role of antioxidant vitamins in the prevention of cancer has been the subject of numerous studies. It was first suspected that vitamin E had chemopreventive properties when studies showed that people in the Mediterranean area, who consume diets rich in vitamin E isoforms, have a lower risk of colon cancer than people in Northern Europe and the USA (reviewed by Constantinou *et al*, 2008).

25. Vitamin E may influence the development of cancer through several mechanisms. α-Tocopherol is a major lipid-soluble chain-breaking antioxidant, which protects cell membranes and DNA from free radical damage that may lead to malignant transformation (Klein *et al*, 2000). It has a strong inherent potential for autoxidation of highly reactive and genotoxic electrophiles, such as hydroxyl, superoxide, lipid peroxyl and hydroperoxyl, and nitrogen radicals, thereby preventing propagation of free radical damage in biological membranes, and decreasing mutagenesis and carcinogenesis (Burton and Ingold, 1981).

26. Vitamin E also blocks nitrosamine formation. α-Tocopherol inhibits protein kinase-C activity (Mahoney and Azzi, 1988) and the proliferation of smooth muscle cells (Chatelain *et al*, 1993) and melanoma cells (Ottino *et al*, 1997), thus possibly affecting tumour growth or aggressiveness. Vitamin E also induces the detoxification enzyme NADPH: quinone reductase in cancer cell lines (Wang *et al*, 1995), and inhibits arachadonic acid and prostaglandin metabolism in cultured keratinocytes. Effects on hormones that can increase cellular oxidative stress and proliferative activity and on cell-mediated immunity have also been reported (Traber and Packer, 1995).

27. *In vitro* studies suggest that vitamin E can inhibit the growth of certain human cancer cell lines, including prostate, lung, melanoma, oral carcinoma and breast. Animal experiments show prevention of various chemically induced tumours, including hormonally mediated tumours (Israel *et al*, 1995). *In vivo* and *in vitro* studies have shown that vitamin E inhibits growth and induces apoptosis only in carcinoma cells or transformed cells, but not in normal cells. Mechanistic studies indicated that it induces apoptosis through targeting multiple molecules/signalling pathways, including transforming growth factor-β (TGF-β), Fas (CD95/APO-1), the c-Jun N-terminal kinase (JNK), mitogen-activated protein kinase (MAPK), and Bcl-2 family in various types of carcinoma cells. In addition to pro-apoptotic function, the antitumor activity occurs through blocking cell cycle progression, inducing differentiation, inhibiting invasion and suppressing angiogenesis *in vitro* and/or *in vivo* (Ni *et al*, 2007).

28. Investigations specifically on prostate cancer have shown that the growth of prostate tumours has been slowed by vitamin E *in vitro* as well as *in vivo* (rats and transgenic mice and rat models). For example studies looking at possible mechanisms of action on prostate cancer cell lines have suggested that vitamin E has the potential to trigger both caspase-dependent and -independent DNA damage (Constantinou *et al*, 2012). It was proposed that vitamin E (10 μM α-tocopherol

succinate) may suppress androgen/ androgen receptor (AR)-mediated cell growth and prostate specific antigen (PSA) expression by inhibiting AR expression at both the transcription and translation levels (Zhang *et al*, 2002). It was found that the inhibition was through a G1/S arrest mediated by vitamin E at concentrations of 10-20- μM and significant decrease of the expression of the cell cycle regulatory proteins cyclin D1, D3, and E, cyclin-dependent kinases - cdk2 and 4, but not cdk6 and reduced cdk4 kinase activity, retinoblastoma phosphorylation, and cyclin E mRNA expression (Ni *et al*, 2003). In the case of *RRR*-γ-tocopherol, it was also shown that growth arrest (40%) and PPAR γ[4] mRNA and protein upregulation was achieved in 6 hours (Campbell *et al*, 2009). Proteins downstream of the PPAR γ - cyclin D1, cyclin D3, bel-2 and NF*κ* B proteins were also found to be downregulated following γ-tocopherol treatment, indicating the growth arrest follows a PPAR-γ-dependent mechanism. Other mechanistic studies have shown that 25-100 μM γ-tocopherol induces cell death in a prostate cancer cell line by interrupting *de novo* synthesis of sphingolipids (Jiang *et al*, 2004). It was also suggested that the anti-cancer effect was due to the up-regulation of insulin-like growth factor binding protein-3 (IGFBP-3) mediated by vitamin E ([with 20 μM/L RRR-α-tocopherol succinate] Yin *et al*, 2007).

29. Results from α-tocopherol supplementation studies in human volunteers suggested that the anti-tumour activity was through inhibition of tumour angiogenesis. Serum vascular endothelial growth factor levels (VEGF, a cytokine integrally involved in angiogenesis) were significantly reduced in men who had received the supplement (ATBC study, Woodson *et al*, 2002).

30. ***Other isoforms of tocopherol:*** Reports in the literature have suggested that the other isoforms of tocopherol and the tocotrienols may have important anticancer properties (Ju *et al*, 2010, Jiang *et al*, 2001). It has been postulated that γ-tocopherol is a powerful nucleophile that traps electrophilic mutagens forming stable carbon-centred adducts through the nucleophilic 5-position, which is blocked in α-tocopherol (Christen *et al*, 1997). *In vitro* studies have also shown that 25-50 μM γ-tocopherol exhibits a more significant growth inhibitory effect than 25-50 μM α-tocopherol (Torricelli *et al*, 2012) with the inhibition of cell proliferation, cell cycle progression and DNA synthesis in prostate cancer cells better than with α- tocopherol using the same concentrations (Gysin *et al*, 2002).

31. ***Tocotrienols:*** These vitamin E isoforms with unsaturated side chains also possess antioxidant activity and have been shown to display stronger anticancer potential *in vitro* than tocopherols, with γ- and δ-tocotrienols exhibiting greater potency of cancer preventing effects than α-tocotrienol (Ju *et al*, 2010, Constantinou *et al*, 2012). Their anticancer activity may be independent of the antioxidant activity because some redox-silent tocotrienol derivatives still exhibit anticarcinogenic properties. Tocotrienols have been shown to suppress proliferation and induce apoptosis in a wide variety of tumour cells including those of the prostate (Aggarwal *et al*, 2010, Patel, 2011). A number of mechanisms have been suggested for the

[4] PPAR γ is peroxisome proliferator-activated receptor γ, a nuclear receptor involved in fatty acid metabolism as well as modulation of cell proliferation and differentiation.

anticarcinogenic action of tocotrienols such as antiproliferative effect, induction of apoptosis, modulation of cell cycle, antioxidant activity, inhibition of angiogenesis, and suppression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase activity both *in vivo* and *in vitro* (Wada, 2012).

32. Several *in vitro* and animal studies as well as studies on human volunteers have been carried out examining the effect of vitamin E on prostate cancer. These are summarised in the following paragraphs.

Vitamin E and prostate cancer - *in vitro* studies

33. *In vitro* studies with human prostate carcinoma cell lines have shown that tocopherols and tocotrienols have anti-proliferative action. Tocopherols and their esters significantly inhibited cell proliferation of human prostate carcinoma cells PC3, DU-145 and LNCaP. The inhibition was selective for prostate cancer cells while normal prostate PrEC cells were not significantly affected (Gysin *et al* 2002 [12, 25 & 50 μM], Campbell *et al*, 2009, 2011 [5-100 μM], Israel *et al*, 2000 [12, 23 & 46 μM], Tomasetti *et al*, 2010 [30 μM α-tocopherylsuccinate]).

34. A comparison between tocopherols showed that γ- and δ-tocopherols were more effective at growth inhibition of prostate cancer cells than α-tocopherol and in turn δ-tocopherol was more effective than the γ-form. Tocotrienols were more active than tocopherols with about an 8 to 10 fold difference between the potential growth inhibition by γ- and δ-tocotrienols compared to tocopherols (Campbell *et al*, 2011, Constantinou *et al*, 2012 [10, 20 & 40 μM]).

35. Mechanistic studies with both androgen-dependent and -independent LNCaP cells showed tocotrienols to be effective, (Krycer *et al*, 2012 [1, 2.5 & 10 μM]) with cell death induced by apoptosis (Campbell *et al*, 2011). The mode of action of γ-tocotrienol was similar to γ-tocopherol (Campbell *et al*, 2009); it modulates the expression of PPAR-γ nuclear receptor in the PC3 human prostate cancer cells. γ-Tocotrienol treatment promoted apoptosis, necrosis and autophagy and led to a marked increase of intracellular dihydroceramide and dihydrosphingosine (which potently reduced the viability of the prostate cell lines), the sphingolipid intermediated in *de novo* sphingolipid synthesis pathway but had no effects on ceramide or sphingosine. The elevation of these sphingolipids by γ-tocotrienol preceded or coincided with biochemical and morphological signs of cell death and was much more pronounced than that induced by γ-tocopherol (Jiang *et al*, 2012 [10, 20 & 30 μM]).

36. Selenium ([with 20μg/ml α-tocopherol succinate] Venkateswaran *et al*, 2004), a combination of vitamin K3 and ascorbic acid [with 30-40 μM α-tocopheryl succinate] (Tomasetti *et al*, 2010) and narigenin[5] ([with 100 μM α-tocopherol]

[5] Narigenin - the predominant flavone in grapefruit - is considered to have a bioactive effect on human health as antioxidant, free radical scavenger, anti-inflammatory, carbohydrate metabolism promoter and immune system modulator. It is known to have an inhibitory effect on cell proliferation.

Torricelli *et al*, 2011) were found to potentiate the proliferation-inhibitory effect of vitamin E. Cell proliferation inhibition by vitamin E was potentiated by α-TTP and its expression. It was concluded that individual changes in the expression level or activity of α-TTP (individual genetic traits for example) may determine the responsiveness of prostate cancer patients to intervention strategies involving vitamin E (Morley *et al*, 2010).

37. While *in vitro* studies have demonstrated that tocopherols and tocotrienols have anti-proliferative action towards prostate cancer cell lines and that the action might be selective towards prostate cancer cells, other factors such as the role of α-TTP and its expression in individuals as well as the influence of other agents like selenium also need to be taken into consideration.

Vitamin E and prostate cancer - Animal Studies

38. Various rodent models of prostate cancer have been developed to mimic human prostate cancer (Valkenburg *et al*, 2011).

39. Experiments involving α-tocopherol alone at doses ranging from 5-500 mg/kg bw/day did not show a modification in prostate carcinogenesis (Nakamura *et al*, 1991, McCormick and Rao, 1999, Limpens *et al*, 2006), but in combination with other agents like lycopene (Limpens *et al*, 2006, Siler *et al*, 2004, Cervi *et al*, 2010) and selenium (Venkateswaran *et al*, 2004, 2009), there was significant reduction in growth of prostate cancer cells. One study in the *Lady* prostate cancer mouse model[6] suggested that lycopene was an essential component to produce a reduction in prostate cancer as a combination of α-tocopherol succinate (doses equivalent to 11.4 mg/kg bw/day) and selenium alone was not effective. This study also found that early intervention (within 8 weeks of age in transgenic mice) led to a reduced incidence of prostate cancer and liver metastasis when compared to controls; a delay in intervention times (20 and 36 weeks of age) resulted in a significantly higher proportion of animals developing high grade Prostate Intraepithelial Neoplasia (PIN) and prostate cancer compared to animals receiving intervention at 4 and 8 weeks of age (Venkateswaran *et al*, 2009). Growth rates of transplanted human prostate LNCaP xenografts in mice were found to be lower when treated with 11.4 mg/kg bw all-*rac*-α-tocopherol along with a high-fat diet (Fleshner *et al*, 1999) or α-tocopheryl succinate (100mg/kg bw via intraperitoneal injection) with soybean oil (Basu *et al*, 2007). However, some studies have reported a small increase in prostate cancer incidence when animals were treated with all-*rac*-α-tocopherol (calculated dose 100 and 200 mg/kg bw/day) with and without selenium in Wistar-Unilever rats (where androgen dependent prostate tumours are induced by N-methyl-N-nitrosourea + testosterone) (McCormick *et al*, 2010) or with all-*rac*-α-tocopherol acetate (calculated dose 100 and 200 mg/kg bw/day) in testosterone plus estradiol-treated NBL rats (sex

[6] The *Lady* mouse model is a less aggressive version of the original transgenic adenocarcinoma of the mouse prostate (TRAMP) model and the mice develop precursor lesions [PIN] followed by localised and eventually metastatic prostate cancer, mimicking progressive forms of the human disease thereby affording an opportunity to study the events in prostate cancer progression.

hormone-induced oxidative mechanisms and prostatic inflammation) (Özten *et al*, 2010).There was a statistically significant decrease in survival rates of the rats that received a higher dose of all-rac-α-tocopherol (200 mg/kg bw/day) and a marginally significant increase in incidence of cancers confined to the dorsolateral plus anterior prostate.

40. ***γ-Tocopherol***: Animal studies using γ-tocopherol seemed to indicate significant inhibition of prostate carcinogenesis. Experiments on transgenic adenocarcinoma mouse prostate[7] (TRAMP) mice at 15, 45 and 150mg/kg bw/day (Barve *et al*, 2009, 2010) and transgenic rat for adenocarcinoma of prostate[8] (TRAP) rats (Takahashi, 2009) treated with γ-tocopherol showed a significant reduction in tumour incidence in the treated group compared to control animals. Treatment of TRAMP mice with 15mg/kg bw/day γ-tocopherol also significantly increased expression levels of most detoxifying and antioxidant enzymes (Barve *et al*, 2009). In 5-week old TRAP rats that received γ-tocopherol (dose calculated to be 5 or 10 mg/kg bw/day for 10 weeks) and α- tocopherol (5 mg/kg bw/day), there were no differences in incidences of PIN or adenocarcinoma between the treated rats and controls (on a vitamin E free diet). However, in the γ-tocopherol treated rats, sequential progression from PIN to adenocarcinoma was significantly suppressed in a dose-dependent manner in the ventral lobe while α- tocopherol did not show any influence. Three-week old rats given γ-tocopherol (dose calculated to be 5.9, 11.8 or 23.6 mg/kg bw/day for 7 weeks) showed a significant dose-dependent suppression of prostatic lesions in the ventral but not lateral lobe. The numbers of apoptotic cells in the ventral prostate of animals treated with γ-tocopherol were significantly increased and caspases 3 and 7 were clearly activated compared to controls (on a vitamin E free diet). It was concluded that γ-tocopherol suppresses prostate carcinogenesis with induction of apoptosis through caspase activation (Takahashi, 2009). In another study on the growth of androgen-dependent Dunning R3327-H rat[9] prostate adenocarcinomas; Copenhagen rats were given γ-tocopherol (calculated dose 20 mg/kg bw/day), selenium and lycopene alone or in combination. Only selenium was found to decrease tumour weight and final tumour area with no changes in tumour proliferation or apoptosis rates from consuming lycopene and/or γ-tocopherol (Lindshield *et al*, 2010).

41. ***Tocotrienols****:* TRAMP mice treated with mixed tocotrienols (15, 45 and 150 mg/kg bw/day incorporated in the diet for 24 weeks) were reported to have a lower incidence of tumor formation (compared to controls) along with a significant reduction in the average wet weight of genitourinary apparatus in a dose-dependent

[7] The transgenic adenocarcinoma mouse prostate (TRAMP) mouse model demonstrates the progression of the disease from early PIN lesions to a more aggressive metastatic adenocarcinoma that closely mimics the various stages in human prostate cancer.

[8] The TRAP model features the development of high-grade PIN from 4 weeks and well-moderately differentiated adenocarcinomas with high incidences by 15 weeks of age.

[9] The Dunning R-3327H model is a transplantable tumour model that originated from a spontaneous tumour in a Copenhagen rat. It is reported to be a slow-growing, non-metastatic, androgen-responsive tumour that responds to dietary interventions.

manner (significantly in the case of the 45 and 150 mg/kg bw/day mixed tocotrienols group) (Barve, 2010).The mixed tocotrienol treatment significantly decreased the percentage of high grade neoplastic lesions compared to control animals.

42. In summary, animal studies seem to indicate that α-tocopherol alone may not be successful in reducing the risk of prostate cancer, but combining it with other nutrients like selenium and/or lycopene might be more effective. The timing of introducing the supplement could be important; an early intervention could be more successful in reducing the risk. γ-Tocopherol and tocotrienols have also shown a more protective action towards prostate cancer compared to α-tocopherol.

Vitamin E and prostate cancer – Human studies

43. Human studies are summarised at the end of this statement in Appendix 1.

44. Conflicting results have been reported from supplementation studies where substances other than vitamin E have been administered but the dataset used to compare blood vitamin E between prostate cancer cases and matched controls. A null association was reported for serum concentrations of α-tocopherol and subsequent development of prostate cancer in participants taking either β-carotene or retinol supplements in one study (Beilby *et al*, 2010) while a similar study of smokers with β-carotene and retinol supplementation (CARET study, Goodman *et al* 2003 and Cheng *et al*, 2011) showed a statistically significant reduction in the risk of prostate cancer (total and aggressive) for higher serum α- and γ-tocopherol levels; baseline serum α- and γ-tocopherol levels were significantly lower in prostate cancer cases.

45. Most human studies included in this review measured the plasma vitamin E level. Some studies estimated vitamin E intakes through dietary questionnaires and compared the relative risk of developing prostate cancer. Details on all of these studies can be found in appendix 1. The Committee noted that the intakes of vitamin E varied considerably between studies and that the use of food frequency questionnaires and food diaries are likely to be a significant source of variation between studies.

Case-control Studies

46. A range of studies have concluded that vitamin E may perform a protective role against the development of prostate cancer (Adaramoye, 2010; Akinloye, 2009; Battisti, 2011; Knekt, 1988; Goodman, 2003; Cheng, 2011; Weinstein, 2005; Kristal, 1999; Vlajinac, 1997; Tzonou, 1999; Bidoli, 2009; Deneo-Pellegrini, 1999). In contrast, a number of studies have concluded that vitamin E has no effect on the development of prostate cancer (Nomura, 1997; Hsing, 1990; Helzlsouer, 2000; Huang, 2003; Key, 2007; Gill, 2009; Beilby, 2010; Gilbert, 2012). Studies were adjusted for a range of factors, the most common ones being age, BMI, smoking, alcohol intake and family history of prostate cancer. The factors adjusted for each study and the form of vitamin E studied (if available) can be found in the tables in appendix 1.

47. Some case-control studies indicated that significantly lower plasma vitamin E levels (form not specified) were found in prostate cancer cases compared to controls and were inversely related to the PSA levels[10] and Gleason scores[11] indicating lower plasma vitamin E is associated with increased risk of prostate cancer (Akinloye, 2009, Adaramoye, 2010, Battisti *et al*, 2011). It was proposed that the lower plasma vitamin E levels in these patients could be because the vitamin E rapidly reacts with molecular oxygen and free radicals generated during prostate carcinogenesis. This argument was also supported by significantly higher levels of lipid peroxidation products in prostate cancer patients compared to controls. It was suggested that vitamin E acts as a free radical scavenger protecting polyunsaturated fatty acids from peroxidation reactions in prostate cancer patients (Battisti *et al*, 2011).

48. In a population based case-control study from King County, Washington, USA, the association of dietary supplement use - including vitamin E (no form stated) - with prostate cancer risk in men aged 40 - 64 years (Kristal *et al*, 1999) showed some evidence of a protective effect for vitamin E for individuals who took vitamin E supplements seven or more times a week, although this was not statistically significant (dosage not recorded; odds ratio of 0.76 (95% CI = 0.54 - 1.08) compared to those who had taken no vitamin E supplements).

49. In a more recent report (Weinstein *et al*, 2012), results from a nested case-control study in the screening arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial showed that higher baseline serum α-tocopherol levels were associated with a statistically significantly lower risk of prostate cancer although there was no difference in vitamin E intake (diet plus supplements) between cases and controls. The association was particularly marked in smokers (current and recent quitters; OR for lowest vs. highest quintile was 0.39 (95% CI = 0.14 - 1.04)). There was no association in never-smokers (OR 1.02; 95% CI = 0.51 - 2.05). In contrast, prostate cancer risk appeared elevated among men in all quintiles of serum γ-tocopherol concentrations above the first, suggesting an increased risk of prostate cancer for higher circulating levels of γ-tocopherol. This positive association was strongest in current smokers and recent quitters (OR 2.95; 95% CI = 0.91 - 9.56), although not statistically significant. For α-tocopherol, the relationship between serum levels with prostate cancer development was significant for both non-aggressive and aggressive types of the disease; however, in the case of γ-tocopherol elevated risk for higher serum levels appeared stronger for non-aggressive disease.

[10] A high level of PSA can be an indication of cancer. However, a number of factors, other than the presence/absence of cancer, can affect the levels of PSA, such as the age of the man, obesity and the presence of benign prostatic hypertrophy. Although a normal blood PSA level is <4 ng/ml, referral guidelines recommend that PSA levels take age into account and cut-off values are 3.0 ng/ml for men aged 50-59, 4.0 ng/ml for men aged 60-69 and >5.0 ng/ml for men aged 70+.

[11] The Gleason Grading system is used in grading of prostate cancer based on the glandular pattern of the tumour. A higher Gleason score indicates a more aggressive cancer. Gleason's original data showed a progressive increase in death due to the cancer with an increasing Gleason score (Gleason, 1966, 1974 and Bailar et al, 1966).

50. In contrast, the EPIC study (Key et al, 2007) found no association between plasma ⟨-tocopherol (OR 0.82 CI 0.61:1.11) and γ-tocopherol (OR 1.33 CI 0.93:1.9) and risk of prostate cancer.

51. The CLUE II[12] study (Helzlsouer *et al*, 2000) found that the risk of prostate cancer was lower among men with higher plasma concentrations of α-tocopherol, γ-tocopherol and selenium. The risk of prostate cancer declined with increasing plasma concentrations of γ-tocopherol with men in the highest fifth of the distribution of γ-tocopherol having a fivefold reduction in the risk of developing prostate cancer (P_{trend} = 0.002).

52. CLUE II also found a decrease in risk of prostate cancer for higher plasma concentrations of selenium and α-tocopherol, which was statistically significant when γ-tocopherol concentration was above the median level, but not when it was below. The authors suggested that since supplementation with α-tocopherol would lower the levels of γ-tocopherol in plasma and tissues, supplementation with combined α- and γ- tocopherols should be considered in future trials. This finding is relevant given the findings of the SELECT study where supplementation was with only selenium and α-tocopherol.

53. A table with more information on the case-control studies and a forest plot (for illustrative purposes only) can be found in appendix 1. Overall, results from these case-control studies show no direct association, either positive or negative, between vitamin E supplementation and risk of prostate cancer with little heterogeneity in the data; especially for α-tocopherol. The available studies show some indication for a protective effect of vitamin E in the case of smokers.

Prospective Cohort Studies

54. Prospective cohort studies have also given contrasting results. In an elderly population living in a retirement community in Los Angeles, results indicated that vitamin E supplementation[13] (median intake of 134 mg RRR-α-tocopherol equivalents/day) had no effect on the risk of developing prostate cancer (Shibata *et al*, 1992). In another UK-based study on a small number of prostate cancer patients (104) with a short follow-up time (2.5 years), a single measurement of baseline blood levels of α-tocopherol and γ-tocopherol did not show a correlation with clinical characteristics such as age, PSA levels or Gleason score (Venkitaraman *et al*, 2010). In contrast to this, a population of Swiss men of working age, smokers with low serum α-tocopherol levels were found to have a higher risk of developing prostate cancer than other groups with higher serum α-tocopherol levels (Eichholzer *et al*, 1996; Eichholzer *et al*; 1999). The factors adjusted for in each study can be found in the tables in appendix 1.

[12] Derived from the slogan 'Give us a CLUE to cancer'

[13] In the majority of prospective and case-control studies, food diaries were used to assess vitamin E intake from food and supplements. No serum levels were taken. In most cases the form of vitamin E from supplements is not stated or may be assumed to be α-tocopherol. Total dietary intake including supplements may be assumed to be all forms of vitamin E.

55. ***Health Professionals Follow-up Study (HPFS)***: Results from this study in 47,780 US male health professionals indicated that supplemental vitamin E intake (form not stated; any dose; 0.1 to ≤ 67mg/day RRR-α-tocopherol equivalents was examined) was not significantly associated with prostate cancer incidence (Chan *et al*, 1999). However among current smokers and recent quitters, those who consumed at least 91mg of all-rac-⟨-tocopherol equivalents had a suggestive reduced relative risk of 0.44 (95% CI = 0.18 - 1.07) for metastatic or fatal prostate cancer compared to those who did not take vitamin E supplements in the same group.

56. The ***Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial*** was a randomized two-arm trial designed to evaluate the effectiveness of screening in reducing mortality from these cancers (Kirsh *et al*, 2006). In this cohort for this ongoing, multicentre, randomized study, there was no overall association between prostate cancer risk and dietary or supplemental intake of vitamin E (form not stated) in men who were randomly assigned to the screening arm of the trial during up to 8 years of follow-up. However, among current and recent smokers, decreasing risks of advanced prostate cancer were associated with increasing dose (RR for >268 mg/day RRR-α-tocopherol equivalents vs. none = 0.29, 95% CI = 0.12 to 0.68; P_{trend} = 0.01) and duration of supplemental vitamin E use (RR for ≥ 10 years of use vs. none = 0.30, 95% CI = 0.09 to 0.96; P_{trend} = 0 .01). This study concluded that a protective effect of vitamin E might be seen specifically in smokers

57. The ***VITamins And Lifestyle (VITAL) Study*** **(**in western Washington State) found that for a 10-year average intake of supplemental vitamin E (form not stated), the risk of prostate cancer was only slightly lower for ≥ 268 mg/day RRR-α-tocopherol equivalents vs. non-use (HR 0.86, 95% CI = 0.65 - 1.1) (White *et al*, 2004 and Peters *et al*, 2008). However, the risk for advanced prostate cancer (regionally invasive or distant metastatic) decreased significantly with greater intake of supplemental vitamin E (HR 0.43, 95% CI 0.19 - 1.0 for 10-year average intake ≥268 mg/day RRR-α-tocopherol equivalents vs. non-use).

58. ***The National Institutes of Health - AARP Diet and Health Study*** on dietary intakes of α-, β-, γ- and δ-tocopherols, supplemental intake of vitamin E and multivitamin use (Wright *et al*, 2007 and Lawson 2007) did not show a relationship between vitamin E supplement use (including from multivitamins) and total or localized prostate cancer (for >0-66, 67-133, 134-267, 268-535, and ≥536 mg/d RRR-α-tocopherol equivalents vs. never use: RR, 0.97, 0.89, 1.03, 0.99, and 0.97 (95% CI, 0.87-1.07) respectively). Although there was a suggestive inverse association for advanced disease, (for ≥ 536 mg/d RRR-α-tocopherol equivalents vs. never use: RR, 0.86; 95% CI, 0.65 - 1.13) it was not statistically significant. However, when multivitamin users were excluded from the analysis, an inverse association was observed for total prostate cancer among men consuming ≥728 mg of RRR-α-tocopherol equivalents per day from single nutrient supplements compared with never users (for ≥728 mg of RRR-α-tocopherol equivalents per day versus never use: RR, 0.78; 95% CI, 0.64-0.96; P_{trend} = 0.03). In smokers, no association was found between supplemental vitamin E (usually *all-rac*-α-tocopherol) intake and prostate cancer risk in the cohort as a whole but when multivitamin users were excluded from the analysis, there was a significant inverse association between use

of high-dose supplemental vitamin E and localized prostate cancer among current/recent smokers (for ≥728 mg of RRR-α-tocopherol equivalents per day vs. never use: RR, 0.52; 95% CI, 0.29-0.94; P_{trend} = 0.06). This was not observed in non-smokers or those who smoked in the distant past.

59. Higher dietary intake of γ-tocopherol was associated with significant reduction in the risk of advanced prostate cancer in a dose-dependent manner, with adjustment for several confounding factors strengthening the observed associations (for > 18.2 mg/day vs. ≤ 9.7 mg/day: RR, 0.68; 95% CI, 0.56-0.84; P_{trend} = 0.001). A similar pattern was noted for δ-tocopherol (Wright *et al*, 2007).

60. The authors of the Netherlands Cohort study reported that there was no significant reduction in risk of prostate cancer with increased vitamin E intake (form not stated) (Schuurman *et al*, 2002). Vitamin E intakes were estimated from food-frequency questionnaires and a relative risk of 0.96 (95%CI = 0.61 - 1.5) was calculated for the highest (> 23.6 mg/day) vs. lowest (<7.1 mg/day) quintile of vitamin E intake.

61. In the ***Cancer Prevention Study II Nutrition Cohort (CPS II)*** regular vitamin E supplementation (form not stated, doses of up to 268 mg RRR-α-tocopherol equivalents ≥ 4 times per week) was not associated with overall risk of prostate cancer and there was no trend with increasing dose (Rodriguez *et al*, 2004). Current smokers taking vitamin E supplements regularly had a slightly lower risk of developing prostate cancer than smokers who did not take supplements.

62. ***Prostate Cancer Prevention Trial***: As part of a larger trial (United States and Canada) of finasteride,[14] the nutritional risk factors for prostate cancer were examined as a nested cohort (Kristal *et al*, 2010). There were no associations of any nutrient or supplement with prostate cancer risk overall; neither dietary nor supplemental intakes of vitamin E (form not stated) were significantly associated with cancer risk (for intake of > 30 mg/day vs. < 8 mg/day, OR, 1.08; 95% CI, 0.96 - 1.23).

63. A table with more information on the prospective cohort studies and a forest plot (for illustrative purposes only) can be found in appendix 1.

Randomised Controlled Trials

64. Reports from randomised controlled trials (RCTs) of vitamin E supplementation have indicated a decrease in risk of prostate cancer in some cases, while others seem to show no effect. The various individual studies are summarised below and the details are given in the table in appendix 1.

65. ***The Alpha Tocopherol Beta Carotene (ATBC) Cancer Prevention Study:*** The ATBC study was the first large scale randomised, double-blind, placebo-controlled primary-prevention trial designed to investigate whether α-tocopherol and β-carotene supplementation could play a role in the prevention of lung and other cancers (ATBC study group, 1994, Albanes *et al*, 1995, Heinonen *et al*, 1998). The

[14] Finasteride is a 5α-reductase inhibitor (which suppresses the production of dihydrotestosterone in men).

study was conducted among 29,133 white, male smokers (five or more cigarettes a day, aged 50-69) residing in Finland who were assigned to four groups - α-tocopherol alone (as 2-ambo-α-tocopheryl[15] acetate, 50 mg/day), β-carotene alone (20 mg), α-tocopherol (50 mg/day) + β-carotene (20 mg) or placebo. There were no differences in background factors between the intervention groups and supplementation was continued for 5-8 years (median, 6.1 years).

66. Results from this study suggested that long-term supplementation with α-tocopherol could reduce prostate cancer incidence and mortality in male smokers. The incidence of prostate cancer was 36% lower (95% CI = -56% to -6%) in the α-tocopherol-alone group, 16% lower (95% CI = -41% to 20%) in the α-tocopherol + β-carotene group and 20% higher (95% CI = -13% to 66%) in the β-carotene-alone group. Among subjects receiving α-tocopherol compared with those not receiving, there was a 32% decrease (95% CI = -47% to -12%) in the incidence of prostate cancer. In contrast, an increasing trend in the incidence of prostate cancer was observed in men receiving β-carotene compared with those not receiving it, but the 23% difference (95% CI = -4% to 59%) was not statistically significant. The incidence of clinical tumours (stage II-IV) decreased by 40% in subjects receiving α-tocopherol (95% CI = -55% to -20%) but increased by 35% in subjects receiving β-carotene (95% CI = 1% to 80%). Neither agent had a statistically significant effect on latent (stage 0 - I) cancers. The mortality from prostate cancer was 41% lower in men receiving α-tocopherol (95% CI = -65% to -1%) than in those not receiving it and 15% higher in men receiving β-carotene (95% CI = -30% to 89%) than in those not receiving it. Supplementation did not influence survival time after diagnosis.

67. ***Serum vitamin E levels in the ATBC study***: Investigations of the association between prostate cancer and baseline serum α-tocopherol concentrations seem to indicate a protective effect for α-tocopherol intervention (Hartman *et al*, 1998). Higher serum α-tocopherol at baseline was associated with improved prostate cancer survival, especially among cases who had received α-tocopherol and who were in the highest quintile of α-tocopherol at baseline or at the 3-year follow-up measurement (Watters *et al*, 2009).

68. In a nested case-control study from this cohort (100 cases and 200 controls), the risk of prostate cancer was lower where baseline serum levels of α-tocopherol and γ-tocopherol were higher (Weinstein *et al*, 2005). Further analyses indicated that the association was stronger in the α-tocopherol-supplemented group than in those not receiving α-tocopherol.

69. ***Post-intervention follow-up of the ATBC study:*** In the 2003 follow-up report, (ATBC study group, Virtamo *et al*, 2003) potential late effects from the intervention (which stopped in 1993) were described (total mortality for 8 years and cancer incidence and cause-specific mortality for 6 years) in participants who were alive at the beginning of the post-trial period (May 1993). There was no statistically significant difference in prostate cancer incidence in the post-trial period between α-

[15] A form of vitamin E no longer manufactured; consisting of 50% RRR-α-tocopherol and 50% SRR-α-tocopherol.

tocopherol recipients compared to non-recipients, although a reduced risk was suggested (RR, 0.88; 95% CI = 0.76 - 1.03).

70. In discussing the reduction (by 34%) of prostate cancer incidence in the original study, the follow-up report stated that the preventive effect of α-tocopherol was observed ~18 months after the start of intervention, and was present throughout the 6-year post-trial period; however it was substantially attenuated even within the first 3 post-trial years. It was therefore suggested that α-tocopherol prevents the progression of prostate cancer in a later phase of carcinogenesis, and that this effect is transient, diminishing fairly rapidly following cessation of supplementation.

71. Further follow-up in 2014 concluded that α-tocopherol decreased post-trial prostate cancer mortality (RR 0.84, 95% CI, 0.70 : 0.99) but no relationship was found with cancer incidence (Virtamo *et al*, 2014)

72. ***The HOPE and HOPE-TOO Trials***: The Heart Outcomes Prevention Evaluation (HOPE) trial was an international, multicentre, double-blind, randomised, placebo-controlled, 2x2 factorial design trial that evaluated ramipril[16] (vs. placebo) and 268 mg/day *RRR*-α-tocopheryl acetate vs. placebo. (The HOPE and HOPE-TOO trial investigators, 2005). The HOPE study reported no apparent effects of *RRR*-α-tocopheryl acetate on cardiovascular outcomes. The extended HOPE-TOO study (HOPE - The Ongoing Outcomes; to assess whether longer duration of treatment would prevent cancer and/or cardiovascular disease) with a median follow-up of 7 years indicated no overall effect of *RRR*-α-tocopheryl acetate on the incidence of fatal and nonfatal cancers; there was no reduction in the incidence of prostate cancer.

73. The ***Prevention Research Veteran Affairs E-vitamin Nutrition Trial*** was a randomised, double-blind, placebo controlled study designed to assess the effects of vitamin E supplementation (form not stated) on biomarkers associated with prostate cancer risk (Hernández *et al*, 2005). Patients (n=44) with increased PSA and/or abnormal digital rectal examination on initial evaluation were randomized to receive 268mg RRR-α-tocopherol equivalents daily vs. placebo (18 months). Serum α-tocopherol levels were significantly increased by oral supplementation of vitamin E, but there was no effect on serum androgens, IGF-1 or levels of PSA.

74. Another randomised placebo-controlled study produced similar results; 70 patients with hormonally untreated carcinoma of the prostate and rising serum PSA levels were given a nutritional supplement containing 522 mg/day RRR-*α*-tocopherol from natural sources, selenium, vitamin C and coenzyme Q10 for 21 weeks (Hoenjet *et al*, 2005). Although the plasma levels of vitamin E, selenium and coenzyme Q10 increased significantly over the study period, there were no significant differences in serum levels of PSA, testosterone, dihydrotestosterone, luteinizing hormone or sex hormone binding globulin between the intervention and control group.

75. ***The Physicians' Health Study II*** was a randomized, double-blind, placebo-controlled factorial trial of vitamins E and C in male physicians in the United States,

[16] Ramipril, an angiotensin-converting-enzyme inhibitor was found to significantly reduce the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients in the HOPE trial.

initially aged 50 years or older (Gaziano *et al*, 2009). Supplementation with 400 mg of synthetic all-rac-α-tocopherol (vs. placebo) every other day for a mean follow-up of 8 years did not indicate a reduction in the risk of prostate cancer.

76. ***The Heart Protection Study***: The study was conducted in UK adults with coronary disease, other occlusive arterial disease, or diabetes; who were randomly allocated to receive antioxidant vitamin supplementation (600 mg all-rac-α-tocopherol, 250 mg vitamin C, and 20 mg β-carotene daily) or matching placebo (HPS Group, 2002). The serum α-tocopherol levels of those who took the supplement were nearly doubled (49·5±0·6 µmol/l) compared to those on placebo (27.0±0.2 µmol/l); but there were no significant differences in the incidence of prostate cancer.

77. ***The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study*** was a randomized, double-blind, placebo-controlled primary prevention trial that tested whether an adequate and well-balanced intake of antioxidant nutrients reduced the incidence of cancers and ischemic cardiovascular disease (CVD) in a middle-aged general population in France (Hercberg *et al*, 2004). Subjects took a single daily capsule of a combination of ascorbic acid, α-tocopherol (30 mg), β-carotene, selenium, and zinc, or a placebo. Overall, there was a non-significant reduction in prostate cancer rate associated with the supplementation after a median follow-up time of 9 years in the supplement arm and 8.8 years in the placebo arm (Meyer *et al*, 2005). However, among men with normal PSA, there was a statistically significant reduction in the rate of prostate cancer for men receiving the supplements (HR = 0.52; 95% CI = 0.29 - 0.92). In men with elevated PSA at baseline, the supplementation was associated with a non-significant increased incidence of prostate cancer (HR = 1.54; 95% CI = 0.87 - 2.72). The supplementation had no effect on PSA levels. Timing of supplementation may, therefore, be important with vitamin E supplementation prior to a rise in PSA levels being associated with a reduced risk of prostate cancer.

78. In the ***PRP.1 trial***, a double blind, placebo controlled phase III study conducted by the National Cancer Institute of Canada Clinical Trials Group, the effects of vitamin E (form not stated), soy and selenium supplementation in preventing the progression of high-grade prostatic intraepithelial neoplasia (HGPIN)[17] to prostate cancer was investigated (Fleshner *et al*, 2011). A daily dose of a combination of vitamin E (536 mg RRR-α-tocopherol equivalents) along with soy protein and selenium for 3 years did not prevent a progression of HGPIN to prostate cancer. There were no differences in PSA levels and severity between the supplemented and placebo groups.

79. In a 6-month study that looked at supplementation with selenium, 20.1mg RRR-α-tocopherol equivalents, and soy isoflavonoids in men diagnosed with isolated HGPIN (Joniau *et al*, 2007) a decrease in PSA levels while taking the supplement predicted a significantly lower risk of prostate cancer in future biopsies.

[17] HGPIN is considered a precursor lesion to development of invasive prostatic adenocarcinoma.

80. Complications relating to the genitourinary tract were analysed in subjects from the ***Age-Related Eye Disease Study*** - a randomised, placebo-controlled study which examined the effects of zinc and antioxidants (Johnson *et al*, 2007). The four groups were placebo, antioxidants (500 mg vitamin C, 268mg RRR-α-tocopherol equivalents and 15 mg β-carotene), 80 mg zinc and antioxidant plus zinc. A significant decrease in prostate cancer diagnoses was seen in patients receiving antioxidants vs. placebo (RR = 0.6, 0.49 to 0.86). Subgroup analysis revealed that this finding was significant in men who smoked but not in non-smokers.

81. In a double-blind cross-over RCT, prostate cancer patients (n=49) with rising PSA levels after radical prostatectomy or radiotherapy were given supplements containing soy isoflavones, lycopene, silymarin and antioxidants (75 mg/day α-tocopherol) or control for 10 weeks followed by a 4 week wash-out period. Supplementation delayed the rise in PSA levels compared to placebo, which may have been attributable to components of the supplement other than α-tocopherol (Schroder *et al*; 2005).

82. Other than the ATBC study, results from most of these RCTs indicate little or no association between vitamin E supplementation and risk of prostate cancer. The risk was lower when supplementation was with vitamin E and nutrients like soy and other antioxidant vitamins. There seemed to be a protective effect in the case of smokers. This is in agreement with the positive results of the ATBC study which was among smokers and results from various case-control studies.

83. A table with more information on the randomised-controlled trials and a forest plot (for illustrative purposes only) can be found in appendix 1.

Meta-analyses

84. A meta-analysis of RCTs on the role of vitamin E in the prevention of cancer concluded that vitamin E supplementation was associated with a significant reduction in the incidence of prostate cancer (a relative risk of 0.85; 95% CI, 0.73-0.96 p=0.01, number needed to treat = 500), but it did not reduce the incidence of any other types of cancer (Alkhenizan, 2007); another showed a weak association (Zhang *et al*, 2009). On the other hand, another meta-analysis which looked at the efficacy of antioxidant vitamin supplements (including vitamin E) and selenium in prostate cancer prevention included 9 RCTs and concluded that antioxidant vitamins and selenium supplements did not reduce the incidence and mortality of prostate cancer (RR 0.96; 95% CI, 0.85-1.08; p=0.03) (Jiang *et al*, 2010). Stratton and Godwin (2011) reported no association between vitamin E intake and risk of prostate cancer in their meta-analysis of 14 studies which included RCT's, case control and cohort studies. Cui *et al* (2014) carried out a meta-analysis of case-control studies using plasma α-tocopherol and *γ*-tocopherol levels. They concluded that plasma α-tocopherol was inversely associated with the risk of prostate cancer. The data for *γ*-tocopherol was more heterogeneous. The different conclusions from these meta-analyses could be due to the different studies included. Also Jiang *et al* looked at just supplementation studies; Cui *et al* looked at just plasma levels of tocopherols and others looked at a range of different studies.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

85. SELECT was a very large phase III randomised, double-blinded, placebo-controlled, prospective, 2x2 factorial clinical trial of selenium (200 µg/day from *L*-selenomethionine) and/or *all-rac*-α-tocopheryl acetate (400 mg/day) and had a primary endpoint of clinical incidence of prostate cancer (Klein *et al*, 2000, Lippman *et al*, 2005). It was based on the results of previous studies, described above, that had suggested that vitamin E and selenium were associated with a reduction in the risk of prostate cancer and was planned for a minimum of 7 years (maximum of 12 years).

86. The study population was 35,553 men recruited from 427 sites in the United States, Canada and Puerto Rico who were at least 55 years old (lowered to 50 in the case of African-American men because of the higher risk of prostate cancer in this group). The participants had a serum PSA level of not more than 4 ng/mL and a digital rectal examination (DRE) which was not suspicious for prostate cancer.

87. The trial started in July 2001 and the data on prostate cancer incidence were reviewed in 2008 (median follow-up of 5.46 years). Although there was no statistically significant difference in rates of prostate cancer between the four groups, there was an apparent increased risk of prostate cancer in the *all-rac*-α-tocopheryl acetate alone group (relative risk, 1.13; 99% CI = 0.95 - 1.35; p = 0.06). Participants were asked to stop taking the supplements since selenium and *all-rac*-α-tocopheryl acetate did not prevent prostate cancer in this population of healthy men (Lippman *et al*, 2009).

88. Since 2008, participation follow-up continued in an un-blinded fashion and in July 2011, trial data were reviewed and details of the analysis of the latest data are shown in Table 1 below:

		placebo	*all-rac*-α-tocopheryl acetate	Selenium	*all-rac*-α-tocopheryl acetate + selenium
Number of participants		8696	8737	8752	8703
Number of prostate cancer cases	Oct 2008	416	473	432	437
	July 2011	529	620	575	555
Hazard ratios for prostate cancer (99% CIs)	Oct 2008	1	1.13 (0.95 - 1.35)	1.04 (0.87 -1.24)	1.05 (0.88 - 1.25)
p value			0.06	0.62	0.52

		placebo	*all-rac*-α-tocopheryl acetate	Selenium	*all-rac*-α-tocopheryl acetate + selenium
Hazard ratios for prostate cancer (99% CI)	July 2011	1	1.17 (1.004 - 1.36)	1.09 (0.93 -1.27)	1.05 (0.89 - 1.22)
p value			0.008	0.18	0.46
Absolute risk (prostate cancers per 1000 person years)		9.3	10.9	10.1	9.7

Table 1: SELECT data until July 2011 (Klein *et al*, 2011).

89. In 2011 after seven years of median follow-up, the men who took *all-rac*-α-tocopheryl acetate alone had a 17% relative increase in numbers of prostate cancers compared to men on placebo and this difference was now statistically significant (Klein *et al*, 2011). This difference had become apparent during the participants' third year in the trial (HR = 1.10) and increased slightly each year thereafter. These findings suggested that *all-rac*-α-tocopheryl acetate supplementation in the general population of healthy men significantly increases the risk of being diagnosed with prostate cancer.

90. Men taking selenium alone, or *all-rac*-α-tocopheryl acetate and selenium, were also at a higher risk of developing prostate cancer than men taking placebo, but those increases were smaller and not statistically significant. It was also found that there was a significant interaction between *all-rac*-α-tocopheryl acetate and selenium (p=0.02) suggesting no increased risk of prostate cancer when *all-rac*-α-tocopheryl acetate and selenium were taken together.

Potential reasons for the unexpected results seen in the SELECT trial

91. Following the publication of the results of the SELECT study, several potential reasons were proposed as to why these unexpected results were observed.

92. ***Dose of α-tocopherol****:* One possible reason for the observed results could be that the high dose (400 mg/day all-rac-α-tocopherol compared to 50 mg/day in the ATBC study) might have been less effective (Lippman *et al*, 2009 and Ledesma *et al*, 2011). It was suggested that achieving higher plasma or tissue levels of α-tocopherol within the physiological range (such as with a 50 mg/day supplement in the ATBC study) might have a cancer preventive effect such as arresting cell proliferation or tumour growth inhibition, whereas a higher dose might have unanticipated effects such as pro-oxidation, tissue peroxidation or interference with CYP450 enzymes (Brown *et al*, 1997). This seems to be supported by the SU.VI.MAX study (30 mg α-tocopherol) where there was a statistically significant reduction in the risk among men with normal PSA levels.

93. ***Role of γ-tocopherol***: In recent preclinical studies, γ-tocopherol had been found to be a more effective anticancer agent (discussed in detail in the following section; paragraph 105). It had also been shown that high levels of supplemental α-tocopherol can significantly suppress levels of γ-tocopherol (Huang and Appel, 2003), which could lead to an increased risk of prostate cancer. Indeed, plasma levels of γ-tocopherol in a subset of individuals taking *all-rac*-α-tocopheryl acetate supplements (alone) were reduced from 1.43 µg/mL (baseline) to 0.80 µg/mL (4th annual visit) compared to the placebo arm (1.31 µg/mL at baseline and 1.69 µg/mL at 4th annual visit). This suppression in levels of γ-tocopherol could have been less at the lower levels of α-tocopherol in the ATBC and SU.VI.MAX studies.

94. ***Placebo***: If the placebo was an agent that was protective against prostate cancer rather than being inert, α-tocopherol might actually have no effect but might appear to increase the risk in comparison to an active placebo. In response to a journal query about the exact nature and composition of the placebo used (Hoskote *et al* 2012), it was revealed that the placebo was composed of soybean oil (Klein, 2012). Plant-derived oils are known to be rich sources of vitamin E (both tocopherols and tocotrienols). Literature reports (EFSA, 2008) show that soybean oil is one of the richest sources of γ-tocopherol (797 mg/kg) and δ-tocopherol (266 mg/kg) and in addition to small amounts of α-tocopherol (75 mg/kg) it also contains α- tocotrienol (2 mg/kg) and β- tocotrienol (1 mg/kg)[18]. This marginally higher intake of γ- and δ-tocopherols and tocotrienols by the placebo group in addition to the concurrent lowering of γ-tocopherol levels in the supplemented group may be the reason for the relatively lower number of prostate cancer cases in the placebo group.

95. This hypothesis is supported by the observation that the median serum γ-tocopherol levels of the placebo group had increased from 1.3 µg/ml (baseline) to 1.69 µg/ml after 4 years while that of the *all-rac*-α-tocopheryl acetate only group had decreased from 1.43 µg/ml (baseline) to 0.80 µg/ml after 4 years. α-Tocopherol, the active substance in the study, might have had a lower effect or no effect, but appear to increase the risk in comparison to the unintentionally active placebo. At baseline, the vitamin E status of participants was not significantly different.

96. ***Smoking status***: It had also been suggested that the smoking status of individuals might be important. The ATBC study, CARET study, the PLCO Cancer Screening (PLCO) Trial (Kirsh *et al*, 2006), the Basel Study, the Physicians' Health Study II and the US Health Professionals Follow-up Study had indicated that vitamin E is more protective against prostate cancer in smokers when compared to non-smokers. However SELECT could not make this assessment as only 7.5% of SELECT population were current smokers. A subgroup analysis of current and former smokers in SELECT did not show a reduction in prostate cancer (placebo, 4.6%, 223/4863 vs. *all-rac*-α-tocopheryl acetate alone, 4.8%, 232/4853).

97. ***Confounders***: Finally, confounding factors like obesity and other dietary factors are not considered in the SELECT study. The ATBC study had suggested

[18] A daily intake of 400 mg of soybean oil by the placebo group would be around 0.32 mg of γ-tocopherol

that the negative impact of extreme obesity was greater than the positive impact of taking a vitamin E supplement (Ledesma *et al*, 2011).

Issues to consider with results of epidemiological studies

98. When considering conflicting results from the case-control studies and intervention trials on vitamin E, there are several factors which could have influenced the seemingly inconsistent results; these include:

99. ***Amount and form of the supplemented α-tocopherol:*** Different trials used different amounts of α-tocopherol in various forms. For instance the ATBC study used 50 mg *all-rac*-α-tocopheryl acetate[19], the SELECT Trial used 400 mg of *all-rac*-α-tocopheryl acetate, the SU.VI.MAX study used 30 mg of all-rac-α-tocopherol, the CHAOS Study used capsules of *RRR*-α-tocopherol (from natural sources in soya oil), 268 or 537 mg daily (Stephens *et al*, 1996), while the HOPE - TOO trial used 268 mg/day *RRR*-α-tocopheryl acetate. As discussed earlier, the absorption and bioactivity of the various forms of tocopherol are different and depending on the dosage, could affect the activity of the other isoforms of the vitamin. Animal studies used doses of between 5 and 500mg/kg bw/day. It has been proposed that many antioxidants have biphasic effects that differ at higher and lower doses and some dietary antioxidants can act both as antioxidants and pro-oxidants under different circumstances (Lee and Lee, 2006, Chiang *et al*, 2009 and Calabrese *et al*, 2010). It has been suggested that high levels of α-tocopherol in the body and subsequent oxidative stress would result in higher levels of α-tocopherol radicals capable of initiating potentially deleterious processes such as lipid peroxidation. This has been demonstrated *in vivo* in otherwise healthy asthmatics given α-tocopherol supplements or placebo and studied for a marker of lipid peroxidation (ferrous oxidation xylenol; FOX) (Pearson et al, 2006). The presence of other anti-oxidants in the body significantly reduces the ability of vitamin E to act as a pro-oxidant. The anti-oxidant status of an individual as well as the dose of α-tocopherol would therefore be important in dictating the pro-oxidant capacity of α-tocopherol (Rietjens et al, 2002). This theory has been supported by *in vitro* studies using human plasma and low-density lipoprotein (LDL) (Bowry et al, 1992).

100. ***Inaccurate estimates*****:** Several trials assessed vitamin E intake from food frequency questionnaires, dietary recall questions and questionnaires on supplement usage and there is the possibility that estimates were not accurate and/or not representative of long-term intakes. Vitamin E is concentrated in many vegetable oils and fats and the amounts as well as the nature of oil and fat added during food preparation is difficult to assess (Mayne, 2003). Given that the absorption and rates of metabolism of the isoforms and stereoisomers are different, it has been noted that the fact that positive effects of vitamin E are observed in some studies and not in others is not surprising (Brigelius-Flohé *et al*, 2002).

101. ***Mode of intake*****:** vitamin E is absorbed together with lipids and thus has to be taken with a meal containing a sufficient amount of fat. The uptake of vitamin E has been shown to vary (both intra- and inter individually) depending on the fat intake

[19] 1 mg of *all-rac*-α-tocopheryl acetate = 1 IU; 0.67 mg of *RRR*-α-tocopherol = 1 IU (IOM, 2000; page 191)

(Dimitrov *et al*, 1991). These requirements do not appear to have been consistently considered in various trials with some making no mention of dietary fat intake at all whilst others do not mention whether supplements have been consumed with a fatty meal to maximise absorption.

102. ***Serum concentrations of vitamin E:*** Epidemiological studies often report plasma or serum concentrations of α-tocopherol as a biomarker for exposure; however it has been found that while these correlated with supplemental vitamin E intake, they were not associated with dietary intake estimates from either 24-hour dietary recalls (Ford and Sowell, 1999) or food frequency questionnaires (Jackson *et al*, 2011). It has therefore been suggested that if plasma or serum α-tocopherol levels are to be used as an index of measurement, then corresponding cholesterol levels should also be measured and adjustments applied. For example it was found that lipid-adjusted group means for serum concentrations of vitamin E were considerably lower than the unadjusted values (Willett *et al*, 1984). Lipid-adjustment of vitamin E plasma levels was not done in all studies (Eichholzer *et al*, 1999, 2000).

103. ***Confounders*****:** Confounding effects of other antioxidant vitamins, supplements, nutrients and over-the-counter and prescription medications taken by participants are not always taken into consideration. For instance, a small study (Grainger *et al*, 2008) among participants in the prostate cancer prevention trial (PCPT) found that 85% had a high propensity for use of dietary supplements (including vitamin E), herbal products and other common medications including aspirin, nonsteroidal anti-inflammatory drugs and statins (some of which are being investigated as chemopreventive agents). Also, other lifestyle factors like smoking, exercise, body size etc. have not always been considered in all the studies. Diets vary between countries and crops grown in different soils vary in their micronutrient content therefore direct comparisons between studies from different countries could be affected by confounding factors. As an example, selenium is an active anti-cancer agent and the selenium content of wheat from the UK and the US vary considerably (MAFF, 1997). The tables in appendix 1 give the confounders which have been adjusted for when provided for each study.

104. ***Placebo used***: In most of the RCTs the nature and composition of the placebo is not mentioned. Therefore, it is not possible to be certain that the placebo was a physiologically inert substance and that the results were measured as a relative difference between an active substance (vitamin E) and an inert one.

Association of γ-tocopherol and prostate cancer

105. Most large-scale intervention studies carried out with α-tocopherol (usually large doses) have not demonstrated a reduced risk of cancer. One possible explanation for the inconsistency in results could be because high doses of α-tocopherol decrease the blood and tissue levels of γ- and δ-tocopherols.

106. A study by Clarke *et al* (2006) found that supplementation with α-tocopherol (as *RRR*-α-tocopherol) compared to 500 mg mixed tocopherols (315 mg γ-, 75 mg α- and 110 mg δ-) or placebo for 6 weeks reduced the levels of γ-tocopherol. Serum and cellular γ-tocopherol increased 4-fold in the mixed tocopherol group. While both treatment groups showed increased serum levels of α-tocopherol, supplementation

with α-tocopherol alone significantly decreased erythrocyte γ-tocopherol levels (decreases in serum and platelet levels were not statistically significant). Supplementation with α-tocopherol also significantly increased the excretion of γ-tocopherol metabolites suggesting that the decrease may be the result of increased metabolism of γ-tocopherol, reflecting the displacement of γ-tocopherol by α-tocopherol.

107. A similar lowering of γ-tocopherol levels with α-tocopherol supplementation was reported (Tsavachidou et al, 2008) in 39 prostate cancer patients before prostatectomy receiving selenium, α-tocopherol (268mg), both or placebo (a phase IIA study to identify potential antioxidant therapeutic targets and biomarkers for prostate cancer to complement the SELECT study). While there were statistically significant increases in plasma α-tocopherol levels in the *all-rac*-α-tocopheryl acetate alone and *all-rac*-α-tocopheryl acetate + selenium groups, the levels of γ-tocopherol were significantly lowered with α-tocopherol treatment. Similar lowering of γ-tocopherol levels were observed in the SELECT study (paragraph 93).

108. Despite high intake of γ-tocopherol, plasma concentrations of γ-tocopherol are about 10 times lower than those of α-tocopherol. The reason for the plasma preference for α-tocopherol is in its specific selection by α-TTP. α-TTP not only specifically selects the α- form of all tocopherols but also has a preference for 2R-stereoisomers (Liebler, 1993 and Wen *et al*, 2007).

109. An association between the isoforms of vitamin E and risk of prostate cancer was clearly demonstrated in CLUE I and CLUE II studies (paragraphs 51 and 52, Huang *et al*, 2003 and Helzlsouer *et al*, 2000). Higher serum concentrations of both α-tocopherol and γ-tocopherol showed lower risk of prostate cancer but the strongest association was observed for γ-tocopherol. Similar results were shown in the NIH-AARP Diet and Health Study (Wright *et al*, 2007). These results suggest that increased consumption of γ-tocopherol from foods is associated with a reduced risk of clinically relevant disease.

110. Owing to its strong nucleophilic properties, γ- tocopherol is more effective than α- tocopherol in trapping ROS and reactive nitrogen species (RNS) (Campbell *et al*, 2003, Cooney *et al* 1993). This is supported by *in vitro* (Gysin *et al*, 2002 and Torricelli *et al*, 2012) and animal (Yu *et al*, 2009) studies with γ-tocopherol exhibiting a more significant anti-cancer effect than α-tocopherol in prostate cancer cells. Anticancer actions of the γ-form *in vivo* and *in vitro* were reduced by α-tocopherol (Yu *et al*, 2009).

111. It has been suggested that γ-tocopherol, due to its strong anti-inflammatory and other activities, may be the more effective form of vitamin E in cancer prevention (Ju *et al*, 2010). It has been proposed that a mixture of tocopherols, at ratios similar to those in the diet, could be a better cancer chemopreventive agent. It has even been suggested that vitamin E, as ingested in the diet or in supplements that are rich in γ- and δ-tocopherols, is cancer preventive; whereas supplementation with high doses of α-tocopherol is not (Yang *et al*, 2012).

Vitamin E, smoking status and prostate cancer risk

112. Results from observational studies consistently show an inverse association between intake levels or blood levels of vitamin E and prostate cancer risk in smokers (Eichholzer *et al*, 1996, Chan *et al*, 1999; Gann *et al*, 1999, Huang *et al*, 2003; Rodriguez *et al*, 2004 and Kirsh *et al*, 2006; Key *et al*, 2007; Weinstein *et al*, 2007; Cheng *et al*, 2011). For example in a prospective nested case-control study within the CARET study (a randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial of β-carotene and retinol among asbestos-exposed workers and heavy smokers, Goodman *et al* 2003), in the control-only population (416 participants), there was a significant association between tobacco use and serum α-tocopherol concentration; current smokers had statistically significantly lower mean levels of α-tocopherol compared with former smokers. It has been suggested that smoking depletes the body's supply of antioxidants (Handelman *et al*, 1996).

113. Various reasons have been proposed for the association between vitamin E intake and prostate cancer risk being different in smokers. For example, male smokers are known to have higher serum levels of testosterone, free testosterone, total estradiol or sex hormone-binding globulin (SHBG) than non-smokers. Also, serum α-tocopherol was statistically inversely related with testosterone, estradiol and SHBG levels (Mondul *et al*, 2011, Moyad, 2002). In a follow-up of the ATBC study, it was found that long-term α-tocopherol supplementation decreased serum testosterone concentrations and it was suggested that this may lead to a reduction in risk of prostate cancer in smokers (Hartman *et al*, 2001).

114. Interactions between serum α-tocopherol and exposure to cigarette smoke (as measured by serum cotinine levels) for total testosterone, total estradiol and SHBG were found with inverse association between serum α-tocopherol and circulating testosterone, estradiol and SHBG were observed only among smokers. This finding supports the hypothesis that vitamin E may selectively protect against prostate cancer in smokers, probably through an hormonal mechanism.

115. In contrast, a prospective nested case-control study examining levels of serum androgens and estrogens in 116 randomly selected prostate cancer cases of the ATBC study (all smokers) and 232 matched controls did not indicate a significant association between the individual androgens or estrogens and risk of prostate cancer (Dorgan *et al*, 1998).

Genotype, serum vitamin E levels and prostate cancer risk

116. Family history of prostate cancer is associated with an increased risk of the malignancy. The diverse mechanisms by which antioxidants exert their effect may, in part, be affected by genetic polymorphisms in genes encoding for antioxidant proteins, which may lead to different effects in different people exposed to the same antioxidant dose (Özten-Kandaş *et al*, 2011). There are a few studies that show the association between prostate cancer risk and polymorphism in various oxidative stress related genes and vitamin E transport genes. These include superoxide dismutases (SODs) - the family of enzymes responsible for the detoxification of superoxide free radicals (Kang *et al*, 2007, Woodson *et al*, 2003), myeloperoxidase (Cheng *et al*, 2011), vitamin E transport genes TTPA and SEC14L2 (Wright *et al*,

2009) and BUD13, ZNF259 and APOA5 (Major *et al*, 2014) and tocopherol associated protein 1 (*hTAP1*) and associated genes (Zingg *et al*, 2009). Preliminary work on the polymorphisms in the *XRCC1* gene, which is a key player in the base excision repair (BER) pathway, (van Gils *et al*, 2002) indicated that the risk of prostate cancer was lower for men with one or two copies of variant alleles of *XRCC1* compared to those who were homozygous for the common allele.

117. Variations in NKX3.1, an androgen-regulated prostate tumour suppressor gene was found to be statistically significantly related to prostate cancer status and vitamin E consumption in the SELECT cohort (HR1.450, 95% CI 1.117 : 1.882) (Martinez *et al*, 2014).

118. Results from these studies have indicated that genetic variation could be responsible for varying risks for prostate cancer and that polymorphisms might have an impact on the effect of vitamin supplementation regimens on prostate cancer risk.

Summary of findings

119. Several studies on vitamin E and risk of prostate cancer in humans have suggested a protective action of vitamin E against the development of prostate cancer. This has been supported by a range of animal and *in vitro* studies. Other studies report no effect. SELECT is the only study that has reported an increased risk of prostate cancer with vitamin E supplementation.

120. Higher serum α-tocopherol levels were associated with a reduced risk of prostate cancer in certain studies and one study found that prostate cancer patients had lower blood levels of α-tocopherol (Battisti, 2011). It was suggested that this is because vitamin E rapidly reacts with molecular oxygen and generates free radicals. This was also backed up by the occurrence of significantly higher levels of lipid peroxidation products in prostate cancer cases.

121. SELECT used a higher dose of *all-rac*-α-tocopherol than many intervention studies suggesting there might be a U-shaped dose-response curve for vitamin E effects. Studies that used lower levels (ATBC study, SU.VI.MAX study) showed a significant reduction in risk. It has been proposed that many antioxidants have biphasic effects that differ at higher and lower doses and some dietary antioxidants can act both as antioxidants and pro-oxidants under different circumstances (Lee and Lee, 2006, Chiang *et al*, 2009 and Calabrese *et al*, 2010). It has been suggested that high levels of α-tocopherol in the body and subsequent oxidative stress would result in higher rates of lipid peroxidation. This has been demonstrated *in vivo* in otherwise healthy asthmatics given α-tocopherol supplements or placebo and studied for a marker of lipid peroxidation (FOX) (Pearson et al, 2006). The presence of other anti-oxidants in the body significantly reduces the ability of vitamin E to act as a pro-oxidant. The anti-oxidant status of an individual as well as the dose of α-tocopherol would therefore be important in dictating the pro-oxidant capacity of α-tocopherol (Rietjens et al, 2002). This theory has been supported by *in vitro* studies using human plasma and LDL (Bowry et al, 1992).

122. The other isoforms of vitamin E might be important; higher γ-tocopherol serum levels appear to be associated with a lower incidence of prostate cancer than α-tocopherol. This is also supported by the positive results of CLUE II: there was a five-fold reduction in the risk of prostate cancer for men in the highest quintile of serum γ-tocopherol levels (Huang *et al*, 2003). The highest risk for prostate cancer was in men with a combination of high α-tocopherol and selenium serum levels with a low concentration of γ-tocopherol. High serum levels of α-tocopherol appear to suppress levels of γ-tocopherol and this might be one of the reasons for the increased risk of prostate cancer in SELECT. The potential implications for public health could be important, given the popularity of α-tocopherol supplementation which may unintentionally deplete the body of γ-tocopherol (Hensley *et al*, 2004).

123. The placebo used in SELECT was soybean oil which is known to have high levels of γ-tocopherol. This higher intake of γ-tocopherol (which may have a greater protective effect than α-tocopherol) may be the reason for the lower incidence of prostate cancer in the placebo group compared to the treatment group. α-Tocopherol might have had a lower effect or no effect, but appeared to increase the risk in comparison as the relative risk is compared between the two groups.

124. Genetic variation in genes encoding for antioxidant proteins and in vitamin E transport genes could be associated with an increased risk of prostate cancer. Genetic polymorphisms could lead to different effects in different people exposed to the same antioxidant dose (Özten-Kandaş *et al*, 2011).

125. It is likely that the timing of supplementation is important in relation to stage of tumour development. The SU.VI.MAX study (Hercberg, 2004) indicated a greater reduction in cancer rate in men with normal PSA levels. There was a borderline non-significant increase in prostate cancer for men with elevated PSA levels.

126. Vitamin E intake was associated with a reduced risk of advanced /aggressive prostate cancer. This could be because it halts the progression of localized prostate cancer to advanced-stage prostate cancer (ATBC study group, 1994, Gann *et al*, 1999, Goodman *et al* 2003, Wright *et al*, 2007, Lawson 2007and Cheng *et al*, 2011).

Conclusions

127. Vitamin E is a strong antioxidant which may have a role in preventing the development of some forms of cancer. However, depending on the dose, vitamin E may act both as antioxidant and pro-oxidant.

128. Human studies looking at dietary and supplemental vitamin E intakes have generally shown no relationship or have indicated a decrease in risk of prostate cancer with higher intakes or serum levels of vitamin E. The SELECT study is the only study to show an apparent increase in development of prostate cancer with increasing vitamin E intakes. There is some evidence that the less common isoforms of vitamin E such as γ-tocopherol and the tocotrienols could reduce the risk of prostate cancer.

129. Supplementation with high doses of α-tocopherol (the most common form used in supplements) could decrease levels of the other isoforms which may increase the risk of developing prostate cancer.

130. The apparent increased risk of prostate cancer reported in the SELECT study could be an unreliable result as the placebo used in this study (soybean oil) is known to be rich in γ-tocopherol. As the placebo was not a physiologically inert substance but could have had a more protective effect than the active substance, the relative increase in risk might not be a true indicator of an increased risk with α-tocopherol supplementation.

131. Differences between UK and American diets with regards to α-/ γ-tocopherol ratios may also mean that the results of the SELECT study are not directly relevant to the UK.

132. The Committee noted that variation in screening methods between studies renders comparison difficult when reviewing the database on vitamin E and prostate cancer.

133. Overall, the Committee concluded that the available evidence does not indicate that vitamin E supplementation increases the risk of prostate cancer. The Committee has not reviewed possible associations with other types of cancer. The inverse relationship between vitamin E and prostate cancer risk in smokers seems to indicate that vitamin E supplementation might reduce the risk of prostate cancer in smokers.

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Appendix 1: Tables and Forest Plots on Human Studies

Case-Control Studies

Study Name	Description of population and study	Author conclusions	Definition of group corresponding to numerator of ratio	Definition of group corresponding to denominator of ratio	Endpoint related to ratio	Adjusted for:	Ratio type	OR/ RR/ HR	95% confidence interval limits	
									Lower	Upper
Study from Nigeria (Adaramoye, 2010 and Akinloye, 2009)	120 Nigerian patients from the Cancer Screening Unit, Ibadan, with prostate cancer and 50 controls. Blood PSA levels (ng/l) were compared with serum vitamin E in cases and controls.	Vitamin E levels were significantly lower in cases and were inversely related to PSA levels. Form not specified.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Case-control study from Brazil (Battisti et al 2011)	55 PCa patients at the Oncology Hematology Laboratory at Santa Maria; 55 healthy controls. Gleason score (degree of cancer progression) and vitamin E status compared.	Serum vitamin E levels were significantly lower in prostate cancer patients compared to 55 healthy controls. Significantly higher levels of lipid peroxidation products identified in prostate cancer patients compared to controls. Form not specified.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nested case-control study (Beilby et al, 2010)	Cases (n=96) and controls (n=225) taken from Australian asbestos workers (vitamin A supplementation)	No difference in baseline α-tocopherol levels between cases and controls.	Highest tertile of plasma α-tocopherol (17.54-40.07mg/L)	Lowest tertile of plasma α-tocopherol (9.0-14.36 mg/L)	Risk of developing PCa.	Age; administered vitamin A supplement	OR	1.46	0.78	2.73

PCa = Prostate cancer

Italian Study - five areas of Italy. (Bidoli et al, 2009)	1294 cases; 1451 controls. Vitamin E intake estimated through FFQ.	Estimated total vitamin E intake (dietary and supplemental; no differentiation made between forms) was statistically significantly inversely associated with risk of prostate cancer.	Highest tertile of vitamin E intake	Lowest tertile of vitamin E intake	Risk of developing PCa.	Age; study centre; period of interview; education; BMI; alcohol intake; smoking habits; family history of prostate cancer; total energy intake.	OR	0.78	0.58	0.96
Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	No observed associations between serum α-tocopherol and PCa risk overall.	Highest quartile of serum α-tocopherol levels (15.95-49.62mg/L). All subjects.	Lowest quartile of serum α-tocopherol levels (3.48-9.89mg/L). All subjects.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking status; smoking pack year; BMI; serum cholesterol.	OR	0.82	0.61	1.1
Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	No observed associations between serum α-tocopherol and PCa risk in former smokers.	Highest quartile of serum α-tocopherol levels (15.95-49.62mg/L). Former smokers.	Lowest quartile of serum α-tocopherol levels (3.48-9.89mg/L). Former Smokers.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking pack year; BMI; serum cholesterol.	OR	0.97	0.64	1.48
Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	Inverse association of α-tocopherol with prostate cancer risk in current smokers. High serum α-tocopherol associated with aggressive PCa in current smokers. Myeloperoxidase polymorphisms were found to influence results with greater risk of PCa in MPO G/A+A/A genotypes.	Highest quartile of serum α-tocopherol levels (15.95-49.62mg/L). Current smokers.	Lowest quartile of serum α-tocopherol levels (3.48-9.89mg/L). Current smokers.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking pack year; BMI; serum cholesterol.	OR	0.62	0.4	0.96

PCa = Prostate cancer

Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	No observed associations between serum γ-tocopherol and PCa risk overall.	Highest quartile of serum γ-tocopherol levels (3.61-15.27mg/L). All subjects.	Lowest quartile of serum γ-tocopherol levels (0.18-1.85mg/L). All subjects.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking status; smoking pack year; BMI; serum cholesterol.	OR	0.83	0.63	1.09
Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	687 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	No observed associations between serum γ-tocopherol and PCa risk in former smokers.	Highest quartile of serum γ-tocopherol levels (3.61-15.27mg/L). Former smokers.	Lowest quartile of serum γ-tocopherol levels (0.18-1.85mg/L). All subjects.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking pack year; BMI; serum cholesterol.	OR	0.86	0.58	1.25
Nested case-control study within β-Carotene and Retinol Efficacy Trial CARET; US based, multi-centre (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls.	High serum γ-tocopherol associated with aggressive PCa in current smokers. Myeloperoxidase polymorphisms were found to influence results with greater risk of PCa in MPO G/A+A/A genotypes.	Highest quartile of serum γ-tocopherol levels (3.61-15.27mg/L). Current smokers.	Lowest quartile of serum γ-tocopherol levels (0.18-1.85mg/L). All subjects.	Risk of developing PCa.	Age at enrolment; race; assigned group; family history of prostate cancer in first degree relatives; alcohol consumption; smoking pack year; BMI; serum cholesterol.	OR	0.78	0.53	1.16
Study from Montevideo, Uruguay (Deneo-Pellegrini et al, 1999)	175 cases and 233 controls	Estimated total vitamin E intake was statistically significantly lower in cases compared to controls and were inversely related to PSA levels. (dietary and supplemental. No differentiation made between forms of vitamin E.	Highest quartile of dietary intake of vitamin E (>7.9mg/day)	Lowest quartile of dietary intake of vitamin E (<5mg/day)	Risk of developing PCa.	Age; place of residence; urban/rural status; education; family history of prostate cancer; BMI; total energy intake.	OR	0.6	0.3	1.1

PCa = Prostate cancer

Nested case-control study in the ProTeCT cohort - an RCT of treatments for prostate cancer in the UK (Gilbert et al, 2012)	1,433 prostate cancer cases and 1,433 healthy controls	No evidence of associations between plasma vitamin E and risk of PCa or more aggressive PCa phenotypes. Form not specified.	Highest quintile of plasma Vitamin E levels (11.22-31.65mg/L).	Lowest quintile of plasma Vitamin E levels (0.22-2.4mg/L).	Risk of developing PCa.	Age.	OR	0.85	0.62	1.18
Nested case-control study in the Multi-ethnic cohort, Hawaii and California; Gill et al, 2009	Multi-ethnic Cohort, data collected between 1993 and 1996; residents of Hawaii and California, *n* = 29,009	No association between plasma α-tocopherol and risk of PCa or advanced PCa.	Highest quartile of plasma α-tocopherol levels (median 0.09mg/L)	Lowest quartile of plasma α-tocopherol levels (median 0.25mg/L)	Risk of developing PCa.	BMI; family history of prostate cancer; years of education; age at blood draw; number of fasting hours prior to blood draw.	OR	0.95	0.65	1.41
Nested case-control study in the Multi-ethnic cohort, Hawaii and California; Gill et al, 2009	Multi-ethnic Cohort, data collected between 1993 and 1996; residents of Hawaii and California, *n* = 29,009	No association between plasma γ-tocopherol and risk of PCa or advanced PCa.	Highest quartile of plasma γ-tocopherol levels (median 0.006mg/L)	Lowest quartile of plasma γ-tocopherol levels (median 0.034mg/L)	Risk of developing PCa.	BMI; family history of prostate cancer; years of education; age at blood draw; number of fasting hours prior to blood draw.	OR	0.95	0.65	1.39
Nested case-control study within β-Carotene and Retinol Efficacy Trial (CARET); US based, multi-centre (Goodman et al, 2003)	CARET study - a randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial of β-carotene 30 mg and retinol 25,000 IU/day. Current and former smokers; no never-smokers. 1985 – 1995.	α-Tocopherol levels statistically significantly lower in PCa cases compared to controls.	Highest quartile of plasma α-tocopherol levels (>16.79 mg/L)	Lowest quartile of plasma α-tocopherol levels (<10.66mg/L)	Risk of developing PCa.	No differences to results were found on adjusting for: Smoking; BMI; alcohol use; supplemental vitamins; asbestos exposure; carotenoid intake.	OR	0.59	0.34	1.04
Nested case-control study within β-Carotene and Retinol Efficacy Trial (CARET); US based, multi-centre (Goodman et al, 2003)	CARET study - a randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial of β-carotene 30 mg and retinol 25,000 IU/day. Current and former smokers; no never-smokers. 1985 – 1995.	No association found between γ-tocopherol and risk of PCa.	Highest quartile of plasma γ-tocopherol levels (>3.57 mg/L)	Lowest quartile of plasma γ-tocopherol levels (<1.75mg/L)	Risk of developing PCa.	No differences to results were found on adjusting for: Smoking; BMI; alcohol use; supplemental vitamins; asbestos exposure; carotenoid intake.	OR	0.86	0.5	1.48

PCa = Prostate cancer

Nested case-control study from CLUE I cohort; Washington County USA (Helzlsouer et al, 2000, Huang et al, 2003)	Campaign run in 1974 and samples collected from 9,804 men. Until 1996, 182 men had developed PCa. Two matched controls were selected for each case.	Serum α- tocopherol concentrations found to be slightly lower in cases compared to controls, but not statistically significant.	Highest quintile of plasma α-tocopherol level (>15.5mg/L)	Lowest quintile of plasma α-tocopherol levels (< 9.6mg/L).	Risk of developing PCa.	Age at diagnosis; number of years since blood was drawn; disease stage at diagnosis; history of cigarette smoking; BMI at 21 years; total blood lipid levels; hours since last meal; education.	OR	0.58	0.31	1.06
Nested case-control study from CLUE I cohort; Washington County USA (Helzlsouer et al, 2000, Huang et al, 2003)	Campaign run in 1974 and samples collected from 9,804 men. Until 1996, 182 men had developed PCa. Two matched controls were selected for each case.	Serum γ-tocopherol concentrations found to be statistically significantly lower in cases compared to controls. Statistically significant decrease in risk of PCa for higher concentrations of selenium and α-tocopherol when γ-tocopherol was above median level but not below.	Highest quintile of plasma γ-tocopherol level (>3.5mg/L)	Lowest quintile of plasma γ-tocopherol levels (< 1.6mg/L).	Risk of developing PCa.	Age at diagnosis; number of years since blood was drawn; disease stage at diagnosis; history of cigarette smoking; BMI at 21 years; total blood lipid levels; hours since last meal; education.	OR	0.77	0.42	1.43
Nested case-control study from CLUE II cohort; Washington County USA (Helzlsouer et al, 2000, Huang et al, 2003)	Campaign run in 1989 and samples collected from 10,456 men. Until 1996, 142 men had developed PCa. Two matched controls were selected for each case.	Serum α- tocopherol concentrations found to be slightly lower in cases compared to controls, but not statistically significant. A statistically significant decrease in PCa risk was associated with higher concentrations of selenium and α-tocopherol when γ-tocopherol was above the median level, but not when it was below.	Highest quintile of plasma α-tocopherol level (>17.5mg/L)	Lowest quintile of plasma α-tocopherol levels (< 10.4mg/L).	Risk of developing PCa.	Age at diagnosis; number of years since blood was drawn; disease stage at diagnosis; history of cigarette smoking; BMI at 21 years; total blood lipid levels; hours since last meal; education.	OR	0.78	0.41	1.5

PCa = Prostate cancer

Nested case-control study from CLUE II cohort; Washington County USA (Helzlsouer et al, 2000, Huang et al, 2003)	Campaign run in 1989 and samples collected from 10,456 men. Until 1996, 142 men had developed PCa. Two matched controls were selected for each case.	Serum γ-tocopherol concentrations found to be statistically significantly lower in cases compared to controls. Statistically significant decrease in risk of PCa for higher concentrations of selenium and α-tocopherol when γ-tocopherol was above median level but not below.	Highest quintile of plasma γ-tocopherol level (>4.1mg/L)	Lowest quintile of plasma γ-tocopherol levels (< 1.8mg/L).	Risk of developing PCa.	Age at diagnosis; number of years since blood was drawn; disease stage at diagnosis; history of cigarette smoking; BMI at 21 years; total blood lipid levels; hours since last meal; education.	OR	0.21	0.08	0.54
Nested case-control study from Washington County, USA (Hsing et al, 1990)	Samples collected in 1974 from blood collection campaign; 13 year follow-up.	Difference in serum levels between cases and controls not significant. Authors conclude there is no association between serum tocopherol levels and PCa.	Highest quartile serum total tocopherol levels (median for range 13mg/L)	Lowest quartile serum total tocopherol levels (median for range 9 mg/L)	Risk of developing PCa.	No differences to results were found on adjusting for: cigarette smoking; hours since last meal; years of education.	OR	1	0.37	2.69
Nested case-control study from Washington County, USA (Hsing et al, 1990)	Samples collected in 1974 from blood collection campaign; 13 year follow-up.	Difference in serum levels between cases and controls not significant. Authors conclude there is no association between serum tocopherol levels and PCa.	Highest quartile serum α- tocopherol levels (median for range 12.3mg/L)	Lowest quartile serum α- tocopherol levels (median for range 7.5 mg/L)	Risk of developing PCa.	No differences to results were found on adjusting for: cigarette smoking; hours since last meal; years of education.	OR	1	0.29	3.45
Nested case-control study from Washington County, USA (Hsing et al, 1990)	Samples collected in 1974 from blood collection campaign; 13 year follow-up.	Difference in serum levels between cases and controls not significant. Authors conclude there is no association between serum tocopherol levels and PCa.	Highest quartile serum γ- tocopherol levels (median for range 2.9mg/L)	Lowest quartile serum γ-tocopherol levels (median for range 1.4 mg/L)	Risk of developing PCa.	No differences to results were found on adjusting for: cigarette smoking; hours since last meal; years of education.	OR	1.17	0.39	3.47

PCa = Prostate cancer

Nested case-control study; The European Prospective Investigation into Cancer and Nutrition study (EPIC) (Key et al, 2007)	Blood samples from 137,001 men in 8 European countries collected between 1992 and 2000. After a mean of 6 years, 966 incident cases of prostate cancer with plasma were available. 1064 control subjects were selected and were matched.	No association between the plasma concentrations of α- and γ-tocopherol and PCa risk.	Highest quintile serum α- tocopherol levels (>168.0 mg/L)	Lowest quintile serum α- tocopherol levels (<113.2mg/L)	Risk of developing PCa.	Smoking status; alcohol intake; BMI; physical activity; marital status; education level.	OR	0.82	0.61	1.11
Nested case-control study; The European Prospective Investigation into Cancer and Nutrition study (EPIC) (Key et al, 2007)	Blood samples from 137,001 men in 8 European countries collected between 1992 and 2000. After a mean of 6 years, 966 incident cases of prostate cancer with plasma were available. 1064 control subjects were selected and were matched.	No association between the plasma concentrations of α- and γ-tocopherol and PCa risk.	Highest quintile serum γ- tocopherol levels (>16.11 mg/L)	Lowest quintile serum γ- tocopherol levels (<6.25mg/L)	Risk of developing PCa.	Smoking status; alcohol intake; BMI; physical activity; marital status; education level.	OR	1.33	0.93	1.9
Nested Case-control study from Finland (Knekt et al, 1988)	21,172 men from a screening study during 1966-1972; follow-up during 1968-1977.	Higher serum vitamin E levels associated with lower PCa risk.	Highest two quintiles of serum α- tocopherol levels (8.71->10.31 mg/L)	Lowest three quintiles of serum α-tocopherol levels (<6.1 - 8.7 mg/L)	Risk of developing PCa.	Age; municipality. No differences found on adjusting for smoking or serum cholesterol.	RR	0.58	0.19	1.76
Case-control study from King County, Washington, USA (Kristal et al, 1999)	Population based case-control study examining the association of dietary supplement use - including vitamin E - with PCa risk	Some evidence of a protective effect for individuals who took α-tocopherol supplements seven or more times per week.	Those consuming supplements containing vitamin E >7 times per week.	No supplements consumed	Risk of developing PCa.	Age; race; family history of prostate cancer; education; BMI; No of screening PSA tests in the 5 yrs before enrolment; dietary intakes of energy and fat.	OR	0.86	0.57	1.28

PCa = Prostate cancer

Nested case-control study in Japanese-American men in Hawaii (Nomura et al, 1997)	Examined from 1971 - 1975; follow-up of more than 20 years. 142 cases of PCa randomly selected from 284 cases identified.	Difference in mean serum levels between cases and controls not statistically significant.	Highest quartile of serum total tocopherol (levels not given)	Lowest quartile of serum total tocopherol (levels not given)	Risk of developing PCa.	Not given.	OR	0.9	0.5	1.9
Nested case-control study in Japanese-American men in Hawaii (Nomura et al, 1997)	Examined from 1971 - 1975; follow-up of more than 20 years. 142 cases of PCa randomly selected from 284 cases identified.	Difference in mean serum levels between cases and controls not statistically significant.	Highest quartile of serum α- tocopherol (levels not given)	Lowest quartile of serum α- tocopherol (levels not given)	Risk of developing PCa.	Not given.	OR	1.4	0.7	2.9
Nested case-control study in Japanese-American men in Hawaii (Nomura et al, 1997)	Examined from 1971 - 1975; follow-up of more than 20 years. 142 cases of PCa randomly selected from 284 cases identified.	Difference in mean serum levels between cases and controls not statistically significant.	Highest quartile of serum γ- tocopherol (levels not given)	Lowest quartile of serum γ- tocopherol (levels not given)	Risk of developing PCa.	Not given.	OR	0.7	0.3	1.5
Greek Study- greater Athens area. (Tzonou et al, 1999)	320 patients with confirmed PCa and 246 controls. Vitamin E intakes estimated through food frequency questionnaire.	Estimated total vitamin E intake was statistically significantly inversely associated with risk of prostate cancer. Form not specified.	Individuals showing an increment of 1 SD of daily intake amongst controls	Individuals showing an increment of 1 SD of daily intake amongst cases	Risk of developing PCa.	Age; height; BMI; years of education; total energy intake.	OR	0.53	0.3	0.94
Serbian Case-Control study; Vlajinac et al, 1997	101 patients and 202 matched controls.	Estimated total vitamin E intake was statistically significantly inversely related to prostate cancer. No dose-response relationship observed however.	Highest tertile of estimated dietary α-tocopherol levels (levels not given)	Lowest tertile of estimated dietary α-tocopherol levels (levels not given)	Risk of developing PCa.	Total dietary energy, [protein and fat; saturated fatty acids; carbohydrates; sugar; fibre; retinol; retinol equivalent; folic acid; vitamin B12, sodium; potassium; calcium; phosphorus; magnesium and iron.	OR	0.15	0.05	0.53
Nested case-control study in the ATBC cohort (Weinstein et al, 2005)	100 cases and 200 controls randomly chosen from the ATBC study.	Higher serum α-tocopherol was associated with a lower risk of PCa.	Highest tertile of serum α- tocopherol levels (>15.78 mg/L)	Lowest tertile of serum α- tocopherol levels (<12.60 mg/L)	Risk of developing PCa.	Serum cholesterol. No differences were found on adjusting for age at randomisation; BMI; height; smoking;	OR	0.49	0.24	1.01

PCa = Prostate cancer

Nested case-control study in the ATBC cohort (Weinstein et al, 2005)	101 cases and 200 controls randomly chosen from the ATBC study.	Higher serum γ-tocopherol was associated with a lower risk of PCa.	Highest tertile of serum γ- tocopherol levels (>1.08 mg/L)	Lowest tertile of serum γ- tocopherol levels (<0.76 mg/L)	Risk of developing PCa.	benign prostatic hyperplasia; physical activity; urban residence; education; marital status.	OR	0.57	0.31	1.06
Nested Case-control study in the PLCO screening trial, US based. (Weinstein et al; 2012)	Serum α- and γ-tocopherol concentrations in prostate cancer patients and controls	Higher α-tocopherol status is associated with a decreased risk of developing PCa. Association strongest in current and recent smokers.	Highest quintile of serum α- tocopherol levels (>24.5 mg/L)	Lowest quintile of serum α- tocopherol levels (<12.3 mg/L)	Risk of developing PCa.	Age; "several dietary and serum factors"; serum cholesterol concentration. No differences to results were found on adjusting for: height; weight; smoking status; physical activity; educational attainment; marital status; aspirin and ibuprofen use; history of diabetes; history of benign prostatic hyperplasia; family history of prostate cancer; average no. of prostate screens per year; serum selenium; month of blood draw; vitamin supplement use; intakes of total energy; fat; fruit; vegetables; alcohol; red meat; heterocyclic amines; lycopene; vitamin C; calcium.	OR	0.63	0.44	0.92
Nested Case-control study in the PLCO screening trial, US based. (Weinstein et al; 2012)	Serum α- and γ-tocopherol concentrations in prostate cancer patients and controls	Risk of PCa non-significantly elevated amongst men with higher γ-tocopherol levels.	Highest quintile of serum γ- tocopherol levels (>24.5 mg/L)	Lowest quintile of serum γ- tocopherol levels (<12.3 mg/L)	Risk of developing PCa.		OR	1.35	0.92	1.97

PCa = Prostate cancer

Prospective Cohort Studies

Study Name	Description of population and study	Authors conclusions	Definition of group corresponding to numerator of ratio	Definition of group corresponding to denominator of ratio	Endpoint related to ratio	Adjusted for:	Ratio type	OR/ RR/ HR	95% confidence interval limits	
									Lower	Upper
Health Professionals Follow-up Cohort Study (HPFS) (Chan et al, 1999)	47,780 US male health professionals and risk of PCa examined. 1896 PCa cases diagnosed between 1986 and 1996. Non-smokers.	Supplemental vitamin E intake not significantly associated with prostate cancer incidence.	Non-smokers using vitamin E supplements (intake of >100mg/day)	Non-smokers not using vitamin E supplements	Diagnosis of PCa	Time period within study; age; family history of prostate cancer; vasectomy status; quintiles of current BMI; quintiles of BMI at 21 yrs; physical activity at enrolment; quintiles of total calories, calcium, lycopene, fructose and fat intake per day at enrolment.	RR	1.02	0.86	1.21
Health Professionals Follow-up Cohort Study (HPFS) (Chan et al, 1999)	47,780 US male health professionals and risk of PCa examined. 1896 PCa cases diagnosed between 1986 and 1996. Non-smokers.	Supplemental vitamin E intake not significantly associated with prostate cancer incidence.	Non-smokers using vitamin E supplements (intake of >100mg/day)	Non-smokers not using vitamin E supplements	Diagnosis of metastatic PCa		RR	1.42	0.87	2.32
Health Professionals Follow-up Cohort Study (HPFS) (Chan et al, 1999)	47,780 US male health professionals and risk of PCa examined. 1896 PCa cases diagnosed between 1986 and 1996. Smokers.	Supplemental vitamin E intake not significantly associated with prostate cancer incidence.	Smokers using vitamin E supplements (intake of >100mg/day)	Smokers not using vitamin E supplements	Diagnosis of PCa		RR	1.27	0.97	1.66
Health Professionals Follow-up Cohort Study (HPFS) (Chan et al, 1999)	47,780 US male health professionals and risk of PCa examined. 1896 PCa cases diagnosed between 1986 and 1996. Smokers.	Supplemental vitamin E intake not significantly associated with prostate cancer incidence.	Smokers using vitamin E supplements (intake of >100mg/day)	Smokers not using vitamin E supplements	Diagnosis of metastatic PCa		RR	0.44	0.18	1.07
Cohort Study; Basel, Switzerland (Eichholzer et al, 1996, 1999)	Healthy smokers from 1971 - 1973; followed-up in 1990.	Low plasma vitamin E levels in smokers statistically significantly related to increased risk of PCa.	Healthy smokers with low vitamin E status (<12.91 mg/L) - survivors	Healthy smokers with low vitamin E status (<12.91 mg/) - deaths from PCa.	Death from PCa	Age; smoking; plasma lipid concentration; cholesterol.	RR	3.26	1.27	8.36

PCa = Prostate cancer

Cohort Study; Basel, Switzerland (Eichholzer et al, 1996, 1999)	Healthy non-smokers from 1971 - 1973; followed-up in 1990.	No relationship between vitamin E status and risk of PCA in non-smokers.	Healthy non-smokers with low vitamin E status (<12.91 mg/L) - survivors	Healthy non-smokers with low vitamin E status (<12.91 mg/) - deaths from PCa.	Death from PCa	Age; smoking; plasma lipid concentration; cholesterol.	RR	0.76	0.25	2.36
Nested cohort from PLCO study (Kirsh et al, 2006)	Dietary and supplemental intakes evaluated. After a median follow-up of 4.2 years, 1338 out of 29,631 men were diagnosed with PCa.	No association between prostate cancer risk and dietary or supplemental intake of vitamin E in general population.	Men with a supplemental intake >400mg/day vitamin E	Men with a supplemental intake of 0mg/day vitamin E	Diagnosis of PCa	Age; total energy; race; study centre; family history of prostate cancer; BMI; smoking status; physical activity; total fat intake; red meat intake; history of diabetes; aspirin use; number of screening examinations during follow-up period.	RR	0.97	0.83	1.13
Nested cohort from PLCO study (Kirsh et al, 2006)	Dietary and supplemental intakes evaluated. After a median follow-up of 4.2 years, 1338 out of 29,631 men were diagnosed with PCa.	No association between prostate cancer risk and dietary or supplemental intake of vitamin E in general population.	Men with a dietary intake >15.8mg/day vitamin E	Men with a median dietary intake of 8.6mg/day vitamin E	Diagnosis of PCa	Age; total energy; race; study centre; family history of prostate cancer; BMI; smoking status; physical activity; total fat intake; red meat intake; history of diabetes; aspirin use; number of screening examinations during follow-up period.	RR	0.93	0.78	1.12
Nested cohort from PLCO study (Kirsh et al, 2006)	Dietary and supplemental intakes evaluated. After a median follow-up of 4.2 years, 1338 out of 29,631 men were diagnosed with PCa.	Among current and recent smokers a decreasing risk of developing PCa was found with increasing vitamin E supplementation.	Current and recent smokers with a supplemental intake >400mg/day vitamin E	Current and recent smokers with a supplemental intake of 0mg/day vitamin E	Diagnosis of PCa	Age; total energy; race; study centre; family history of prostate cancer; BMI; smoking status; physical activity; total fat intake; red meat intake; history of diabetes; aspirin use; number of screening examinations during follow-up period.	RR	0.29	0.12	0.68

PCa = Prostate cancer

A nested cohort study in the Prostate Cancer Prevention Trial (Kristal et al, 2010)	9,559 participants. Nutrient and supplement-use intake assessed using a food frequency questionnaire.	No association between prostate cancer risk and supplemental intake of vitamin E in general population. Data for dietary vitamin E intake too poor to draw conclusions.	Participants with a supplemental intake >30mg/day vitamin E and a Gleason score of 2-7 (low grade)	Participants with a supplemental intake of <8mg/day vitamin E and a Gleason score of 2-7 (low grade)	Diagnosis of PCa	Age; race/ethnicity; family history of prostate cancer in first degree relatives; treatment arm; BMI.	OR	1.08	0.96	1.23
A nested cohort study in the Prostate Cancer Prevention Trial (Kristal et al, 2010)	9,559 participants. Nutrient and supplement-use intake assessed using a food frequency questionnaire	No association between prostate cancer risk and supplemental intake of vitamin E in general population. Data for dietary vitamin E intake too poor to draw conclusions.	Participants with a supplemental intake >30mg/day vitamin E and a Gleason score of 8-10 (high grade)	Participants with a supplemental intake <8mg/day vitamin E and a Gleason score of 8-10 (high grade)	Diagnosis of PCa	Age; race/ethnicity; family history of prostate cancer in first degree relatives; treatment arm; BMI.	OR	1.21	0.82	1.78
The National Institutes of Health - AARP Diet and Health Prospective Study (Wright et al 2007 and Lawson 2007)	295,344 men aged 50 to 71 years, enrolled in the NIH-AARP Diet and Health Study in 1995 - 1996. Data on supplemental vitamin E intake, multivitamin use etc. collected through questionnaires	No relationship observed for vitamin E supplementation and total or localised PCa. A suggested inverse association observed for total PCa but not statistically significant.	Men with a supplemental intake >800mg/day of α-tocopherol equivalents.	Men with a supplemental intake of 0mg/day α-tocopherol equivalents.	Diagnosis of PCa	Age; race; smoking status; education; personal history of diabetes; family history of prostate cancer; BMI; dietary intakes of red meat,α-linolenic acid, vitamin C and β-carotene (inc. supps).	RR	0.86	0.65	1.13
The National Institutes of Health - AARP Diet and Health Prospective Study (Wright et al 2007 and Lawson 2007)	295,344 men aged 50 to 71 years, enrolled in the NIH-AARP Diet and Health Study in 1995 - 1996. Data on supplemental vitamin E intake, multivitamin use etc. collected through questionnaires	Increased consumption of γ-tocopherol from foods is associated with a statistically significantly reduced risk of PCa.	Men in the top quintile of γ-tocopherol dietary intake (18.2-57.5 mg/day)	Men in the bottom quintile of γ-tocopherol dietary intake (0.53-9.7 mg/day)	Diagnosis of PCa	Age; race; smoking status; education; personal history of diabetes; family history of prostate cancer; BMI; dietary intakes of red meat,α-linolenic acid, vitamin C and β-carotene (inc. supps).	RR	0.68	0.56	0.84

PCa = Prostate cancer

The National Institutes of Health - AARP Diet and Health Prospective Study (Wright et al 2007 and Lawson 2007)	295,344 men aged 50 to 71 years, enrolled in the NIH-AARP Diet and Health Study in 1995 - 1996. Data on supplemental vitamin E intake, multivitamin use etc. collected through questionnaires	Association between supplemental vitamin E and prostate cancer risk did not vary according to smoking status. When multivitamin users were excluded, a significant inverse relationship was found between high dose supplemental vitamin E users and localised prostate cancer amongst current/recent smokers.	Male smokers with a supplemental intake >800mg/day of α-tocopherol equivalents.	Male smokers who never use supplements	Diagnosis of PCa	Age; race; education; personal history of diabetes; family history of prostate cancer; BMI; dietary intakes of red meat,α-linolenic acid, vitamin C and β-carotene (inc. supps).	RR	0.52	0.29	0.94
The National Institutes of Health - AARP Diet and Health Prospective Study (Wright et al 2007 and Lawson 2007)	295,344 men aged 50 to 71 years, enrolled in the NIH-AARP Diet and Health Study in 1995 - 1996. Data on supplemental vitamin E intake, multivitamin use etc. collected through questionnaires		Male non-smokers with a supplemental intake >800mg/day of α-tocopherol equivalents.	Male smokers who never use supplements	Diagnosis of PCa	Age; race; education; personal history of diabetes; family history of prostate cancer; BMI; dietary intakes of red meat,α-linolenic acid, vitamin C and β-carotene (inc supps).	RR	0.86	0.59	1.24
The National Institutes of Health - AARP Diet and Health Prospective Study (Wright et al 2007 and Lawson 2007)	295,344 men aged 50 to 71 years, enrolled in the NIH-AARP Diet and Health Study in 1995 - 1996. Data on supplemental vitamin E intake, multivitamin use etc. collected through questionnaires		Men who smoked more than ten years ago with a supplemental intake >800mg/day of α-tocopherol equivalents.	Male smokers who never use supplements	Diagnosis of PCa	Age; race; education; personal history of diabetes; family history of prostate cancer; BMI; dietary intakes of red meat,α-linolenic acid, vitamin C and β-carotene (inc supps).	RR	0.83	0.61	1.12

PCa = Prostate cancer

Large US prospective cohort study VITamins And Lifestyle (VITAL) study (White et al, 2004 and Peters et al, 2008)	35,242 men recruited between 2000 and 2002 from western Washington State completed a questionnaire about vitamin E and selenium supplement intake during the past 10 years from multivitamins and single supplements. 830 new cases of PCa identified up to 2004.	A 10 year average intake (~400mg/day) of supplemental vitamin E was not associated with a reduced risk of PCa.	Men with a supplemental intake >400mg/day vitamin E	Men who never used supplements	Diagnosis of PCa	Age; family history of prostate cancer; benign prostatic hyperplasia; income; multivitamin use; stratified on PSA screening in the 2 years before baseline.	HR	0.86	0.65	1.1
Large US prospective cohort study VITamins And Lifestyle (VITAL) study (White et al, 2004 and Peters et al, 2008)	35,242 men recruited between 2000 and 2002 from western Washington State completed a questionnaire about vitamin E and selenium supplement intake during the past 10 years from multivitamins and single supplements. 830 new cases of PCa identified up to 2004.	Intakes of =/> 400mg/day vitamin E supplements statistically significantly decreased risk of advanced PCa.	Men with a supplemental intake >400mg/day vitamin E	Men who never used supplements	Diagnosis of advanced PCa	Age; family history of prostate cancer; benign prostatic hyperplasia; income; multivitamin use; stratified on PSA screening in the 2 years before baseline.	HR	0.43	0.19	1
US-based Rodriguez et al; 2004	Following enrolment in 1992-3, 72704 men completed a detailed questionnaire of supplement use. 4281 cases of PCa were identified	Regular vitamin E supplement use was not associated with overall risk of PCa.	Men with a supplemental intake >400mg/day vitamin E	Men who never used supplements	Diagnosis of PCa	Age; race; BMI; education; energy adjusted calcium; total fat; lycopene intake; total calorie intake; family history of prostate cancer; PSA history.	RR	0.98	0.89	1.08

PCa = Prostate cancer

US-based Rodriguez et al; 2005	Following enrolment in 1992-3, 72704 men completed a detailed questionnaire of supplement use. 4281 cases of PCa were identified	Among current smokers, a non-statistically significantly reduced risk of PCa was observed.	Smokers with a supplemental intake >400mg/day vitamin E	Smokers who never used supplements	Diagnosis of PCa	Age; race; BMI; education; energy adjusted calcium; total fat; lycopene intake; total calorie intake; family history of PCa; PSA history.	RR	0.87	0.58	1.31
Study from the Netherlands (Schuurman et al 2002)	58,279 men aged 55-69. 642 cases of prostate carcinoma were identified.	Estimated total vitamin E levels were not statistically significantly related to risk of PCa.	Men in the highest quintile of vitamin E intake (mean intake 23.6mg/day)	Men in the lowest quintile of vitamin E intake (mean intake 7.1 mg/day)	Diagnosis of PCa	Age; family history of prostate cancer; socioeconomic status; alcohol from white or fortified wine.	RR	0.94	0.68	1.29
Prospective Cohort study (Shibata et al, 1992)	Prospective Cohort study in an initially healthy US based elderly cohort. 208 cases of prostate cancer were diagnosed.	No significant effect of vitamin E supplementation was observed on prostate cancer incidence.	Those taking vitamin E supplements.	Those not taking vitamin E supplements.	Diagnosis of PCa	Age; smoking.	RR	1.00	0.76	1.31
Prospective Study; Royal Marsden Hosp. UK (Venkitaraman et al, 2010)	PCa patients on active surveillance in 2002, followed up after 2.5 years	Tocopherol levels were not related to PSA levels; PSA velocity; disease progression; Gleason score; adverse histology and biopsy.	Time to progression of PCa	Serum α-tocopherol levels	Time to disease progression defined by adverse histology on repeat biopsy or significant elevation in PSA level.	Nothing. No changes to ratio when adjusted for age or initial PSA result (and others but not specified).	HR	1.01	0.895	1.142
Prospective Study; Royal Marsden Hosp. UK (Venkitaraman et al, 2010)	PCa patients on active surveillance in 2002, followed up after 2.5 years	Tocopherol levels were not related to PSA levels; PSA velocity; disease progression; Gleason score; adverse histology and biopsy.	Time to progression of PCa	Serum γ-tocopherol levels	Time to disease progression defined by adverse histology on repeat biopsy or significant elevation in PSA level.	Nothing. No changes to ratio when adjusted for age or initial PSA result (and others but not specified).	HR	0.87	0.236	3.232

PCa = Prostate cancer

Randomised Controlled Trials

Study Name	Description of population and study	Authors conclusions	Definition of group corresponding to numerator of ratio	Definition of group corresponding to denominator of ratio	Endpoint related to ratio	Ratio type	OR/ RR/ HR	95% confidence interval limits	
								Lower	Upper
ATBC study (Albanes et al, 1995, ATBC study group 1994, Heinonen et al, 1998)	α-Tocopherol and β-carotene supplementation in 29,133 white, male smokers from Finland. Supplementation with all rac - α-tocopherol alone (50mg) or in combination with β-carotene was continued for 5-8 years 1985 - 1993 (median, 6.1 years) 246 cases of PCa.	No significant associations between baseline serum α-tocopherol or dietary vitamin E and PCa overall.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fleshner et al, 2011	Randomised Phase III double-blind study in 303 men with diagnosed HGPIN. Patients received 20g soy protein, 400 IU of vitamin E and 100mcg selenium or a whey based control twice a day for 3 years.	No significant relationship between supplementation and progression of HGPIN to PCa.	Three year disease free survival in those not taking supplement	Three year disease free survival in those taking supplement	Disease-free survival	HR	1.034	0.67	1.61
Physicians' Health Study II (PHS II) (Gaziano et al, 2009)	Randomized, double-blind, placebo-controlled factorial trial of vitamins E and C. From 1997-2007. 14,641 male physicians in the US (50 years or older. mean follow-up of 8 years	Supplementation was not associated with a reduction in risk of PCa.	Group receiving vit E supplements (400mg/day)	Groups receiving placebo	Incidence of PCa.	HR	0.97	0.85	1.09
Randomised trial (Joniau et al, 2007)	100 men diagnosed with HGPIN received a supplement containing 100mcg selenium, 30mg vitamin E and 50mg soy isoflavonoids twice a day for 6 months. No control was used.	A decrease in the PSA levels whilst taking the supplement was associated with a statistically significant reduction in risk of PCa.	N/A	N/A	N/A	N/A	N/A	N/A	N/A

PCa = Prostate cancer

ATBC trial based cohort study (Hartman et al, 1998)	See ATBC study group for description. 9 years follow-up (median 7 y); 317 cases of PCa.	No significant associations between baseline serum α-tocopherol or dietary vitamin E and PCa overall.	Highest quartile of serum α-tocopherol levels in individuals assigned to the supplementation arm of trial (>13.6mg/L)	Lowest quartile of serum α-tocopherol levels in individuals assigned to the supplementation arm of trial (<9.78mg/L)	Risk of developing PCa	RR	0.76	0.42	1.37
ATBC trial based cohort study (Hartman et al, 1998)	See ATBC study group for description. 9 years follow-up (median 7 y); 317 cases of PCa.	No significant associations between baseline serum α-tocopherol or dietary vitamin E and PCa overall.	Highest quartile of serum α-tocopherol levels in individuals assigned to the control arm of trial (>13.6mg/L)	Lowest quartile of serum α-tocopherol levels in individuals assigned to the control arm of trial (<9.78mg/L)	Risk of developing PCa	RR	0.98	0.6	1.6
The Heart Protection Study: (HPS Group, 2002).	Randomised controlled trial of antioxidant supplementation carried out between 1994 and 2001. 15,454 men UK-based aged 40-80.	No significant difference in the incidence of PCa between the supplementation (1.8% developed PCa) and placebo (2.0% developed PCa) groups.	Individuals allocated to receive supplements.	Individuals allocated to receive placebo.	Risk of developing cancer of the genito-urinary tract - all types.	RR	0.86	0.73	1.02
SU.VI.MAX (Hercberg et al, 2004; Meyer et al, 2005)	5141 French men aged 45-60 years recruited from 1994 to 1995. Median follow-up of 9 years in the supplement arm and 8.8 years in the placebo arm. A daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E (α-tocopherol), 6 mg of β-carotene, 100 µg of selenium, and 20 mg of zinc, or a placebo. 103 cases of PCa diagnosed.	A non-significant reduction in PCa rate found in the supplementation group when compared to placebo. In men with baseline PSA <3µg/l (>90% of the population) there was a statistically significant reduction in rate of PCa with supplementation. For men with elevated PSA at baseline, supplementation was associated with a non-significant increased incidence of PSA.	Individuals allocated to receive supplements.	Individuals allocated to receive placebo.	Development of PCa.	HR	0.88	0.6	1.29
Randomised, double blind controlled trials - HOPE and HOPE-TOO (HOPE and HOPE-TOO trial investigators, 2005)	Double-blind, randomised, placebo-controlled trial. From 1993 - 1999; extended to 2003, median follow-up of 7 years. HOPE (n=9541) and HOPE-TOO (n=7030)	No overall effect of vitamin E on the incidence of fatal and non-fatal cancers.	Individuals allocated to receive supplements In HOPE trial	Individuals allocated to receive placebo in HOPE trial.	Development of PCa.	RR	0.98	0.76	1.26

PCa = Prostate cancer

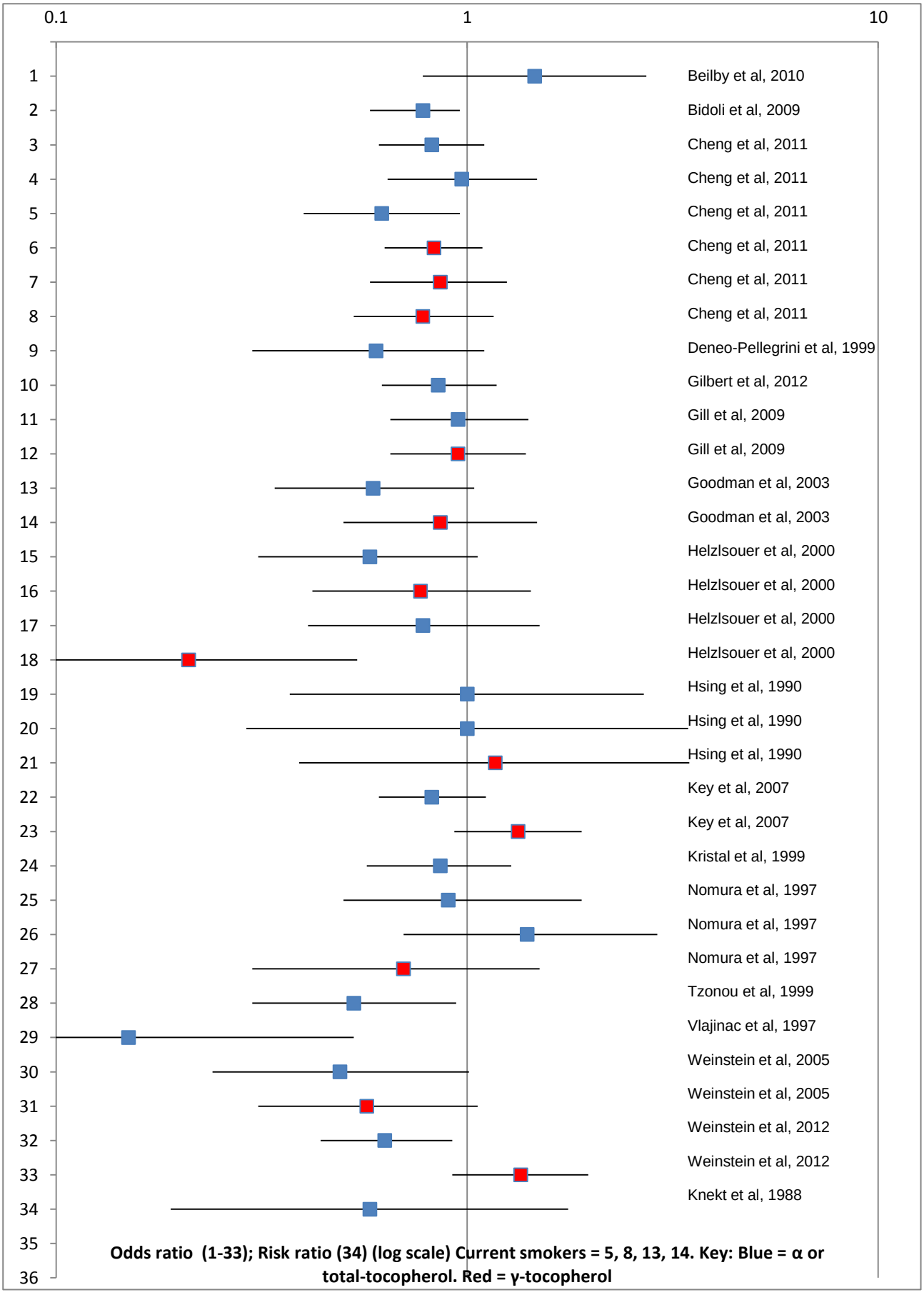
Randomised, double blind controlled trials - HOPE and HOPE-TOO (HOPE and HOPE-TOO trial investigators, 2005)	Double-blind, randomised, placebo-controlled trial. From 1993 - 1999; extended to 2003, median follow-up of 7 years. HOPE (n=9541) and HOPE-TOO (n=7030)	No overall effect of vitamin E on the incidence of fatal and non-fatal cancers.	Individuals allocated to receive supplements In HOPE-TOO trial	Individuals allocated to receive placebo in HOPE-TOO trial.	Development of PCa.	RR	0.9	0.68	1.19
Age-related eye disease study (Johnson et al, 2007)	A randomised, placebo controlled trial in 3640 patients with age-related macular degeneration. Patients received zinc, antioxidants (500mg vitamin C, 400mg vitamin E and 15mg β-carotene), both or neither.	A statistically significant decrease in PCa cancer diagnoses were seen innpatients receiving antioxidants compared to the placebo group. This was significant in men who smoked but not in non-smokers.	Patients receiving anti-oxidants	Patients receiving placebo	Development of PCa.	RR	0.6	0.49	0.86
The Prevention Research Veteran Affairs E-vitamin Nutrition Trial (Hernandez et al, 2005)	Pilot RCT in 44 patients with increased PSA and/or abnormal digital rectal examination assigned to receive 400 IU α-tocopherol (form not stated) for 18 months or placebo. Serum PSA, androgens and IGF-1 were measured at 3, 6, 9, 12, 15 and 18 months.	α-tocopherol did not affect the levels of PSA, serum androgens or IGF-1 in patients with increased PSA and/or abnormal digital rectal examination.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Supplemental treatment in patients with hormonally untreated carcinoma (Hoenjet et al, 2005)	RCT in 80 patients with hormonally untreated prostate carcinoma and elevated PSA levels were randomised to receive a daily supplement containing 350mg RRR-α-tocopherol along with selenium, vitamin C and coenzyme Q10 or placebo for 21 weeks.	Supplementation did not affect serum PSA or hormone levels in patients with hormonally untreated carcinoma of the prostate.	N/A	N/A	N/A	N/A	N/A	N/A	N/A

PCa = Prostate cancer

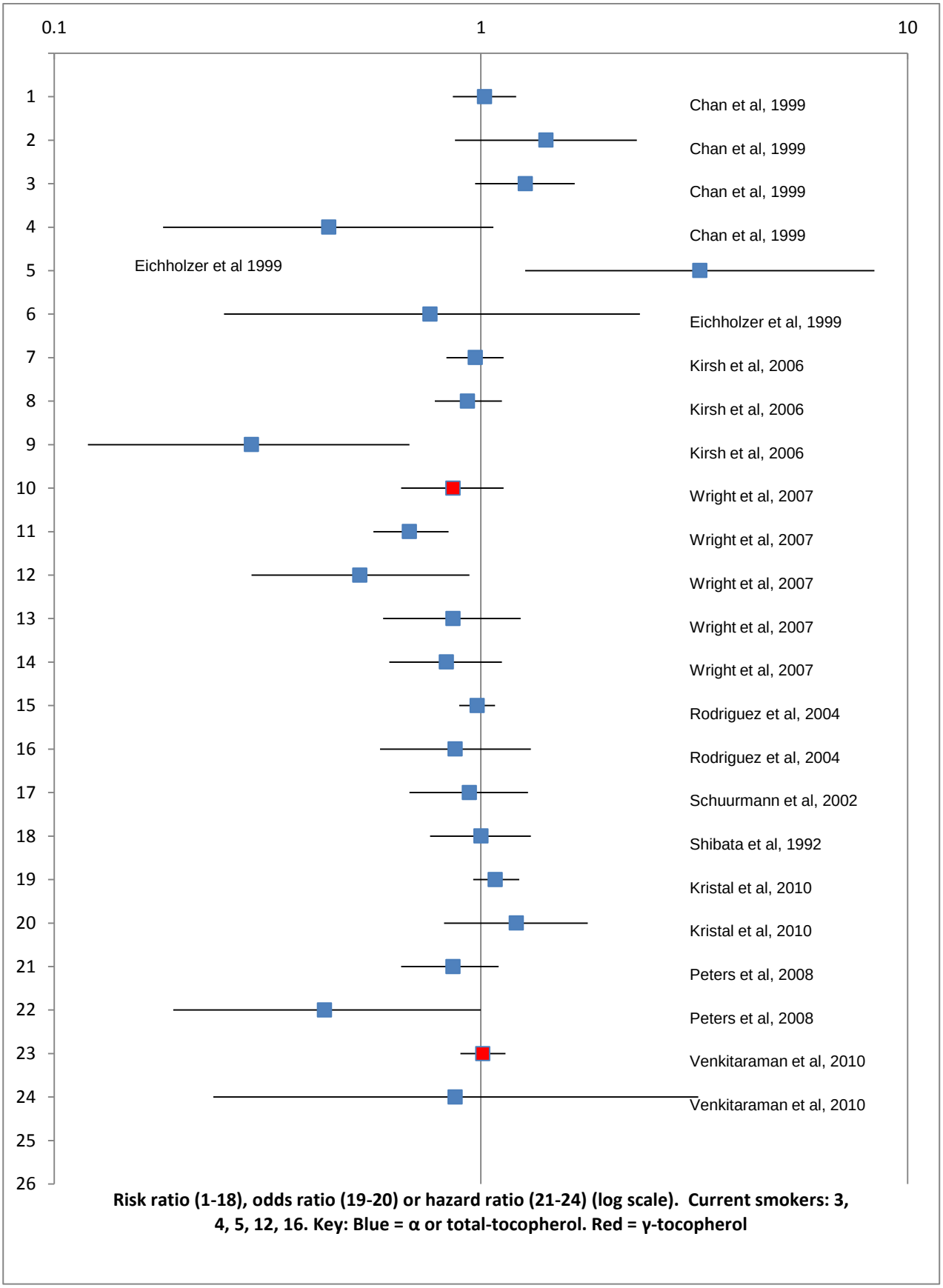
Randomised double blind placebo-controlled trial - Selenium and Vitamin E Cancer Prevention Trial (SELECT); US, Canada and Puerto Rico. (Lippman et al, 2009; Klein et al, 2000; Klein et al, 2011)	Phase III prospective, 2x2 factorial clinical trial of selenium and/or vitamin E for a minimum of 7 years (maximum of 12 years). 35,553 men recruited from 427 sites. Data reviewed in 2008 and supplementation stopped. Followed up until July 2009.	The risk of PCa at 7 years of median follow-up was increased by 17% in men supplemented with vitamin E alone.	Patients receiving vitamin E (99% CI)	Patients receiving placebo (99% CI)	Development of PCa.	HR	1.13	0.95	1.35
Effect of a dietary supplement on the rate of increase of PSA (Schröder et al, 2005)	Randomised, double-blind, placebo-controlled crossover study in 49 men with PCa and rising PSA. main ingredients of the supplement were soy, isoflavones, lycopene, silymarin and antioxidants (an α-tocopherol level of 75 mg per daily dose).	Supplement delayed PSA progression. A 2.6-fold increase in PSA doubling time from 445-1150 days for supplement vs. control group.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ATBC-trial based cohort study (Watters et al, 2009)	See ATBC study group for description. Followed up until 2005 (20 years); 1,891 cases of PCa, 395 deaths due to PCa	Higher baseline serum α-tocopherol levels and α-tocopherol supplementation was associated with improved PCa survival.	Highest quintile of α-tocopherol supplementation at 3 years into the study	Lowest quintile of α-tocopherol supplementation at 3 years into the study	Death from prostate cancer	HR	0.26	0.09	0.71

PCa = Prostate cancer

Forest Plot – Case-Control Studies

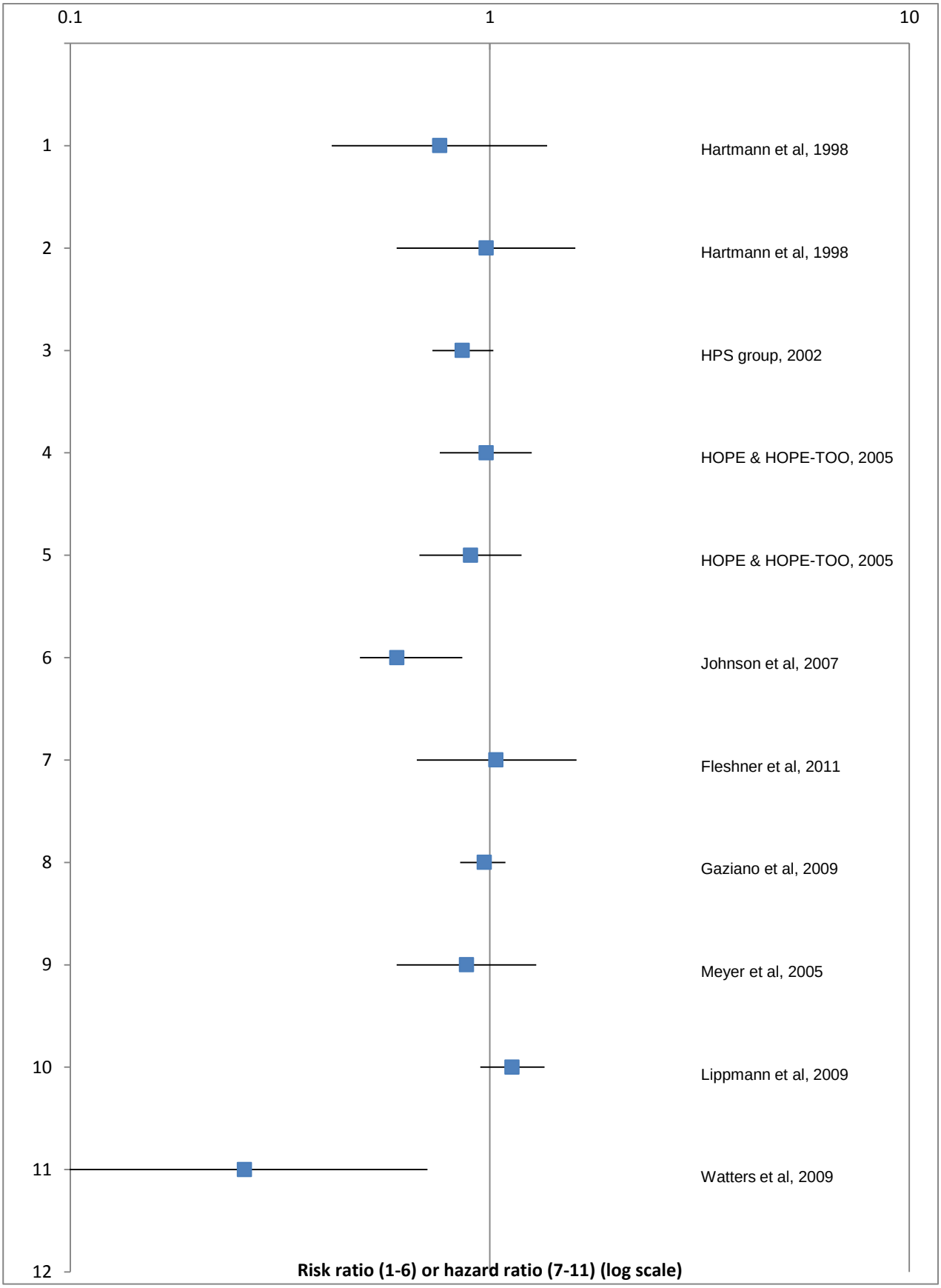


Forest Plot –Prospective Cohort Studies



Risk ratio (1-18), odds ratio (19-20) or hazard ratio (21-24) (log scale). Current smokers: 3, 4, 5, 12, 16. Key: Blue = α or total-tocopherol. Red = γ-tocopherol

Forest Plot – Randomised Controlled Trials



Executive Summary

134. Vitamin E is an antioxidant and may help control cell damage that can lead to cancer. While some *in vitro* studies in human prostate carcinoma cell lines, animal experiments in a range of species as well as some observational and intervention studies in humans had indicated that vitamin E could prevent and reduce the risk of prostate cancer; other studies have shown no significant association. Results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which investigated the hypothesised chemoprotective effects of selenium and vitamin E, suggested that vitamin E supplementation in the general population of healthy men significantly increased the risk of prostate cancer. SELECT is the first study that has reported an increased risk of prostate cancer with vitamin E supplementation.

135. The results from this study prompted the Food Standards Agency to request an opinion from the Committee on Carcinogenicity (COC) on the current literature on vitamin E and prostate cancer with an emphasis on the SELECT study.

136. Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds. Vegetable oils and vegetable oil-containing products such as margarine, mayonnaise and shortening are the richest sources of natural vitamin E in the diet, followed by whole-wheat products and nuts.

137. Vitamin E is the collective name for at least eight different biologically active compounds called tocopherols and tocotrienols of which each come in 4 different isoforms: α-, β-, γ- and δ-. α-Tocopherol has the greatest biological activity but there is evidence to suggest that γ-tocopherol may be involved in anti-carcinogenic pathways, especially of the prostate. Additionally there was some evidence to suggest that high intakes of α-tocopherol may interfere with this protective activity of γ-tocopherol.

138. The Committee noted the evidence that vitamin E can act as both an anti-oxidant and a pro-oxidant depending on the dose. Therefore high doses of vitamin E may increase the risk of cancer.

139. The balance of evidence suggests that supplemental doses of vitamin E at average levels have no effect on the risk of prostate cancer although the Committee noted that there may be a protective effect in smokers. The results from the SELECT study were considered to be anomalous and the Committee discussed the reasons for this:

a. The high doses of α-tocopherol used in the SELECT study may act as a pro-oxidant and cause oxidative stress thus increasing the risk of cancer. The high doses of α-tocopherol may also interfere with the protective activity of γ-tocopherol.

b. The placebo used was soya-bean oil, known to be high in γ-tocopherol and δ-tocopherol in addition to small amounts of α-tocopherol, α-tocotrienol and β-tocotrienol. This marginally higher intake of γ- and δ- tocopherols and tocotrienols by the placebo group in addition to the concurrent lowering of γ-tocopherol levels in the supplemented group may be the reason for the relatively lower number of prostate cancer cases in the placebo group.

c. Members felt that many important confounders were not adequately dealt with in the SELECT study such as obesity, genetic variation and other dietary factors.

140. The Committee concluded that the results from the SELECT study were anomalous and that the balance of evidence suggests that vitamin E status has no effect on the risk of prostate cancer in non-smokers. There is limited evidence to suggest that vitamin E may be protective against prostate cancer in smokers. The Department of Health advise that most people can obtain all the vitamin E they need from a healthy balanced diet.

Lay summary

Vitamin E is a nutrient that is necessary for healthy functioning of the body. It is fat-soluble and acts as an anti-oxidant in the fat rich areas of each cell in the body. Anti-oxidants prevent the oxidation of other molecules in the body. Oxidation reactions can produce chemicals called free-radicals which can initiate chain reactions in the cells of the body which can result in damage to the cells or even cell death. Vitamin E can be found in a range of fatty foods from vegetable and animal origin. Vitamin E is also commonly taken in supplement form either on its own or in multi-vitamins.

Vitamin E is actually the collective term for a family of different molecules which all have slightly different chemical structures. There are at least eight different types of vitamin E that have biological activity: alpha-, beta-, gamma- and delta- tocopherol and alpha-, beta-, gamma- and delta-tocotrienol. The form with traditional vitamin E activity is α-tocopherol and this is also the most common form absorbed into the body from the diet. The other forms are absorbed by the body but are not active as vitamin E. There is, however, some evidence that γ-tocopherol could have anti-cancer properties and animal studies have suggested an anti-cancer role for γ-tocopherol in the prostate.

A number of studies have been carried out looking at the relationship between vitamin E consumption and the development of prostate cancer. These include, in vitro studies using individual animal or human cell lines, animal studies and studies in human population groups. The vast majority of these studies have found vitamin E to either be protective against prostate cancer or to have no effect on prostate cancer incidence.

The SELECT study was a large study of 35,553 men from the US, Canada and Puerto Rico with no signs of having developed prostate cancer. The study was designed to find out whether vitamin E, selenium or the combination could reduce the risk of prostate cancer occurring. The group was divided into four, with the following treatment regimens: 1) placebo (a sham or inactive treatment); 2) selenium; 3) Vitamin E or 4) selenium + vitamin E. After following up the participants for 7 years, the group who had consumed the vitamin E alone had a 17% relative increase in cases of prostate cancer compared to the placebo group.

The concerns raised by this study prompted the Food Standards Agency to request that the Committee on Carcinogenicity in Foods, Consumer Products and the Environment review the literature available on vitamin E and prostate cancer with a focus on the SELECT study.

The Committee identified a number of short-comings in the SELECT study which may have contributed to the unexpected results. These included the following:

1) The doses of α-tocopherol used in the SELECT study were very high. As with all substances in the body, too much vitamin E can cause adverse effects at high levels. This means that there is an optimal dose of vitamin E which may be exceeded in the SELECT study.
2) There is some evidence that high doses of the α-tocopherol as were used in the SELECT study could inhibit the anti-cancer activity of γ-tocopherol.
3) The placebo used was soya bean oil; this may not have been inactive as a placebo should have been, as it is known to be rich in γ-tocopherol and could have been more protective against prostate cancer than the selenium and vitamin E supplements which were being investigated. Therefore the perceived relative increase in prostate cancer in the vitamin E group may actually be a relative reduction in prostate cancer in the placebo group.

Other differences between the study designs make it difficult to compare the SELECT study with other studies looking at vitamin E intake and prostate cancer. These include the way that vitamin E intake is calculated and other lifestyle factors such as obesity and smoking which are known to affect the risk of prostate cancer occurring, but were not always taken into account.

Overall, the Committee concluded that the available evidence does not indicate that vitamin E supplementation increases the risk of prostate cancer. The Committee has not reviewed possible associations with other types of cancer. The Department of Health advises that the best way for most people to get the required vitamin E is by eating a balanced, varied diet.