CC/2014/09

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

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

Introduction

1. The Committee considered a review of the literature on vitamin E and the risk of prostate cancer at its meeting in July 2012. Members agreed that a draft statement should be produced which was reviewed at the meeting in September 2013 and is provided in Annex 1. Minutes from the meeting held in September 2013 can also be found in Annex 1. Following comments from the Committee, a revised draft statement is presented in Annex 2. Annex 3 contains tables summarising the studies on vitamin E and risk of prostate cancer described in the statement along with the findings.

2. A literature search was carried out in PubMed in June 2014 for years 2013 and 2014 to identify any new publications since the previous draft statement was seen by the Committee. These have been included in the draft statement and tables.

3. Members are invited to comment on the second draft statement on vitamin E and the risk of prostate cancer in Annex 2 and the tables in Annex 3.

Secretariat
June 2014

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

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

Minutes from the meeting held on the 19th September 2013 for
"ITEM 5: Vitamin E and risk of prostate cancer – 1st Draft Statement" (CC/2013/8)

22. The Committee had considered a review of the literature on vitamin E and the risk of prostate cancer at its meeting in July 2012. This had been prompted by the results of the SELECT intervention study which appeared to indicate that treatment with vitamin E increased the risk of prostate cancer.

23. When the issue was discussed at the July 2012 meeting, Members had enquired about the nature of the placebo used in the SELECT study an issue also raised in a recent letter to the Journal of American Medical Association[1]. The authors of the SELECT study had responded that the placebo was composed of soybean oil. Since plant-derived oils were known to be rich sources of vitamin E (both tocopherols and tocotrienols) it was possible that rather than being a physiologically inert substance, as a placebo should be, it was possible that it was having a protective effect against prostate cancer. Results from both in vitro and animal studies have suggested that the γ- and δ- tocopherols and the tocotrienols showed a more protective action against prostate cancer than α-tocopherol, with comparable findings in human studies. It had also been shown that high levels of supplemental α-tocopherol (269 mg/day RRR-α-tocopherol equivalents; same dose as the SELECT study) could suppress levels of γ-tocopherol (median level lowered from 0.92 µg/ml to 0.42 µg/ml after 2 months), which could lead to an increased risk of prostate cancer. Therefore the vitamin E intervention might actually have a lower effect or no effect but appear to increase the risk in comparison. This higher intake of γ- and δ- tocopherols and tocotrienols by the placebo group in the SELECT study and concurrent lowering of γ-tocopherol levels in the supplemented group may be the reason for relatively lower number of prostate cancer cases in the placebo group. This hypothesis was 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 vitamin E only group had decreased from 1.43 µg/ml (baseline) to 0.80 µg/ml after 4 years.

24. It was unclear whether the suppressive effect of α-tocopherol on γ-tocopherol levels had been observed in other randomised controlled trials as γ-tocopherol levels were rarely measured. However it had been demonstrated in some human studies.

25. In light of the nature of the placebo used, Members agreed that the results of the SELECT study could be flawed and that the relative increase in risk with α-

[1] Hoskote SS, Nadkarni GN, Fried ED. (2012). Prostate cancer risk and vitamin E. JAMA. 307(5):454; author reply 454

tocopherol supplementation might not be a true indicator of the increased risk of prostate cancer.

26. Members considered that although the SELECT study was flawed, it was still worthwhile preparing a detailed statement as a compilation of the available data on vitamin E and prostate cancer.

27. Members had reviewed the data and agreed that a statement would be produced outlining the Committee's views on the available data. This statement and its accompanying tables were attached in Annexes 1 and 2. Members made a number of suggestions with regard to wording and structure for incorporation in the next draft of the statement."

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

Annex 2 to CC/2014/09

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

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

Draft statement July 2014

Introduction

1. 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). Due to the results of this study, the Food Standards Agency asked the Committee to review the information available on vitamin E and the risk of prostate cancer, including epidemiological, animal and *in vitro* studies on this topic.

2. 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 like smoking, exercise and body size. The incidence of prostate cancer has tripled over the last 35 years but much of this increase (both in the UK and in many other countries worldwide) could possibly be attributed to screening (Cancer Research UK, 2012). Previously many prostate cancer cases would have been asymptomatic and undetected. Longer lifespan and a stable mortality rate may also contribute to this apparent increase in incidence.

3. 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 like 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) and minerals like calcium, iron and selenium have been studied for their potential to prevent and reduce the risk of prostate cancer (Crawford, 2003 and Grönberg, 2003).

4. Vitamin E is an antioxidant and may help control cell damage that can lead to cancer. While some *in vitro* studies, animal experiments, observational and intervention studies had indicated that vitamin E could prevent and reduce the risk of prostate cancer, other studies have shown no significant association. SELECT is the first study that has reported an increased risk of prostate cancer with vitamin E supplementation (Klein et al 2011).

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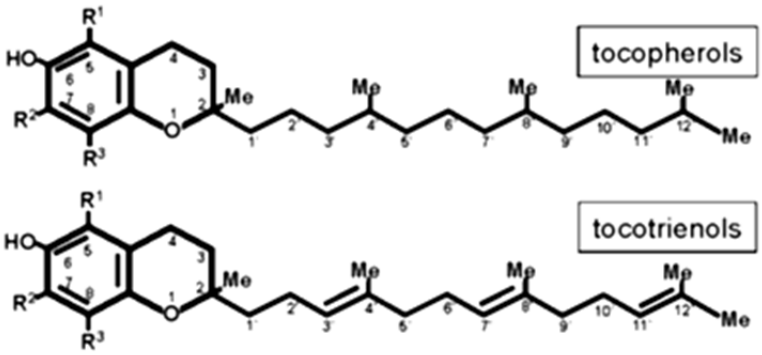
Vitamin E - sources, structure and stereoisomers

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

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

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 hydrolyzes 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 - recommended amounts, supplements and safe limits

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

[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.

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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.

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 (tocopherol transfer protein) 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 though 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 increases 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.

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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.

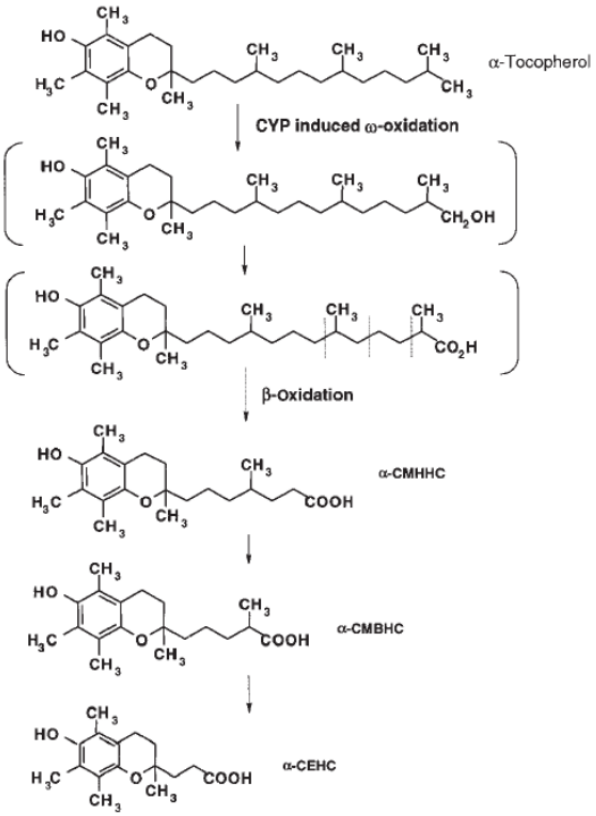

Figure 2: Proposed pathway of side-chain degradation of α-tocopherol via ω- and β-oxidation (from Brigelius-Flohé et al 2002)

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. Chemopreventive properties of vitamin E were first

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suspected 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. 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 s*tudies 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/signaling 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). Studies on 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 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-mcM 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

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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 NFκ 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 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 (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:*** Recent literature has 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-centered adducts through the nucleophilic 5-position, which is blocked in α-tocopherol (Christen et al, 1997). *In vitro* studies have also shown that γ-tocopherol exhibits a more significant growth inhibitory effect than α-tocopherol (Torricelli et al, 2012) with better inhibition of cell proliferation, cell cycle progression and DNA synthesis in prostate cancer cells than α- tocopherol (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 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.

[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.

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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, Campbell et al, 2009, 2011, Israel et al, 2000, Tomasetti et al, 2010).

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).

35. Mechanistic studies with both androgen-dependent and -independent LNCaP cells showed tocotrienols to be effective (Krycer et al, 2012), 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).

36. Selenium (Venkateswaran, Fleshner and Klotz, 2004), a combination of vitamin K3 and ascorbic acid (Tomasetti et al, 2010) and narigenin[5] (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.

[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.

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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 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 at 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 and selenium alone was not effective. This study also found that early intervention (within 8 weeks of age in transgenic mice) led to a significant reduction in 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 (Venkateswaran et al, 2009). Growth rates of transplanted human prostate LNCaP xenografts in mice were found to be lower when treated with vitamin E (form not specified) along with a high-fat diet (Fleshner et al, 1999) or α-tocopheryl succinate with soybean oil (Basu et al, 2007). However, some studies have reported a small increase in prostate cancer incidence when animals were treated with α-tocopherol acetate 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) and in testosterone plus estradiol-treated NBL rats (sex 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 (4000 mg/kg diet) 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 (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 γ-tocopherol also significantly increased expression levels of most detoxifying and

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[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.

[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.

antioxidant enzymes (Barve et al, 2009). In TRAP rats that received γ-tocopherol (50 or 100 mg/kg diet for 10 weeks) and α- tocopherol (50mg/kg diet), 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. Rats given γ-tocopherol (50, 100 or 200 mg/kg diet 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). However in another study on the growth of androgen-dependent Dunning R3327-H rat[9] prostate adenocarcinomas in male Copenhagen rats given γ-tocopherol, 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 (0.1%, 0.3% or 1% 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 manner (significantly in the case of the 0.3% and 1% 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 Annex 3, tables 2.1 to 2.5.

44. Conflicting results have been reported from supplementation studies where substances other than vitamin E have been administered and blood vitamin E levels were compared between prostate cancer cases and matched controls. A null association was reported for serum concentrations of vitamin E 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

[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.

Cheng et al, 2011) showed a statistically significant reduction in the risk of prostate cancer (total and aggressive) for higher serum tocopherol levels; baseline serum tocopherol levels were significantly lower in prostate cancer cases.

45. Most human studies measured the plasma vitamin E level and these studies can be found in Annex 3 tables 2.1-2.4 depending on the form measured.

46. Some studies estimated vitamin E intakes through dietary questionnaires and compared the relative risk of developing prostate cancer. These studies can be found in Table 2.5 in Annex 3.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 variable between studies.

Case-control Studies

47. Case-control studies have given mixed results. 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).

48. Some case-control studies indicated that significantly lower plasma vitamin E levels were found in prostate cancer cases compared to controls and were inversely related to the PSA levels[10] and Gleason scores[11] indicating decreased plasma vitamin E is associated with increased risk of prostate cancer (Akinloye, 2009, Adaramoye, 2010, Battisti et al, 2011). It was proposed that the decrease in vitamin E 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).

49. 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

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[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).

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 none).

50. 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.

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. Overall, results from these case-control studies show no direct association, either positive or negative, between vitamin E supplementation and risk of prostate cancer. However, there is evidence for a protective effect 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

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

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).

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-α-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).

[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.

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 had a slightly lower risk than men who did not smoke.

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

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

cancer risk (for intake of > 30 mg/day vs. < 8 mg/day, OR, 1.08; 95% CI, 0.96 - 1.23).

Randomised Controlled Trials

63. 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 tables 2.1 - 2.5 in Annex 3.

64. ***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 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).

65. 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.

66. ***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).

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

67. 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.

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

69. 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.

70. 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)

71. ***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 vitamin E 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 vitamin E on the incidence of fatal and nonfatal cancers; there was no reduction in the incidence of prostate cancer.

72. 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 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.

[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.

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73. 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.

74. ***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, 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.

75. ***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.

76. ***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.

77. 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

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

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cancer. There were no differences in PSA levels and severity between the supplemented and placebo groups.

78. 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.

79. 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.

80. 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).

81. 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.

Meta-analyses

82. A meta-analysis of RCTs on the role of vitamin E in the prevention of cancer concluded that vitamin E 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 RCTs, 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 but not γ-tocopherol were inversely associated with the risk of prostate cancer.

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The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

83. 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).

84. 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.

85. 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 vitamin E alone group (relative risk, 1.13; 99% CI = 0.95 - 1.35; p = 0.06) (Table 2). Participants were asked to stop taking the supplements since selenium and vitamin E did not prevent prostate cancer in this population of healthy men (Lippman et al, 2009).

86. 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	Vitamin E	Selenium	Vitamin E + 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

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		placebo	Vitamin E	Selenium	Vitamin E + 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).

87. In 2011, after seven years of median follow-up, the men who took vitamin E 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 vitamin E supplementation in the general population of healthy men significantly increases the risk of being diagnosed with prostate cancer.

88. Men taking selenium alone, or vitamin E 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 vitamin E and selenium (p=0.02) suggesting no increased risk of prostate cancer when vitamin E and selenium were taken together.

Potential reasons for the unexpected results seen in the SELECT trial

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

90. ***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.

91. ***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). 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 vitamin E 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.

92. ***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 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 relatively lower number of prostate cancer cases in the placebo group.

93. 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 vitamin E 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.

94. ***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. vitamin E alone, 4.8%, 232/4853).

95. ***Confounders***: Finally, confounding factors like obesity and other dietary factors are not considered in the SELECT study. The ATBC study had suggested that the negative impact of extreme obesity was greater than the positive impact of taking a vitamin E supplement (Ledesma et al, 2011).

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

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Issues to consider with results of epidemiological studies

96. 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:

97. ***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.

98. ***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-Rlohé et al, 2002).

99. ***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 (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.

100. ***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).

101. ***Confounders*:** Confounding effects of other antioxidant vitamins, supplements, nutrients and over-the-counter and prescription medications taken by

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

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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, such as smoking, exercise and body size, 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).

102. ***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

103. 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.

104. 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.

105. A similar lowering of γ-tocopherol levels with α-tocopherol supplementation was reported (Tsavachidou ei 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 vitamin E alone and vitamin E + 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 90).

106. 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- tocopherol transfer

protein (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).

107. 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.

108. 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).

109. 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

110. 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).

111. 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 nonsmokers. 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

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testosterone concentrations and it was suggested that this may lead to a reduction in risk of prostate cancer in smokers (Hartman et al, 2001).

112. 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 a hormonal mechanism.

113. 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

114. 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.

115. 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).

116. 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

117. 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.

118. Higher serum α-tocopherol levels have been 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 reacts rapidly with molecular oxygen and generates free radicals. This was also backed by significantly higher levels of lipid peroxidation products in prostate cancer cases.

119. 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).

120. 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).

121. 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.

122. 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).

123. 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.

124. In a number of studies, 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).

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Proposed conclusions

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

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

131. 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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Annex 3 to C/2014/09

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

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

Tables summarising human studies on vitamin E and risk of prostate cancer described in the statement.

Secretariat
June 2014

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Table 2.1 Studies on serum vitamin E (total or form not specified) levels and prostate cancer risk.

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported	RR or OR (95% CI)	Summary of findings
Cohort Study; Basel, Switzerland (Eichholzer et al, 1996, 1999)	2,974 healthy men from 1971 - 1973; 17 year follow-up in 1990. Out of the 290 deaths, 30 were from PCa	vitamin E	30 deaths from PCa	33.3±1.0 µmol/l	3.26 (1.27 - 8.35)	Low plasma levels in smokers related to increased risk of PCa. (Adjusted for cholesterol & triglycerides). RR for low vitamin E for the non-smoker was 0.76 (0.25 - 2.36) and normal vitamin E (>30.02 µmol/l) for smokers was 1.28 (0.49 - 3.33).
			2173 survivors	34.7±0.1 µmol/l	<30.02 µmol/l; smoker	
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. Median levels quoted.	Total tocopherols	142 cases	14.26 µg/ml	by quartiles 1.4 (0.7-2.6) 1.1 (0.6-2.2) 0.9 (0.5-1.9)	Difference in mean serum levels between cases and controls not statistically significant.
			142 controls	14.71 µg/ml		
Nested case-control study from Washington County, USA (Hsing et al, 1990)*	Samples collected in 1974 from blood collection campaign; 13 year follow-up. Median and 25th and 75th percentiles also given	Total tocopherols	103 cases	10 mg/l (9,13)	1.00 (0.37 - 2.68)	Difference in serum levels between cases and controls not significant. OR quoted for highest quartile. Authors conclude there is no association between serum tocopherol levels and PCa.
			103 controls	11 mg/l (10, 12)		
Case-control study from Nigeria (Adaramoye, 2010 and Akinloye, 2009)	120 Nigerian patients from the Cancer Screening Unit, Ibadan, with prostate cancer and 50 controls. Related to PSA levels (ng/l).	vitamin E	PSA < 3 (normal)	5.65±0.97 mg/dl		vitamin E levels were significantly lower in cases and were inversely related to the PSA levels
			PSA 5 - 10	3.93±0.81 mg/dl		
			PSA 11 - 20	2.97±0.67 mg/dl		
			PSA > 20	1.30±0.56 mg/dl		

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported	RR or OR (95% CI)	Summary of findings
Case-control study from Brazil (Battisti et al 2011)	55 PCa patients at the Oncology Hematology Laboratory at Santa Maria; 55 healthy controls. Only charts of vitamin E levels given; levels quoted are approximate estimates from the charts.	vitamin E	55 patients (all)	12.5 µmol/l		Serum vitamin E levels were significantly lower in prostate cancer patients compared to 55 healthy controls. Significantly higher levels of lipid peroxidation products in prostate cancer patients compared to controls
			patients Gleason[1] <7	13 µmol/l		
			patients Gleason =7	12.5 µmol/l		
			patients Gleason >7	11.5 µmol/l		
			55 controls	16.5 µmol/l		

[1] Gleason scores are used to grade prostate cancer based on the glandular pattern of the tumour; a higher score indicates a more aggressive cancer.

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Table 2.2 Studies on serum levels of α-tocopherol (and other isoforms) and prostate cancer risk.

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
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.	α-tocopherol	37 cases	7.77 mg/l	7.77	0.58 (0.19 - 1.76)	Higher serum vitamin E levels associated with lower PCa risk. RRs for the two highest quintiles of serum vitamin E compared to the lower three. Adjustment for confounders (smoking, cholesterol) did not influence results.
			68 controls	8.05 mg/l	8.05		
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. Median levels quoted.	Total tocopherols	142 cases	14.26 µg/ml	14.26	by quartiles 1.4 (0.7-2.6) 1.1 (0.6-2.2) 0.9 (0.5-1.9)	Mean serum levels between cases and controls not statistically significant.
			142 controls	14.71 µg/ml	14.71		
		α-tocopherol	142 cases	13.20 µg/ml	13.20	1.8 (0.9-3.6) 1.6 (0.8-3.3) 1.4 (0.7-2.9)	ORs do not indicate any association.
			142 controls	13.13 µg/ml	13.13		

[2] 1 mg α-tocopherol = 2.33 µmol; 1 µmol α-tocopherol = 0.43 mg

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
Nested case-control study Washington County, USA; (Hsing et al, 1990)*	samples collected in 1974 from blood collection campaign; 13 year follow-up. Median and 25th and 75th percentiles also given	Total tocopherols	103 cases	10 mg/l (9,13)	10	1.00 (0.37 - 2.68)	difference in serum levels between cases and controls not significant. OR quoted for highest quartile. Authors conclude there is no association between serum tocopherol levels and PCa.
			103 controls	11 mg/l (10, 12)	11		
	sub-set of samples tested for α and γ-tocopherol levels	α-tocopherol	27 cases	9.2 mg/l (7.5, 12.3)	9.2	1.00 (0.29 - 3.45)	
			27 controls	9.6 mg/l (8.5, 11.4)	9.6		
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. Median serum concentrations and interquartile ranges are shown.	α-tocopherol	182 cases	1.1 mg/dl (1.0 - 1.3)	11	OR by quintile : 0.93 (0.54-1.62) 0.80 (0.45-1.41) 0.99 (0.58-1.70) 0.58 (0.31-1.06) p_{trend} = 0.11	Concentration slightly lower in cases; not statistically significant (p=0.11)
			364 controls	1.2 mg/dl (1.1 - 1.5)	12		

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
Nested case-control study from CLUE I and CLUE II* cohort; Washington County, USA (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. Median serum concentrations and interquartile ranges are shown.	α-tocopherol	142 cases	1.3 mg/dl (1.1 - 1.6)	13	OR by quintile: 1.03 (0.56-1.88) 0.74 (0.39-1.43) 0.92 (0.49-1.75) 0.78 (0.41-0 .50) p_{trend} = 0.46	Concentration of slightly lower in cases; not statistically significant (p=0.09). Statistically significant decrease in risk of prostate cancer for higher concentrations of selenium and α-tocopherol when γ-tocopherol was above the median level, but not when it was below.
			284 controls	1.3 mg/dl (1.1 - 1.7	13		
Nested case-control study; The European Prospective Investigation into Cancer and	Blood samples from 137,001 men in 8 European countries collected	α-tocopherol	966 cases	1351 µg/dl (95% CI = 1330, 1373)	13.51	RR by quintile: 0.95 (0.72, 1.26) 0.85 (0.64, 1.13) 0.95 (0.72, 1.25) 0.81 (0.61, 1.08) p_{trend} = 0.37	No association between the plasma concentrations of α- and γ-tocopherols and

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
Nutrition study (EPIC) (Key et al, 2007)	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.		1064 controls	1381 µg/dl (95%CI= 1360, 1402)	13.81		prostate cancer risk.
Prospective Study; Royal Marsden Hosp. UK (Venkitaraman et al, 2010)	Serum concentrations of 104 PCa patients on active surveillance in 2002; 2.5 year follow-up.	α-tocopherol	Mean	9.61 µmol/L	4.13		Tocopherol levels not related to PSA levels, PSA velocity, disease progression, Gleason score, adverse histology and repeat biopsy.
			Median	8.85 µmol/L	3.81		
			Range	4.8 - 37.1 µmol/L	2.06 - 15.95		
			Range	0.11 - 1.33 µmol/L	0.05 - 0.55		
Nested case-control study in the Multiethnic cohort, Hawaii and Califonia;	Multiethnic Cohort, data collected between 1993 and 1996;	α-tocopherol	467 cases; serum conc in quartiles	0.90 mg/dl	9	1	No association between serum level and risk of PCa or advanced PCa.
				1.24 mg/dl	12.4	0.95 (0.66 - 1.37)	

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
Gill et al, 2009	residents of Hawaii and California, *n* = 29,009			1.62 mg/dl	16.2	0.83 (0.57 - 1.21)		
				2.51 mg/dl	25.1	0.95 (0.65 - 1.41)		
Nested case-control study among Australian asbestos workers and their families (vitamin A supplementation) (Beilby et al, 2010)	Participants entered the programme in 1990 and were assigned to take either β-carotene or retinol supplements. Followed up for 1 year; 96 PCa cases identified and matched with 225 controls. ORs quoted for tertiles of serum α-tocopherol concentrations.	α-tocopherol	96 cases	41.2±12.6 µmol/l	17.7±5.4	21.0 - 33.4 µmol/l	1	No difference in the baseline vitamin E levels between cases and controls; p=0.14.
						33.6 - 40.4 µmol/l	1.06 (0.53-2.10)	
			225 controls	39.1±10.6 µmol/l	16.8±4.6	40.8 - 93.2 µmol/l	1.46 (0.78 - 2.73)	
Nested case-control study within β-Carotene and Retinol Efficacy Trial (CARET); US based, multi-centre	CARET study - a randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial of β-	α-tocopherol	205 cases	12600 ng/ml	12.6	0.72 (0.42-1.22) 0.61 (0.35-1.06) 0.59 (0.34-1.04) ORs for quartiles of control tocopherol levels		α-tocopherol levels significantly lower in prostate cancer cases; p = 0.03. (for γ-tocopherol p=0.35).

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
(Goodman et al, 2003)	carotene 30 mg and retinol 25,000 IU/day. Current and former smokers; no never-smokers. 1985 – 1995.		205 controls	13800 ng/ml	13.8			Association between risk of prostate cancer and lower α-tocopherol levels statistically significant (Ptrend = 0.04)
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. ORs shown for the first vs. the 4th quartile of serum tocopherol levels.	α-tocopherol	684 cases	27.9 (23.0 - 36.5) µmol/l	11.997 (9.89 - 15.7)	all	0.82 (0.61-1.10) p = 0.06	Inverse association of α-tocopherol with total prostate cancer risk observed in current smokers High (≥median) compared to low serum concentrations of α- and γ-tocopherol were inversely associated with aggressive prostate cancer in current smokers The risks were found to be modified by polymorphism in
						former smokers	0.97 (0.64-1.48) p = 0.78	
			1441 controls	28.8 (23.0 - 36.9) µmol/l	12.38 (9.89 - 15.87)	current smokers	0.62 (0.40-0.96) p = 0.008	
						non-aggressive disease	0.87 (0.60-1.25) p = 0.30	
						aggressive disease	0.73 (0.47-1.11) p = 0.039	

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
								myeloperoxidase. The association between tocopherol levels and risk of PCa was stronger among those with MPO G/A+A/A genotypes.
Randomised double blind placebo-controlled trial - Selenium and Vitamin E Cancer Prevention Trial (SELECT); US, Canada and Puerto Rico. (Lippmann et al, 2009)	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 till July 2009.	Daily dose of 400 IU of *all-rac*-α-tocopheryl acetate. Serum α-tocopherol levels were measured Median interquartile values shown.	Baseline placebo	12.45 µg/ml	12.45	placebo	1	The risk of prostate cancer at 7 years of median follow-up was increased by 17% in men supplemented with vitamin E alone. no increased risk of prostate cancer when vitamin E and selenium were taken together (RR is 99% Confidence Interval; P>0.15)
			4th annual visit placebo	12.09 µg/ml	12.09			
			baseline vitamin E	12.79 µg/ml	12.79	vitamin E	1.13 (0.95-1.35)	
			4th annual visit vitamin E	16.57 µg/ml	16.57			
			baseline Se	12.58 µg/ml	12.58	Selenium	1.04 (0.87-1.24)	
			4th annual visit Se	12.03 µg/ml	12.03			
			baseline vitamin E +Se	12.20 µg/ml	12.20	vitamin E + selenium	1.05 (0.88-1.25)	
			4th annual visit vitamin E + Se	17.87 µg/ml	17.87			
Nested case-control study in the Prostate Testing for Cancer and	Investigating the association vitamin E with PSA-detected prostate cancer	not specified - assumed to be α-tocopherol	1,433 prostate cancer cases and 1,433 healthy controls	0.5-5.6 µmol/L	0.22 - 2.41	0.93 (0.72 - 1.21)		p_{trend} = 0.49 no evidence of associations of vitamin E levels in the plasma
				5.7-10.9 µmol/L	2.45 - 4.69	1.15 (0.90 - 1.46)		
				11.0-17.8	4.73 -	1		

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[2]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
Treatment (ProTeCT) cohort - a randomised controlled trial of treatments for prostate cancer in the UK (Gilbert et al, 2012)	risk, stage, and grade			µmol/L	7.65		heparin with overall prostate cancer risk or more aggressive prostate cancer phenotypes.
				17.9-26 µmol/L	7.7 - 11.18	0.88 (0.66 - 1.16)	
				26.1-73.6 µmol/L	11.22-31.65	0.85 (0.62 - 1.18)	
Nested Case-control study in the PLCO screening trial, US based. (Weinstein et al; 2012)	Serum a- and g-tocopherol concentrations in prostate cancer patients and controls	α- and γ-tocopherol	680 prostate cancer patients	α- 19 (9.8)	19 (9.8)	By quintile- α-tocopherol: 0.73 (0.52 : 1.03) 0.75 (0.53 : 1.06) 0.67 (0.47 : 0.96) 0.63 (0.44 : 0.92) By quintile- γ-tocopherol: 1.52 (1.09 : 2.13) 1.63 (1.16 : 2.30) 1.34 (0.92 : 1.97) 1.35 (0.92 : 1.97)	Higher α-tocopherol status is associated with a decreased risk of developing prostate cancer. A relationship found to be strongest in current and recent smokers. Risk was non-significantly elevated amongst men with higher γ-tocopherol concentrations.
				γ- 3.2 (2.0)	3.2 (2.0)		
			824 controls	α- 19 (9.5)	19 (9.5)		
				γ- 3.3 (2.0)	3.3 (2.0)		

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Table 2.3 Studies on serum levels of other isoforms of tocopherol and prostate cancer risk.

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[3]	RR or OR (95% CI)	Summary of findings
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. Median levels quoted.	γ-tocopherol	142 cases	1.34 µg/ml	1.1 (0.5-2.2) 0.8 (0.8-1.8) 0.7 (0.3-1.5)	OR for highest quartile indicates association, but not statistically significant
			142 controls	1.50 µg/ml		
		δ-tocopherol	142 cases	0.08 µg/ml	0.8 (0.4-1 .5) 1.1 (0.6-2.2) 1.0 (0.5-2.0)	ORs do not indicate any association.
			142 controls	0.07 µg/ml		
Nested case-control Washington County, USA (Hsing et al, 1990)*	Samples collected in 1974 from blood collection campaign; 13 year follow-up. Sub-set of samples tested for α and γ-tocopherol levels. Median and 25th and 75th percentiles also given.	γ-tocopherol	27 cases	2.0 mg/l (1.4, 2.9)	1.17 (0.39 - 3.47)	Difference in serum levels between cases and controls not significant. OR quoted for highest quartile. Authors conclude there is no association between serum tocopherol levels and PCa.
			27 controls	1.7 mg/l (1.4, 2.4)		
Nested case-control study from CLUE I* and CLUE II 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. Median serum concentrations and interquartile ranges are shown. ORs by quintiles.	γ-tocopherol	182 cases	0.20 mg/dl (0.17 - 0.30)	0.99 (0.57-1.72) 1.14 (0.66-1.97) 0.86 (0.51-1.45) 0.77 (0.42-1.43) p_{trend} = 0.30	concentration significantly lower in cases (p=0.02)
			364 controls	0.24 mg/dl (0.17 - 0.30)		

[3] 1 mg α-tocopherol = 2.33 µmol; 1 µmol α-tocopherol = 0.43 mg

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[3]	RR or OR (95% CI)	Summary of findings
Nested case-control study from CLUE I and CLUE II* cohort; Washington County, USA (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. Median serum concentrations and interquartile ranges are shown. ORs by quintiles.	γ-tocopherol	142 cases	0.25 mg/dl (0.19 - 0.32)	1.27 (0.72-2.24) 0.77 (0.40-1.50) 0.56 (0.28-1.10) 0.21 (0.08-0.54) p_{trend} = <0.001	Concentration significantly lower in cases (p=0.0001). Correlations with selenium also looked at. Statistically significant decrease in risk of prostate cancer for higher concentrations of selenium and α-tocopherol when γ-tocopherol was above the median level, but not when it was below.
			284 controls	0.29 mg/dl) (0.20 -0.38)		

α-Tocopherol	γ-Tocopherol	Selenium	No. of case/control subjects	Matched OR (95% CI)
Low	Low	Low	20/30	1.00 (referent)
Low	Low	High	16/27	0.80 (0.33–1.92)
High	Low	Low	19/32	0.77 (0.33–1.80)
High	Low	High	20/21	1.39 (0.59–3.29)
Low	High	Low	20/28	0.81 (0.32–2.02)
Low	High	High	7/32	0.27 (0.09–0.77)
High	High	Low	7/25	0.34 (0.12–0.99)
High	High	High	8/38	0.27 (0.10–0.72)

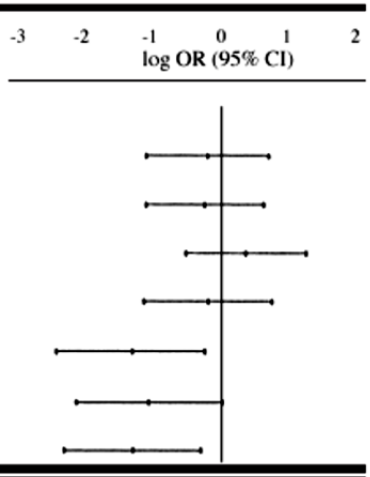

Table taken from Helzlsouer et al, 2000

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[3]	RR or OR (95% CI)	Summary of findings
Nested case-control study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (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. RRs shown for quintiles.	γ-tocopherol	966 cases	97.6 µg/dl (95%CI = 94.0, 101.2)	1.26 (0.93, 1.72) 0.94 (0.68, 1.30) 0.96 (0.68, 1.36) 1.24 (0.88, 1.76) p_{trend} = 0.61	No association between the plasma concentrations of α- and γ-tocopherols and prostate cancer risk.
			1064 controls	100.5 µg/dl (95% CI = 97.0, 104.1)		
Prospective Study; Royal Marsden Hosp. UK (Venkitaraman et al, 2010)	Serum concentrations of 104 PCa patients on active surveillance in 2002; 2.5 year follow-up.	γ-tocopherol	Mean	0.49 µmol/L[4]		Tocopherol levels not related to PSA levels, PSA velocity, disease progression, Gleason score, adverse histology and repeat biopsy.
			Median	0.43 µmol/L		
			Range	0.11 - 1.33 µmol/L		
β-Carotene and Retinol Efficacy Trial (CARET) (Goodman et al, 2003)	Nested case-control study in the CARET 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 -	γ-tocopherol	205 cases	2290 ng/ml	0.91 (0.52-1.59) 0.87 (0.50-1.52) 0.86 (0.50-1.48) ORs given for quartiles of control tocopherol levels	α-tocopherol levels significantly lower in prostate cancer cases; p = 0.03. (for γ-tocopherol p=0.35). association between risk of prostate cancer and lower α-tocopherol levels statistically significant (P_{trend} = 0.04) no association between γ-tocopherol and prostate cancer
			205 controls	2430 ng/ml		

[4] 1µmol γ-tocopherol = 0.416 mg; 1 mg γ-tocopherol = 2.4 µmol

Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[3]	RR or OR (95% CI)		Summary of findings
	1995						(P_{trend} = 0.57)
Nested case-control study in CARET cohort. (Cheng et al, 2011)	684 men with incident PCa (375 nonaggressive and 284 aggressive) and 1441 controls. ORs shown for the first vs the 4th quartile of serum tocopherol levels.	γ-tocopherol	684 cases	6.0 (4.1 - 8.2) µmol/l	all	0.83 (0.63-1.09) p = 0.24	inverse association of α-tocopherol with total prostate cancer risk observed in current smokers High (≥median) compared to low serum concentrations of α- and γ-tocopherol were inversely associated with aggressive prostate cancer in current smokers The risks were found to be modified by polymorphism in myeloperoxidase. The association between tocopherol levels and risk of PCa was stronger among those with MPO G/A+A/A genotypes.
					former smokers	0.86 (0.58-1.25) p = 0.68	
			1441 controls	6.0 (4.3 - 8.4) µmol/l	current smokers	0.78 (0.53-1.16) p = 0.19	
					non-aggressive disease	1.01 (0.72-1.42) p = 0.30	
					aggressive disease	0.69 (0.47-1.01) p = 0.11	
Nested case-control study in the ATBC cohort (Weinstein et al, 2005)	100 cases and 200 controls randomly chosen from the ATBC study. ORs given by tertiles of γ-tocopherol levels for supplemented and non-supplemented groups	baseline serum γ-tocopherol	100 cases	0.09±0.04 mg/dl	0.74 (0.41 - 1.31) 0.57 (0.31 - 1.06) p_{trend} = 0.08		The association of high serum tocopherols with low prostate cancer risk was stronger in the α-tocopherol-supplemented group than in those not receiving α -tocopherol. Participants with higher circulating concentrations of the major vitamin E fractions, α -tocopherol and γ -tocopherol, had similarly lower prostate cancer risk.
			200 controls	0.10±0.04 mg/dl			
			α-tocopherol supplemented		0.31 (0.10 - 0.96) 0.24 (0.08 - 0.76) p_{trend} = 0.02		
			no α-tocopherol supplement		1.04 (0.52 - 2.09) 0.85 (0.40 - 1.83) p_{trend} = 0.69		

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Study (reference)	Brief description of study	Tocopherol form	Subjects	Serum/ plasma conc as reported[3]	RR or OR (95% CI)		Summary of findings
Randomised double blind placebo-controlled trial - Selenium and Vitamin E Cancer Prevention Trial (SELECT); US, Canada and Puerto Rico. (Lippmann et al, 2009)	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 in the US, Canada and Puerto Rico. Data reviewed in 2008 and supplementation stopped. Followed up till July 2009.	Daily dose of 400 IU of *all-rac*-α-tocopheryl acetate. Serum γ-tocopherol levels were measured Median interquartile values shown.	Baseline placebo	1.31 µg/ml	placebo	1	The risk of prostate cancer at 7 years of median follow-up was increased by 17% in men supplemented with vitamin E alone. No increased risk of prostate cancer when vitamin E and selenium were taken together
			4th annual visit placebo	1.69 µg/ml			
			baseline vitamin E	1.43 µg/ml	vitamin E	1.06 (0.95-1.35)	
			4th annual visit vitamin E	0.80 µg/ml			
			baseline Se	1.50 µg/ml	Selenium	1.04 (0.87-1.24)	
			4th annual visit Se	1.90 µg/ml			
			baseline vitamin E +Se	1.44 µg/ml	vitamin E + selenium	1.05 (0.88-1.25)	
			4th annual visit vitamin E + Se	0.69 µg/ml			

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Table 2.4 Studies on Vitamin E supplementation, serum tocopherol levels and prostate cancer risk.

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
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)	α-tocopherol	increase with supplementation	8.2±2.1 µmol/L (baseline 31.0±2.1 µmol/L)	3.5±0.9 (baseline 13.3±0.9)		Supplement delayed PSA progression
			increase with placebo	0.2±1.9 µmol/L (baseline 29.3±1.8 µmol/L)	0.09±0.8 (baseline 12.6±0.8)		

[5] 1 mg α-tocopherol = 2.33 µmol; 1 µmol α-tocopherol = 0.43 mg

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
Randomised, double-blind, placebo-controlled primary-prevention trial α-tocopherol β-carotene study (ATBC) (ATBC study group, 1994, Albanes et al, 1995, 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 (50 IU[6]) or in combination with β-carotene was continued for 5-8 years 1985 - 1993 (median, 6.1 years) 246 cases of PCa.	α-tocopherol	Baseline	26.2±8.2 µmol/l	11.27±4.8		α- tocopherol-alone group • PCa incidence 36% lower (95% CI = -56% to -6%) • Incidence of clinical tumours (stage II-IV) decreased by 40% (95% CI = -55% to -20%) • Mortality from PCa 41% lower (95% CI = -65% to -1%)
ATBC trail based cohort study (Hartman et al, 1998)	9 years follow-up (median 7 y); 317 cases of PCa.	baseline α-tocopherol	317 cases	11.8±3.2 mg/l	11.8±3.2		No significant associations between baseline serum α-tocopherol or dietary vitamin E and PCa overall.
			28,816 non cases	11.9±3.6 mg/l	11.9±3.6		

[6] 1 mg of α-tocopheryl acetate = 1 IU of α-tocopherol

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	RRs of PCa on quartiles of intake of total vitamin E intake including supplements in mg/day (<8.4, 8.41-11.25, 11.26-15.96, >15.96)	α-tocopherol supplemented	n = 127			0.68 (0.41 - 1.15) 0.80 (0.48 - 1.34) 0.52 (0.29 - 0.95)	association between PCa and vitamin E differed significantly by α-tocopherol intervention status, suggests a protective effect for total vitamin E among those who received the α-tocopherol intervention.
		no α-tocopherol supplement	n = 190			0.87 (0.56 - 1.36) 1.09 (0.70 - 1.69) 1.19 (0.76 - 1.86)	
	RRs of PCa on quartiles of serum α-tocopherol levels in mg/l (<9.78, 9.78-11.47, 11.48-13.60, >13.60)	α-tocopherol supplemented	n = 127			0.86 (0.52 - 1.44) 0.82 (0.48 - 1.39) 0.76 (0.42 - 1.37)	
		no α-tocopherol supplement	n = 190			1.04 (0.69 - 1.56) 0.91 (0.58 - 1.42) 0.98 (0.60 - 1.60)	
ATBC-trial based cohort study (Watters et al, 2009)	follow-up till 2005 (20 years); 1,891 cases of PCa, 395 deaths due to PCa	baseline α-tocopherol in PCa cases	1,496 survivors	11.9±3.1 mg/l	11.9±3.1		no significant association between baseline serum α-tocopherol levels between intervention groups.
			395 deaths	11.7±3.1 mg/l	11.9±3.1		
	no of cases (deaths) and HRs for PCa mortality on quintiles of baseline serum α-	α-tocopherol supplemented	202 (44) 200 (56) 214 (38) 170 (35) 201 (49)	<9.4, 9.4-10.9, 10.9-12.2 12.3-14.0 >14.0		0.82 (0.50 - 1.29) 0.64 (0.39 - 1.04) 0.74 (0.44 - 1.23) 0.51 (0.20 - 0.90)	higher baseline serum α-tocopherol and α-tocopherol supplementation associated with improved

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	tocopherol mg/l	no α-tocopherol supplement	177 (39) 178 (35) 175 (38) 198 (36) 176 (25)			1.05 (0.70 - 1.60) 0.71 (0.44 - 1.16) 0.77 (0.46 - 1.29) 0.86 (0.51 - 1.47)	PCa survival (p_{trend}=0.03)
	no of cases (deaths) and HRs for PCa mortality on quintiles of serum α-tocopherol levels at **3 years into the study** mg/l	serum α-tocopherol	315 (66) 301 (60) 341 (78) 295 (44) 305 (55)	<11.5 11.5-13.4 13.5-16.0 16.1-19.0 >19.0		0.96 (0.68 - 1.36) 0.93 (0.67 - 1.30) 0.74 (0.50 - 1.09) 0.80 (0.54 - 1.17)	higher on-study α-tocopherol levels related to improved overall survival (p_{trend} = 0.12)
		α-tocopherol supplemented	26 (5) 73 (16) 169 (39) 221 (31) 265 (47)			0.41 (0.15 - 1.14) 0.36 (0.14 - 0.94) 0.24 (0.09 - 0.64) 0.26 (0.09 - 0.71)	
		no α-tocopherol supplement	289 (61) 228 (44) 172 (39) 74 (13) 40 (8)			0.97 (0.65 - 1.45) 0.95 (0.61 - 1.49) 0.85 (0.45 - 1.63) 0.80 (0.38 - 1.69)	
Nested case-control study in the ATBC cohort (Weinstein et al, 2005)	100 cases and 200 controls randomly chosen from the ATBC study. ORs given by tertiles of α-tocopherol levels for supplemented and non-	baseline serum α-tocopherol	100 cases	1.34±0.34 mg/dl	13.4±3.4	0.73 (0.40 - 1.33) 0.49 (0.24 - 1.01) p_{trend} = 0.05	The association of high serum tocopherols with low prostate cancer risk was stronger in the α-tocopherol-supplemented group than in those not receiving α -tocopherol. Participants with higher circulating concentrations
			200 controls	1.42±0.39 mg/dl	14.2±3.9		
			α-tocopherol supplemented			0.64 (0.23 - 1.76) 0.31 (0.09 - 1.10) p_{trend} = 0.07	
			no α-tocopherol supplement			0.78 (0.36 - 1.67) 0.63 (0.26 - 1.53) p_{trend} = 0.31	

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	supplemented groups	baseline serum γ-tocopherol	100 cases	0.09±0.04 mg/dl	0.9±0.4	0.74 (0.41 - 1.31) 0.57 (0.31 - 1.06) p_{trend} = 0.08	of the major vitamin E fractions, α -tocopherol and γ -tocopherol, had similarly lower prostate cancer risk.
			200 controls	0.10±0.04 mg/dl	1.0±0.4		
			α-tocopherol supplemented			0.31 (0.10 - 0.96) 0.24 (0.08 - 0.76) p_{trend} = 0.02	
			no α-tocopherol supplement			1.04 (0.52 - 2.09) 0.85 (0.40 - 1.83) p_{trend} = 0.69	
Health Professionals Follow-up Cohort Study (HPFS) (Chan et al, 1999)	The effect of supplemental vitamin E intake was prospectively examined in 47,780 US male health professionals and risk of PCa examined. 1896 PCa cases diagnosed between 1986 and 1996.		≥100 IU vit E supplement vs. no supplement	-		1.07 (0.95 - 1.20) for total PCa 1.14 (0.82 - 1.59) for metastatic cancer	Supplemental vitamin E intake not significantly associated with prostate cancer incidence.
			smoker + ≥100 IU vitamin E vs smoker + no vitamin E	-		1.27 (0.97 - 1.66) for total cancer 0.44 (0.18 - 1.07) for metastatic or fatal prostate cancer	Among current smokers/recent quitters, a suggestive inverse association.
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		697 cases and 666 controls; ORs for frequency of vitamin E use (in a week)			0; 1	Some evidence of a protective effect for individuals who took vitamin E supplements seven or more times a week.
						<1; 1.12 (0.57 - 2.20)	
						1-6; 0.85 (0.51 - 1.41)	
						≥7; 0.76 (0.54 - 1.08)	

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
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)	400 IU/day vitamin E (as *RRR*-α-tocopheryl acetate)	HOPE study 116 PCa cases in supplemented group vs 119 in placebo group.	-		HOPE study 0.98 (0.76-1.26) (P=0.86)		No overall effect of vitamin E on the incidence of fatal and nonfatal cancers; there was no reduction in incident prostate cancer.
			HOPE-TOO 91 PCa cases in supplemented group vs 101 in placebo group			HOPE-TOO 0.90 (0.68-1.19) (P=0.46)		
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	Individual supplements of 400 IU of synthetic vitamin E or placebo every other day.	1008 confirmed incident cases of prostate cancer. Active and placebo vitamin E groups, 9.1 and 9.5 events per 1000 person-years.			0.97 (0.85-1.09) P=0.58)		supplementation with vitamin E was not associated with a reduction in the risk of prostate cancer;
A nested cohort study in the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial. Screening arm-based trail	U.S. based randomised two-armed screening trial from 1993 - 2001, and will continue follow-up through 2015. Dietary and		Mean **supplemental** intake 279 IU/day.			0	1.00	Overall, there was no association between prostate cancer risk and dietary or supplemental intake of vitamin E.
						>0-30 IU	1.02 (0.89-1.18)	
						>30-400 IU	0.92 (0.77-1.08)	However, among current and recent smokers,

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
comparing PCa rates and supplemental/dietary vitamin E intakes. (Kirsh et al, 2006)	supplemental intakes evaluated. After a median follow-up of 4.2 years, 1338 out of 29,631 men were diagnosed with PCa.					>400 IU	0.97 (0.83-1.13)	decreasing risks of advanced PCa associated with increasing dose (RR for >400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; P_{trend} =0.01) and duration of use of supplemental vitamin E (RR for ≥ 10 years use versus none = 0.30, 95% CI = 0.09 to 0.96; P_{trend} = 0.01).
			Mean **dietary** intake of 12 mg/day of total α-tocopherol equivalents			8.6	1.00	
						10.2	0.92 (0.77-1.09)	
						11.3	0.94 (0.79-1.13)	
						12.6	0.87 (0.72-1.05)	
						15.8	0.93 (0.78-1.12)	
The Heart Protection Study: (HPS Group, 2002).	Randomised controlled trial of antioxidant supplementation carried out between 1994 and 2001. 15,454 men UK aged 40-80.	Antioxidant vitamin supplementation (600 mg vitamin E (as synthetic vitamin E), 250 mg vitamin C, and 20 mg β-carotene daily) or matching placebo.	Serum α-tocopherol levels of those who took the supplement were nearly doubled compared to those on placebo.	(49·5±0·6 μmol/l)	21.29±0.26	Did not show an association between vitamin E supplementation and incidence of PCa.		There were no significant differences in the incidence of PCa; 138 cases (1·8%) in the vitamins group vs. 152 cases (2·0%) in the placebo group (p=0·4).
				(27.0±0.2 μmol/l)	11.6±0.09			
A nested cohort study in the Prostate Cancer Prevention Trial	Randomized, placebo-controlled trial (United States and Canada, 1994	supplemental vitamin E intakes in three groups:	1,703 PCa cases detected.			Gleason score 2-7		No associations of any nutrient (including vitamin E) or supplement with prostate cancer risk
						< 8 mg	1	

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
(Kristal et al, 2010)	- 2003) that tested whether finasteride, a 5α-reductase inhibitor could reduce the 7-year period prevalence of prostate cancer. 9,559 participants. Nutrient and supplement-use intake assessed using a food frequency questionnaire.	< 8 mg/day 8 - 30 mg/day > 30 mg/day				8 - 30 mg	1.05 (0.91-1.21)	overall. However results for dietary vitamin E and selenium were not reported because, based on very poor correlations between FFQ-based dietary intakes of these nutrients and serum concentrations, it was believed they cannot be assessed using an FFQ.
						> 30 mg	1.08 (0.96-1.23)	
						Gleason score 8-10		
						< 8 mg	1	
						8 - 30 mg	0.82 (0.49-1.35)	
						> 30 mg	1.21 (0.82-1.78)	
Randomized, double-blind, placebo-controlled primary prevention trial: Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) (Hercberg et al, 2004 and 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	baseline - supplement arm	32.3±8.3 µmol/l	13.39±3.57	0.88 (0.60 - 1.29)		non-significant reduction in prostate cancer rate associated with the supplementation
			baseline - placebo arm	32.2±8.5 µmol/l	13.38±3.66			
			47 cases n = 2159	<31.3 µmol/l	<13.46	0.86 (0.56 - 1.31)		
			40 cases n= 2169	≥31.3 µmol/l	≥13.46			
			supplement arm 25 cases n= 1,078	< 31.3 µmol/L		1.11 (0.62 - 1.96)		
			placebo arm 22 cases n=1,081					

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
			supplement arm 19 cases n = 1,118	≥ 31.3 µmol/L		0.82 (0.44 - 1.53)	In men with baseline PSA < 3 µg/l (over 90% of 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.
			placebo arm 21 cases n = 1,051				
			Initial PSA <3 µg/l supplement			0.52 (0.29 - 0.92)	
			Initial PSA <3 µg/l placebo				
			Initial PSA ≥3 µg/l supplement			1.54 (0.87 - 2.72)	
			Initial PSA ≥3 µg/l placebo				
Large US prospective cohort study **VIT**amins **A**nd **L**ifestyle (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, including detailed questions about vitamin E and selenium	overall PCa risk ≥400 IU/day vs. non use				0.86 (0.65 - 1.1) p_{trend} = 0.36	A 10-year average intake of supplemental vitamin E was not associated with a reduced PCa risk overall. risk decreased significantly with greater

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	supplement intake during the past 10 years from brand-specific multivitamins and single supplements. 830 new cases of PCa identified up to 2004.	risk for advanced PCa (regionally invasive or distant metastatic, n = 123) ≥400 IU/day vs. non-use				0.43 (0.19 - 1.0) p_{trend} = 0.03	intake of supplemental vitamin E (HR for 10-year average intake)
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. Dietary intakes of α-, β-, γ- and δ-tocopherols were estimated from food-frequency questionnaires.	≥800 IU/d vs. never use				0.86 (0.65-1.13) P_{trend} = 0.11	No relation between vitamin E supplement use and total or localized prostate cancer. Suggestive inverse association for advanced disease, although not statistically significant
		multivitamin users excluded (n = 152,710) ≥800 IU of vitamin E per day from single nutrient supplements vs. never users				0.78 (0.64-0.96) P_{trend} = 0.03	Inverse association observed for total Pca

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	The food-frequency questionnaire was validated in a subset of the cohort using two 24-hour recalls.	α-, β-, γ- and δ-tocopherol dietary intakes estimated from food-frequency questionnaires (supplement intake not included). RR according to quintiles of intake.				0.77 (0.56 - 0.92) 0.80 (0.67 - 0.96) 0.74 (0.61 - 0.89) 0.68 (0.56 - 0.84) (p=0.001)	Higher intake of γ-tocopherol associated with significant reduction in the risk of advanced PCa in a dose-dependent manner, with adjustment for several confounding factors strengthening the observed associations. Similar pattern for δ-tocopherol.
	Smokers: when multivitamin users were excluded from the analysis, among current/recent smokers	≥800 IU/d vs. never use				0.52 (0.29-0.94) P_{trend} = 0.06	No association found between supplemental vitamin E intake and PCa risk in the cohort as a whole. Significant inverse association between use of high-dose supplemental vitamin E and localized prostate cancer. This was not observed in non-smokers those who
	non-smokers					0.86 (0.59-1.24) P_{trend} = 0.52)	

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Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)		Summary of findings
	smoked in the distant past (quit ≥10 years ago)					0.83 (0.61-1.12) P_{trend} = 0.26		smoked in the distant past, $P_{interaction}$ = 0.10. interaction between dietary γ-tocopherol and smoking status not statistically significant, but it was most protective against advanced prostate cancer in non-smokers and former smokers, with virtually no association apparent in current smokers.
Selenium and Vitamin E Cancer Prevention Trial (SELECT)	Phase III randomised, double-blinded, placebo-controlled, 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 in the United States, Canada and Puerto Rico. Data reviewed in 2008 and supplementation stopped. Followed	Daily dose of 400 IU of *all-rac*-α-tocopheryl acetate. Serum α- and γ-tocopherol levels were measured at 6 months, 1st, 2nd, 3rd and 4th annual visits. Median interquartile values shown.	α- tocopherol				HRs (99%CIs)	The risk of prostate cancer at 7 years of median follow-up was increased by 17% in men supplemented with vitamin E alone. no increased risk of prostate cancer when vitamin E and selenium were taken together
			Baseline placebo	12.45 µg/ml	12.45	Placebo	1	
			4th annual visit placebo	12.05 µg/ml	12.05	vitamin E	1.06 (0.95-1.35)	
			baseline vitamin E	12.79 µg/ml	12.79	Selenium	1.04 (0.87-1.24)	
			4th annual visit vitamin E	16.57 µg/ml	16.57	vitamin E + selenium	1.05 (0.88-1.25)	
			baseline Se supplement	12.58 µg/ml	12.58			
			4th annual visit Se supplement	12.03 µg/ml	12.03			
			baseline vitamin E +Se	12.20 µg/ml	12.20			

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	up until July 2009.		4th annual visit vitamin E + Se	17.87 µg/ml	17.87		
			γ-tocopherol				
			Baseline placebo	1.31 µg/ml	1.31		
			4th annual visit placebo	1.69 µg/ml	1.69		
			baseline vitamin E	1.43 µg/ml	1.43		
			4th annual visit vitamin E	0.80 µg/ml	0.80		
			baseline Se supplement	1.50 µg/ml	1.50		
			4th annual visit Se supplement	1.90 µg/ml	1.90		
			baseline vitamin E +Se	1.44 µg/ml	1.44		
			4th annual visit vitamin E + Se	0.69 µg/ml	0.69		
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.	Not stated		Not reported	Not reported	1.00 vs 1.00 for those taking vs not taking vitamin E supplements. (0.76-1.31)	No significant effect of vitamin E supplementation was observed on prostate cancer incidence.
Randomised controlled trial. (Fleshner et al, 2011)	Randomised Phase III double-blind study in 303 men with diagnosed HGPIN.	Not stated		Not reported	Not reported	1.00 vs 1.03 0.67 to 1.60	No significant relationship between supplementation and progression of HGPIN to PCa.

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

Study (reference)	Brief description of study	tocopherol form		Serum/ plasma conc as reported[5]	Serum/ plasma conc (mg/l)	RR or OR (95% CI)	Summary of findings
	Patients received 20g soy protein, 400 IU of vitamin E and 100mcg selenium or a whey based control twice a day for 3 years.						
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.	Not stated		Not reported	Not reported	No OR or RR	PSA level decreased from baseline in 57.8% of the group and was stable in 4.2%. In this 62%, the risk of finding PCa at biopsy was 25% compared to the 38% that showed an increase in PSA levels that had a risk of 52.2% of developing PCa.

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Table 2.5 Studies on dietary vitamin E intake and risk of prostate cancer – epidemiological studies.

Study (reference)	Brief description of study	Form of vitamin E	Subjects	Mean daily intake of vitamin E (SD)*	RR or OR (95% CI)	Summary of findings
Study from the Netherlands (Schuurman et al 2002)	Prospective cohort study	Total vitamin E	58,279 men aged 55-69. 642 cases of prostate carcinoma were identified; 1525 sub-cohort members were used as controls.	14.4 (6.4) mg	OR by quintile: 1.05 (0.61-1.51) 1.14 (0.84-1.54) 0.94 (0.69-1.29) 0.94 (0.68-1.29) (p=0.42)	Estimated total vitamin E levels were not statistically significantly related to risk of prostate cancer.
				14.7 (6.6) mg		
Greek Study-greater Athens area. (Tzonou, A.et al, 1999)	Case-control study	Total Vitamin E	320 cases	Not indicated	0.53 (95% CI: 0.30-0.94 (p=0.03) Multiple logistic regression-derived, mutually adjusted odds ratio for PC corresponding to an increment of one SD of daily intake among controls.	Estimated total vitamin E was inversely associated with prostate cancer. This relationship was statistically significant.
			246 controls	Not indicated		
Italian Study - five areas of Italy. (Bidoli et al,	Case-Control study	Total Vitamin E	1294 cases	Not indicated	OR by tertile (95% CI) : 0.87 (0.69-1.05)	Estimated total vitamin E was inversely associated with prostate cancer and was statistically

Study (reference)	Brief description of study	Form of vitamin E	Subjects	Mean daily intake of vitamin E (SD)*	RR or OR (95% CI)	Summary of findings
2009)			1451 controls	15.3 mg/day	0.78 (0.58-0.69) (p=0.02)	significant.
Study from Montevideo, Uruguay (Deneo-Pellegrini et al, 1999)	Case-control study	Total vitamin E	175 cases 233 controls	IQR (mg/day) <5 5.1-6.0 6.1-7.8 >7.9	OR by quartile 1.2 (0.7-2.1) 0.6 (0.3-1.1) 0.6 (0.3-1.1) (p=0.03)	Estimated total vitamin E levels were significantly lower in cases and were inversely related to the PSA levels
Serbian Case-Control study; Vlajinac et al, 1997	Case-control study	α-Tocopherol	101 cases 202 controls	8.6 (3.4) mg 10.3 (5.6) mg	Adjusted for nutrients which were significant when unadjusted or adjusted for energy; by tertile 1.17 (0.5-2.77) 0.22 (0.07-0.7) p=<0.05	Estimated total vitamin E intake was significantly inversely related to prostate cancer only when intake was high (tertile 3).
US-based Rodriguez et al; 2004	Prospective Cohort Study	Vitamin E from supplements only	72704	Grouped into none, occasional (1-31 IU/day); regular; (32-<400 IU/day); and high (>400IU/day)	For all cases of prostate cancer: Occasional: 0.99 (0.92-1.07) Regular: 1.06 (0.95-1.19); High: 0.98 (0.89-1.08); (p = 0.83)	Regular vitamin E supplement use was not associated with overall risk of prostate cancer. No trend was seen with increasing dose of vitamin E. Men who reported regular vitamin E use during the study period were not at lower risk of prostate cancer. Among current smokers there was a suggestion of slightly reduced risk with regular vitamin E supplement use RR = 0.87, 95% CI =0.67-1.11.

*Vitamin E content was estimated through average vitamin E levels found in foods multiplied by number of portions consumed as indicated through the food frequency questionnaire. Supplement consumption was also assessed through questionnaire.