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# Vitamin E and cancer prevention[1,2]

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**ABSTRACT** Some animal experiments and human studies suggest that vitamin E may protect against cancer. Serum α-tocopherol concentration was studied for its prediction of cancer in a cohort of 36 265 adults in Finland. During a mean follow-up of 8 y, cancer was diagnosed in 766 persons. The levels of serum α-tocopherol were determined from stored serum samples (at −20 °C) taken from these cancer patients and from 1419 matched control subjects. Individuals with a low level of α-tocopherol had about a 1.5-fold risk of cancer compared with those with a higher level. The strength of the association between serum α-tocopherol level and cancer risk varied for different cancer sites and was strongest for some gastrointestinal cancers and for the combined group of cancers unrelated to smoking. The association was strongest among nonsmoking men and among women with low levels of serum selenium. The findings agree with the hypothesis that dietary vitamin E in some circumstances protects against cancer. *Am J Clin Nutr* 1991;53:283S–6S.

**KEY WORDS** Vitamin E, α-tocopherol, epidemiology, diet, serum, neoplasms

## Introduction

It has been suggested that vitamin E has anticancer effects as a lipid antioxidant and free radical scavenger. During the last decade, increasing interest has been focused on the question of whether ample intake of vitamin E may reduce the risk of cancer. Both experimental studies on animals and human epidemiological studies have been carried out. The majority of the human studies are based on relatively small numbers of cancer cases and thus it is difficult to get a reliable picture of the possible associations from a single study. On the other hand combination of results across several studies may cause biases because of the heterogeneity between different populations. This presentation summarizes the results of a large longitudinal study on serum α-tocopherol concentration and cancer risk (1–4) and compares them with the results of other studies.

## Review of the literature

### *Experiments on animals*

Animal experiments and in vitro studies have shown that vitamin E can block the formation of carcinogenic nitrosamines (5). Studies on the effect of vitamin E on other carcinogens have, however, yielded somewhat conflicting results (1, 5). Most of the studies have concentrated on mammary gland, colon, oral, and skin carcinogenesis. Vitamin E has been shown to inhibit oral carcinogenesis and to inhibit or to have no effect on mammary gland carcinogenesis. Vitamin E has also been shown to inhibit or to enhance skin carcinogenesis and to inhibit, to have no effect on, or to enhance colon carcinogenesis (1, 5, 6). The effect of vitamin E possibly depends on several factors, including the amount of vitamin E administered, the level of modifying factors (eg, dietary selenium and fat), the carcinogens used and the dosage of carcinogen.

### *Epidemiologic studies*

*Dietary vitamin E and cancer.* Although the animal studies provide some support for the hypothesis that vitamin E has an anticancer effect, the role of this micronutrient in cancer prevention in humans is equivocal. In several human epidemiologic studies on diet and cancer, consumption of foodstuffs rich in vitamin E such as vegetables has been found to be inversely related to the risk of different cancers (eg, lung). The possibility, however, cannot be excluded that the associations in these studies are mainly due to carotene or certain other substances in the foodstuff. Possibly for methodological reasons, the results of the few studies on the association between vitamin E intake and cancer risk do not generally show any evidence that vitamin E has a protective effect (7).

*Cross-sectional studies on blood vitamin E level and cancer.* Blood vitamin E levels are directly related to intake of the vitamin (8) and can be used as a proxy measure of vitamin E intake. The results of the few cross-sectional studies on the association between blood vitamin E level and different cancers are somewhat contradictory, presenting an inverse association in respect to several sites of cancer (eg, cancers of the lung, oral cavity, gastrointestinal tract, nervous system, and skin) but not all (eg, cancer of the female reproductive organs) (7). The results of these studies should, however, be interpreted with caution because of the small samples and insufficient adjustment for confounding factors.

*Longitudinal studies on blood vitamin E level and cancer.* The association between serum vitamin E level and subsequent cancer risk has been examined in 12 longitudinal studies, all performed

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as a nested case-control design within the main study (9–20). In 11 of the studies, vitamin E determinations were based on stored frozen serum or plasma samples collected in the baseline examination and thawed for analysis at the end of follow-up. Only one study used fresh plasma samples analyzed at the baseline (9). Nine of the studies reported slightly lower mean serum vitamin E levels in subjects who developed cancer than in controls (9–11, 13–18). Three of them reported statistically significant differences between patients and control subjects in the total sample (10, 14, 16) and three studies reported such differences in subpopulations or in a secondary analysis (13, 18, 21). Overall, the studies showed on average a 3% lower mean $\alpha$-tocopherol level among cancer patients than among control subjects, a statistically significant difference.

In addition to all sites of cancer, the studies mainly concentrated on cancers of the lung and the gastrointestinal tract and hormone-related cancers. With one exception (14), no significant associations with lung cancer were observed (9, 11–13, 16, 18). All the studies performed on colorectal cancers reported a nonsignificantly lower mean level of serum vitamin E among patients than among control subjects (9, 12, 17, 18), whereas the results for stomach cancer are contradictory, showing both inverse associations (12, 21) and no association (9, 18). One study reported a significant positive association between serum vitamin E level and occurrence of pancreatic cancer (20). Three studies have reported on hormone-related cancers (10, 11, 19). Of these Wald et al (10) found an inverse association between serum vitamin E level and breast cancer occurrence, but another study based on the same population failed to confirm that finding (19).

*Clinical trials.* Small-scale studies on the effect of vitamin E supplementation in patients with mammary dysplasia indicate an improvement in clinical signs (5, 22). This could be interpreted as suggesting that the risk of breast cancer may be reduced by vitamin E supplementation. However, the findings of these small scale experiments are not confirmed by later trials (7). Generalization of the findings from chemopreventive trials requires large-scale studies. A number of such randomized, placebo-controlled trials testing whether intake of vitamin E and other micronutrient supplements can lower cancer incidence are currently under way (23). The follow-ups of these trials are too short to allow any result to be presented yet.

## The Finnish Mobile Clinic Health Survey

### *Methods*

The study linked a large health examination data set collected by the Social Insurance Institution's Mobile Clinic Unit with data from the nationwide Finnish Cancer Registry (3). The study population comprised 36 265 individuals initially aged 15–99 y from 25 population groups in different parts of Finland. The baseline examination was conducted in 1968–1972, and during a mean follow-up over 8 y cancer was diagnosed in 766 persons. The levels of serum $\alpha$-tocopherol and other antioxidants were determined from serum samples stored at $-20$ °C taken from these cancer patients and from 1419 control subjects, matched for sex, age, and duration of storage. The statistical analyses were mainly based on the conditional logistic model.

### *Results*

The mean serum $\alpha$-tocopherol level among the cancer cases was 20.5 $\mu$mol/L and, on average, 3% lower than among control subjects. The difference was statistically significant. Individuals with a low level of $\alpha$-tocopherol (among men the three lowest quintiles and among women the lowest quintile of the distribution) had about a 1.5-fold risk of cancer compared with those who had a higher level.

The strength of the association between the serum $\alpha$-tocopherol level and cancer risk varied for different cancer sites (**Table 1**). It was strongest for some gastrointestinal cancers and for the combined group of cancers unrelated to smoking. The relative risk of cancer for those with a low level of serum $\alpha$-tocopherol was $\geq$2.0 compared with those with a higher level of serum $\alpha$-tocopherol for different sites of gastrointestinal cancer (stomach, pancreas, and colorectum), with the exception of colorectal cancer among men. The relative risk of cancer unrelated to smoking was almost 2.0 and differed significantly from unity. No notable association was observed with regard to lung cancer, the combined group of cancers related to smoking (cancers of the lip, oral cavity and pharynx, oesophagus, respiratory organs, and urinary bladder), or hormone-related cancers (cancers of the breast, ovary, endometrium, and prostate). The association was not due to the association between serum cholesterol, serum vitamin A, or serum selenium. It seemed not to be secondary to early cancer because exclusion of the cancer cases occurring during the first 2 y of follow-up did not materially change the results. In fact, there was a significant association between serum $\alpha$-tocopherol and cancer risk even after a follow-up of 7 to 11 y (**Table 2**), suggesting that a single serum $\alpha$-tocopherol determination can be used as a proxy measurement for vitamin E exposure during a relatively long period of time.

The strength of the association between serum $\alpha$-tocopherol level and risk of cancer varied between subgroups in the study population. Nonsmoking men with a low serum $\alpha$-tocopherol level had an almost twofold cancer risk compared with other nonsmoking men. No such association was observed among smoking men. A significant association between serum $\alpha$-tocopherol level and risk of hormone-related cancers was observed only among women with low levels of serum selenium. Subjects with both low serum selenium and low serum $\alpha$-tocopherol levels had a three times higher risk of hormone-related cancer.

### *Discussion*

Both the results of the Finnish Mobile Clinic Health Survey and the combined result of all other longitudinal studies suggest a significant inverse association between serum vitamin E level and cancer risk. The association may be concentrated on the gastrointestinal tract and there is no strong evidence for it in the case of lung cancer or hormonally related cancers. The association may be a direct effect of dietary or serum vitamin E, or may be due to confounding by other factors associated with vitamin E. The studies were generally well designed and any confounding by sex, age, or time of blood collection was controlled for by matching in several of them (2, 3, 11, 14, 17–19). Adjustment for smoking and other potential confounding factors resulted in only minor changes in the strength of the associations (3, 14, 16).

Vitamin E is transported in the lipoproteins and is thus highly correlated with serum cholesterol (24). Because serum cholesterol level has been reported to be inversely associated with cancer risk (25, 26) it is thus possible that the serum vitamin E/cancer association is secondary to the serum cholesterol/cancer association. It is also possible that the $\alpha$-tocopherol/cancer association

TABLE 1
Mean levels of serum α-tocopherol among patients, percentage case-control difference, and relative risk of cancer between low* and higher levels of serum α-tocopherol

| Site of cancer | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | No of sets | Case mean | Percentage case-control difference | Relative risk† | No of sets | Case mean | Percentage case-control difference | Relative risk† |
| | | μmol/L | | | | μmol/L | | |
| All sites | 453 | 18.6 | −3.2 | 1.4 | 313 | 23.2 | −3.8 | 1.8 |
| Stomach | 48 | 17.7 | −8.0 | 2.1 | 28 | 23.5 | −2.2 | 2.9 |
| Colorectal | 21 | 20.0 | +8.4 | 1.0 | 35 | 24.1 | −9.6 | 2.1 |
| Pancreas | 17 | 16.3 | −27.6 | 4.8 | 11 | 27.4 | +9.0 | — |
| Lung | 144 | 18.8 | −3.6 | 1.0 | 8 | 22.3 | +2.2 | 0.8 |
| Breast | — | — | — | — | 67 | 23.2 | +0.1 | 1.4 |
| Cervix uteri | — | — | — | — | 23 | 25.1 | −7.7 | 2.9 |
| Endometrium | — | — | — | — | 12 | 21.4 | −6.3 | 0.7 |
| Ovary | — | — | — | — | 16 | 22.3 | +2.3 | 1.4 |
| Prostate | 37 | 18.1 | −3.6 | 1.0 | — | — | — | — |
| Urinary organs | 26 | 19.3 | −0.2 | 5.6 | 9 | 24.9 | +1.9 | — |
| Skin: basal cell carcinoma | 49 | 19.0 | −2.8 | 1.6 | 38 | 22.3 | −3.8 | 1.5 |
| Nervous system | 9 | 17.2 | −8.1 | 2.6 | 9 | 22.5 | −5.5 | — |
| Lymphomas and leukaemia | 19 | 17.9 | +6.3 | 1.1 | 13 | 23.2 | −5.2 | 2.6 |
| Other or unspecified cancers | 83 | 19.3 | −1.4 | 1.0 | 44 | 22.1 | −11.5 | 3.6 |
| Related to smoking‡ | 185 | 18.8 | −3.2 | 0.9 | 28 | 23.2 | −4.5 | 2.0 |
| Unrelated to smoking§ | 268 | 18.6 | −3.1 | 1.7 | 289 | 23.2 | −3.8 | 1.8 |

* The three lowest quintiles (< 20.2 μmol/L) in men and the lowest quintile (< 18.3 μmol/L) in women.
† Adjusted for smoking and cholesterol.
‡ Includes cancers of the lip, oral cavity and pharynx (ICD 7 codes 140–148), esophagus (code 150), respiratory organs (codes 160–163), and urinary bladder (code 181).
§ Includes cancers other than those listed in the footnote immediately above.

may be secondary to the association between β-carotene or selenium and cancer (1). However, adjustment for serum cholesterol, β-carotene, retinol, and selenium did not materially alter the association between α-tocopherol and cancer in earlier studies (14, 16, 17) and did not do so in our study (2, 3). This suggests that there is an independent association between serum α-tocopherol level and cancer risk. Adjustment for serum cholesterol or other lipids reduced the difference in some (11, 18) but not in all (1, 12, 17) studies.

It is possible that a depressed level of serum vitamin E is a consequence of preclinical cancer in the baseline study when the blood samples were collected. One finding according to which the association between serum vitamin E level and cancer risk is strongest during the first years of follow-up supports that hypothesis (18). There is, however, evidence both from the Finnish Mobile Clinic Health Survey (3) and from several other studies (3, 10, 14, 16, 17) that suggests that preclinical cancer is probably not the only explanation for the inverse association.

The strength of the association between the serum α-tocopherol level and cancer risk may vary between subgroups in the population. In accordance with other studies (13, 18), the Finnish Mobile Clinic Health Survey reported stronger associations among nonsmokers than among smokers. The results concerning the proposed interaction between selenium and vitamin E in protecting against cancer are contradictory. The Finnish Mobile Clinic Health Survey reported an elevated risk of hormonally related cancers among women with a low level of both serum α-tocopherol and selenium (1). Similar findings have been reported in respect of all sites of cancer (13, 27), but with respect to cancers of the lung, colon, and several cancers combined no such associations have been reported (12, 14, 17).

In studies based on single serum samples, the findings might conceivably be weakened by the poor representativeness of the serum sample. A single sample for each person might not be sufficient to reflect any long-term serum levels or dietary intake of vitamin E over a lengthy period of time (28) and thus to

TABLE 2
Smoking-adjusted relative risk of cancer between low* and higher level of serum α-tocopherol during different follow-ups

| Follow-up | All sites | | | |
|---|---|---|---|---|
| | No of sets | Relative risk | 95% confidence interval | Percentage case-control difference |
| y | | | | |
| 1–3 | 299 | 1.9 | 1.3–2.7 | −5.3 |
| 4–6 | 295 | 1.3 | 0.9–1.8 | −1.6 |
| 7–10 | 172 | 1.7 | 1.1–2.7 | −3.0 |

* Low level was defined as the three lowest quintiles (< 20.2 μmol/L) among men and the lowest quintile (< 18.3 μmol/L) among women.

reveal any possible associations with cancer risk. The results of the Finnish Mobile Clinic Health Survey, however, suggest that associations between serum $\alpha$-tocopherol level and cancer risk can be observed after a relatively long follow-up period. The serum samples in the study were stored at $-20$ °C and it has been suggested that degradation during storage may be the cause of the findings (29). This explanation is, however, unlikely in the Finnish Mobile Clinic Health Survey (3).

In conclusion, most data available are in agreement with the hypothesis that dietary vitamin E protects against cancer. Any preventive effect may depend on the causes of the cancer, which varies for different cancer sites. Thus, there are probably cancers the incidence of which does not depend on vitamin E intake. The question of whether increased vitamin E intake reduces the incidence of cancer has not yet been answered. To establish the possible anticarcinogenic effect of vitamin E and to estimate its magnitude in humans, results are needed from ongoing intervention trials on human populations and from large-scale observational studies in varying circumstances.

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