CLINICAL RESEARCH

Risk of cancer in relation to serum concentrations of selenium and vitamins A and E: matched case-control analysis of prospective data

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Abstract

The independent and joint associations of serum selenium and vitamin A (retinol) and E (α tocopherol) concentrations with the risk of death from cancer were studied in 51 case-control pairs—that is, 51 patients with cancer, each paired with a control matched for age, sex, and smoking. Case-control pairs came from a random sample of some 12 000 people aged 30-64 years resident in two provinces of eastern Finland who were followed up for four years.

Patients who died of cancer during the follow up period had a 12% lower mean serum selenium concentration ($p = 0.015$) than the controls. The difference persisted when deaths from cancer in the first follow up year were excluded. The adjusted risk of fatal cancer was 5·8-fold (95% confidence interval 1·2-29·0) among subjects in the lowest tertile of selenium concentrations compared with those with higher values. Subjects with both low selenium and low α tocopherol concentrations in serum had an 11·4-fold adjusted risk. Among smoking men with cancer serum retinol concentrations were 26% lower than in smoking controls ($p = 0.002$).

These data suggest that dietary selenium deficiency is associated with an increased risk of fatal cancer, that low vitamin E intake may enhance this effect, and that decreased vitamin or provitamin A intake contributes to the risk of lung cancer among smoking men with a low selenium intake.

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Introduction

Two recent prospective epidemiological studies have reported an association between a low prediagnostic serum selenium concentration and the risk of cancer.[1 2] Selenium has been found to reduce the incidence and progression of cancer in animals exposed to carcinogens.[3-6] There is also evidence from cohort studies of low retinol concentrations in the serum of people who later develop cancer.[7 8] These observations are supported by the findings of prospective investigations in which retinol intake was estimated by dietary record or interview.[9-12] Studies in animals show that administration of retinoids inhibits tumour growth.[13-16] In two animal studies supplementation with retinoids reduced the incidence of tumours more than did selenium,[17 18] and in another of these[18] the effect of retinyl acetate and selenium was additive. In some studies, however, retinoids enhanced tumour growth in animals treated with carcinogenic chemicals.[19 20] Two recent prospective studies did not find any association between either serum retinol or retinol binding protein concentrations and the risk of cancer.[21 22]

Vitamin E in serum undergoes degradation during storage, so there are few studies of an association of serum vitamin E concentrations and the risk of cancer. A synergistic relation of serum selenium and vitamin E with the risk of cancer has, however, been reported.[1] The results of case-control studies[23-25] with dietary measurements are conflicting. In one prospective study serum vitamin E concentration showed no association with the risk of cancer.[22] Vitamin E supplementation alone had a variable effect on tumour formation in animals exposed to carcinogens,[26-28] but it potentiated the ability of selenium to inhibit development of neoplasia.[29]

Since available evidence on the effect of selenium and vitamins A and E on the development of cancer is insufficient

and controversial,[30-33] we have analysed the independent and joint associations of prediagnostic serum selenium and vitamin A and E concentrations with the subsequent risk of death from cancer in data from a prospective study in eastern Finland.

Subjects and methods

We used the data of the Eastern Finland Heart Survey 1977, which served as the terminal survey of the North Karelia project.[34] The survey comprised a random 6·7% sample of the population aged 30-64 years in 1977 living in two provinces of eastern Finland, North Karelia and Kuopio. This population has an exceptionally high dietary intake of saturated fats and cholesterol.[34 35] The participation rate in the survey was 90%, and altogether 12 155 people were examined.

The survey was carried out during January, February, and March 1977. It included a self administered questionnaire of 148 items, interviews, and physical measurements. Details of the methods of measurement and fieldwork have been reported.[34 35] Venous blood was drawn from each subject and a sample of serum stored at −20°C in closed plastic tubes. The tubes were thawed for the first time in April 1984 for the analysis of selenium, retinol, and α tocopherol.

Selenium concentrations were determined by a graphite furnace atomic absorption spectrometric method after a simple dilution procedure, as described.[36] Serum total retinol and α tocopherol concentrations were determined by high performance liquid chromatography.[37] The interassay coefficient of variation for retinol determinations was 5·2% and for α tocopherol determinations 3·8%.

Data on deaths in the cohort were obtained from the National Death Certificate Register, which records all deaths of Finnish citizens. The underlying cause of death was taken as that assigned at the Central Statistical Office of Finland. All diagnoses of cancer were confirmed from hospital records. This analysis is based on deaths that occurred up to 31 December 1980.

During the four years of follow up 56 subjects in the 1977 cohort died of cancer (all types; International Classification of Diseases (ICD), 8th revision, codes 140-209). One control subject was paired with each of these cases, matched according to sex, age, and number of tobacco products smoked daily in the 1977 survey. Sex, year of birth, and smoking state (smoker or non-smoker) of each control were identical with those of the matched case. For smokers a control with the most similar tobacco consumption was selected. Serum samples were missing for five cases and four original controls, who were replaced by others. Thus 51 cases and 51 matched controls were available for analysis.

The differences in mean serum selenium, retinol, and α tocopherol concentrations between cases and controls were tested with the two sided Wilcoxon signed ranks test for paired samples. Potential confounding factors were explored by comparing the means or proportions of 43 variables measured in the 1977 survey and considered relevant on the basis of other studies. The variables related to socioeconomic state, diet, other health habits, medical history, and clinical characteristics of the subjects. Significant differences between cases and controls were observed only for serum total cholesterol values, years of smoking, and number of reported chronic diseases. None of the women (cases or controls) reported use of oral contraceptives.

To estimate the partial associations and synergism of serum selenium, retinol, and α tocopherol concentrations with the risk of death from cancer, these three variables and the possible confounding factors were entered into the same multiple logistic model. Differences between cases and controls were used as independent variables to estimate the unconditional likelihood in a multiple logistic model when the statistical unit was the pair. The logistic regression technique of the GLIM computing package[38] was used to fit the conditional model to matched pair data. The adjusted relative risks were estimated from these multiple logistic models as antilogarithms of the coefficient estimates of dichotomised variables and their confidence intervals based on the approximate normality of the estimates.

For comparison with other series some values are expressed in mass units. For conversion to substance concentrations 80 μg selenium, 290 μg retinol, and 0·4 mg α tocopherol per litre are roughly equal to 1 μmol/l in each case.

Results

The mean prefollow up serum selenium concentration of the subjects who died of cancer during follow up was 53·7 (SE 1·8) μg/l and that of the controls 60·9 (1·8) μg/l. This difference (of 12%) was statistically significant (Wilcoxon $Z = -2·43$; $p = 0·015$; table I). When deaths from cancer that occurred during the first year of follow up were excluded the respective means were 54·8 (SE 1·9) μg/l for the remaining 44 cases and 61·1 (1·8) μg/l for their matched controls ($p = 0·038$).

The mean serum selenium concentration was 19% lower among the cases than the controls in men ($p = 0·002$), whereas there was no difference among women. Sixteen out of 30 pairs of men were smokers in the 1977 survey, whereas none of the 21 pairs of women were smokers. The mean case-control difference in serum selenium concentration was greatest among the smokers—all of whom were men—(22%; $p = 0·013$) and non-significant among the non-smokers (table I). In the analysis according to the site of cancer the difference in mean serum selenium concentration between cases and controls was greatest and statistically significant only for respiratory cancers, though a difference also existed for gastrointestinal sites and other cancers combined (table II).

The overall mean serum retinol concentration was 483 (SE 17) μg/l in the cases and 524 (16) μg/l in the controls ($Z = -1·73$; $p = 0·084$). The respective means in men were 465 (21) μg/l and 545 (20) μg/l, a difference of 15% ($p = 0·007$). In women the serum retinol concentration was slightly higher among the cases than the controls (table I). Among the smokers the subjects who died had a 26% lower mean serum retinol concentration than the controls ($p = 0·002$), and this difference remained significant when deaths from cancer in the first year of follow up were excluded ($p = 0·006$). The difference among non-smokers was very small and in the opposite direction (table I) among both non-smoking men and women. As for selenium, the greatest mean case-control difference in serum retinol concentration occurred in the group dying of respiratory cancer (table II).

There was a statistically non-significant trend towards lower mean

TABLE I—*Mean prefollow up serum selenium, retinol, and α tocopherol concentrations in smoking and non-smoking men and women aged 35-64 who died of cancer and in controls matched for age, sex, and smoking*

	Men				Women		All	
	Smokers		Non-smokers					
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Selenium (μg/l)	49·3	63·5*	49·9	58·4	59·5	60·5	53·7	60·9*
Retinol (μg/l)	426	579**	508	507	508	495	483	524
α Tocopherol (mg/l)	4·6	5·0	4·4	5·6*	5·4	4·7	4·9	5·0
α Tocopherol:cholesterol ratio (%)	18·7	19·0	18·4	23·2*	19·3	20·6	18·9	20·8
No of pairs	16		14		21		51	

Significance of difference between cases and controls (Wilcoxon's matched pairs signed rank test): *$p < 0·05$; **$p < 0·01$.

TABLE II—*Mean prefollow up serum selenium and retinol concentrations in subjects who died of cancer and in matched controls according to site of cancer*

Site of cancer and ICD code	No of pairs	Selenium (μg/l)		Retinol (μg/l)	
		Cases	Controls	Cases	Controls
Gastrointestinal (codes 150-158)	18	54·9	60·1	495	535
Respiratory (code 160)	15	52·6	62·0*	480	568*
Other (codes 174-203)	18	53·3	60·7	473	478

*Significance of difference between cases and controls (Wilcoxon's matched pairs signed rank test): $p < 0·05$.

serum α tocopherol concentrations among the cases than the controls in smoking men and a significant difference (p = 0·041) in non-smoking men, whereas the difference showed an opposite trend in women (table I). The difference in serum α tocopherol concentrations between the cases and controls was not statistically significant for any specific site of cancer (not shown). The ratios of α tocopherol to serum total cholesterol values were similar. Men with cancer had 11% lower α tocopherol to total cholesterol ratios (p = 0·133) than their controls; among women the difference was even smaller.

With regard to other variables measured in the 1977 survey, the cases differed from the matched controls in the mean serum total cholesterol concentration (6·8 mmol/l (261 mg/100 ml) for cases and 6·3 mmol/l (243 mg/100 ml) for controls; p = 0·028), years of smoking (29·7 and 20·9 years, respectively; p = 0·045), and numbers of drugs used for chronic diseases (1·2 for cases and 0·5 for controls; p = 0·001). Among these potential confounding factors and study variables there was a moderate correlation between α tocopherol and serum cholesterol for both cases (r = 0·43) and controls (r = 0·29). Serum selenium, retinol, and α tocopherol concentrations intercorrelated moderately among the cases and weakly among the controls. Years of smoking correlated positively with serum retinol concentration in the controls (r = 0·37) but not in the cases. Years of smoking showed an inverse correlation with serum selenium in the cases (r = −0·30) but not in the controls.

The associations of serum selenium, total cholesterol, years of smoking, and numbers of drugs for chronic diseases with the risk of death from cancer remained significant in a multiple logistic model among all case-control pairs (table III) and among those excluding the deaths in the first follow up year. A serum selenium concentration of 47 μg/l or less (the lowest tertile) was associated with a relative risk of death from cancer of 5·8 (95% confidence interval 1·2-29·0) in a multiple logistic model allowing for serum retinol, α tocopherol, and their interactions with selenium (table IV).

TABLE III—*Partial coefficients of serum selenium, retinol, and α tocopherol concentrations in multiple logistic model*

	Coefficient	Standard error
Selenium (μg/l)	−0·060*	0·029
Retinol (μg/l)	−0·0026	0·0038
α Tocopherol (mg/l)	−0·254	0·245
Total cholesterol (mmol/l)	0·00101*	0·00036
Smoking years	0·078*	0·034
No of drugs for chronic diseases	1·020*	0·425

*Significance of coefficient: p < 0·05.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

TABLE IV—*Relative risk of death from cancer associated with low* serum selenium, retinol, and α tocopherol concentrations*

	Relative risk†	95% confidence interval
Selenium 47 μg/l or less	5·8‡	1·2-29·0
Retinol 461 μg/l or less	0·9	0·3-2·5
α Tocopherol 4·16 mg/l or less	1·6	0·6-4·5
Selenium-retinol interaction	1·0	0·2-6·4
Selenium-tocopherol interaction	11·4‡	1·2-109·6

*Independent variables dichotomised: 1 if lowest tertile, 0 if otherwise.
†Based on conditional multiple logistic model allowing also for serum total cholesterol concentration (coefficient 0·022; SE 0·0082).
‡Relative risk significantly different from value 1 at p < 0·05.

The respective adjusted relative risk for selenium and α tocopherol interaction was 11·4 (95% confidence interval 1·2-109·6), whereas serum selenium showed no synergism with serum retinol. The sample was too small for multivariate analyses in subgroups. The mean serum selenium concentration for the pairs in the lower half of the α tocopherol distribution was 47·4 (SE 2·0) μl/l among the cases and 63·5 (SE 3·0) μl/l among the controls, the difference being 25% (p < 0·001)—that is, twice that in the whole sample.

Discussion

These data show a strong association between a low serum selenium concentration and an increased risk of death from cancer. The association was strongest in men and in smokers and for respiratory cancers. It appeared to be independent of the serum retinol concentration but was strongly synergistic with serum α tocopherol, whereas serum α tocopherol alone showed no consistent independent relation to the risk of cancer. The association between low serum retinol concentration and an increased risk of cancer exists, on the basis of these data, only among smoking men. Our study sample did not, however, include any smoking women.

Our finding of an inverse relation between serum selenium concentration, which is an estimate of the dietary selenium intake, and the risk of cancer accords with two previous observations in prospective epidemiological studies. In the hypertension detection and follow up programme cohort[1] the risk of cancer was 2·0-fold in the lowest serum selenium quintile (below 115 μg/l) compared with the highest quintile. In that study selenium remained significantly associated with risk of cancer when the effects of serum retinol, vitamin E, and lipid concentrations as well as age, sex, and race were taken into account in a multiple logistic model. The relative risk of cancer for the lowest selenium tertile increased to 6·2 in comparison with the highest selenium tertile in the subgroup of the lowest tertiles of serum vitamins A and E. In contrast with the hypertension detection and follow up programme data, there was no synergism between serum selenium and retinol in our study.

The mean serum selenium concentration among all controls in the hypertension detection and follow up programme cohort was 136 μg/l, which is considerably higher than the respective mean in our sample (61 μg/l). The difference is due to the exceptionally low content of available selenium in Finnish soil and consequently in Finnish foods. Since the dose response relation between selenium intake and risk of cancer is apparently not linear but steeper towards lower intakes of selenium,[2] the impact of selenium on the risk of cancer is greater in the Finnish cohorts. Differential intake of other antioxidants might also play a part. Although selenium deficiency showed the strongest relation with respiratory cancer, it showed almost as sizable an association with other cancers combined—even though within sampling variation.

In two other prospective studies serum retinol[7] and dietary intake of β carotene[11] were associated only with the risk of respiratory cancer and not other types. In our data the relation was significant only for respiratory cancer and for all cancers among smokers (which were mostly respiratory), but was also seen weakly for gastrointestinal cancers, as in the study in Evans County.[8] On the basis of our observations, retinol seems to have its possible preventive effect mainly in respiratory and other squamous cell cancers, whereas the potential preventive effect of selenium is not so site specific.

In contrast with our finding, there was no difference in mean serum retinol concentration between persons with cancer and other matched controls in recently reported hypertension detection and follow up programme data.[22] Nor was a case-control difference found in a Swiss study,[21] which did not, however, take account of smoking either in the design or in the analysis. The British prospective study[39] found no association between serum retinol concentrations and the risk of breast cancer. It has been reported in secondary sources[22 40] that in the analysis of additional data from the Evans County study, based on a longer follow up, the difference in serum retinol values between cases and controls did not reach statistical significance. Thus out of five epidemiological cohort studies, two (ours and that of Wald *et al*[7]) found an association between a low serum retinol concentration and an increased risk of cancer, whereas three others[8 21 22] did not. Both our findings and those from the hypertension detection and follow up programme[1] support the conclusion that a low serum retinol concentration is associated with an increased risk of some cancers among people with low values of serum selenium and possibly other biological antioxidants. The lack of statistical interaction between serum retinol and selenium values in our sample may have been due to the generally low selenium concentrations. Also the mean serum retinol concentration in our controls (524 μg/l) was lower than in any of the other cohort studies in the 1970s, in which

mean serum retinol concentrations in controls ranged from 690 to 820 μg/l. In the Evans County study[8] serum was collected in 1960-2 and the mean serum retinol value in the controls was 470 μg/l.

As in other prospective studies,[7 8] we found a low serum retinol concentration associated with an increased risk of cancer only in men and not at all in women. This sex interaction was explained by smoking state; a retinol-cancer relation existed only in smokers, and there were no smokers among the women in our study.

Provitamin A (β carotene) is metabolised to retinol partly in the intestine and partly in the liver. Thus the circulating retinol concentration is an indicator of the dietary intake of all forms of vitamin A and also of both β carotene and retinol. β Carotene is stored mainly in the adipose tissue. Unbound retinol is stored in the liver, and the total rate of loss of retinol from the liver is dependent on the total amount stored in the liver.[41] Intestine derived retinol, however, does not totally determine the serum concentrations of total retinol.[42] Due to feedback in the metabolism of β carotene and storage of unbound retinol in the liver, the serum retinol concentration does not necessarily reflect a short term dietary intake but merely a long term intake. From the relation between serum retinol and lung cancer it cannot be deduced whether the preventive dietary constituent is β carotene or retinol. According to the Western Electric study, which used dietary interview only, β carotene should have a preventive role.[11] Several case-control studies based on retrospective serum or dietary data collection have been conducted on vitamin A in serum or diet of patients with cancer and their controls.[42 43] These suffer from the potential bias arising from the effect of the disease on the vitamin A measurements.

Vitamin E tends to undergo degradation in serum when stored at −20°C. The mean vitamin E concentration in our controls was 5·0 mg/l, on average 60-70% of values measured in fresh serum samples from subjects in our study area. Thus some degradation of vitamin E probably had taken place in our serum samples during storage. Although this systematic underestimation of serum vitamin E concentrations does not cause any bias in the comparison of cases and controls, our results with vitamin E must be interpreted very cautiously. Also serum retinol may have undergone some degradation during storage, but this was estimated as less than 10% when compared with values obtained on analysis of fresh serum samples.

Vitamin E, like retinol, did not show an association with any specific cancer site. Although the independent relation of vitamin E with risk of cancer was weak and not significant, vitamin E showed strong synergism with selenium on the risk of fatal cancer, so that the impact of selenium deficiency on cancer risk seemed to be noticeably greater at low serum vitamin E concentrations. This accords with findings in animals.[29] Our finding is also in agreement with the proposed biochemical interaction between selenium and vitamin E as endogenous antioxidants in the protection against peroxidative cell damage.[44] The synergism of selenium, a cofactor of glutathione peroxidase, and vitamin E, a lipid soluble antioxidant, emphasises the role of the total antioxidative capacity of the body in the etiology of cancer.

Owing to the design of our study we cannot rule out the possibility that serum concentrations of the substances measured were not the truly protective factors but merely indicators of other compounds or nutrients that were the real causal factors. Nevertheless, other studies and our findings indicate that dietary selenium deficiency increases the risk of cancer, possibly irrespective of site, and that this effect is enhanced by a low vitamin E intake. Furthermore, a decreased intake of β carotene or retinol or both seems to contribute to the risk of lung cancer among smoking men with a low intake of selenium. Additional epidemiological and experimental studies are, however, needed before definite conclusions can be drawn about the role of various forms of vitamin A in the aetiology of cancer. These studies should consider, in addition to effect modification and confounding by sex, smoking, and other antioxidants, the nutrients that covary with vitamin A compounds in foodstuffs in order to establish the real protective factor.

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