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Serum selenium level and risk of lung cancer mortality: a 16-year follow-up of the Copenhagen Male Study

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ABSTRACT: Serum selenium has been implicated as a risk factor for lung cancer, but the issue remains unsettled.

In a cohort of 3,333 males aged 53–74 yrs, we tested the hypothesis that a low serum selenium concentration would be associated with an increased risk of lung cancer mortality.

Over 16 yrs, 167 (5.1%) subjects died of lung cancer: 48 (5.0%) out of 965 with low serum selenium (0.4–1.0 μmol·L^{-1}), 57 (5.1%) out of 1,141 with medium serum selenium (1.1–1.2 μmol·L^{-1}) and 62 (5.1%) out of 1,227 with high serum selenium (1.3–3.0 μmol·L^{-1}). After adjustment for age, referencing the lowest level of serum selenium, hazard ratios (HRs) for medium and high levels of serum selenium were 0.97 (95% CI 0.66–1.43) and 0.99 (95% CI 0.68–1.45), respectively. Taking into account pack-years of smoking, spirits intake, dietary markers (salt and fat preferences) and health measures (chronic bronchitis and peak flow), referencing the lowest level of serum selenium, HRs were 1.17 (95% CI 0.79–1.75) and 1.43 (95% CI 0.96–2.14), for medium and high levels respectively. Among heavy smokers, a high serum selenium concentration was associated with a significantly increased risk of lung cancer mortality after taking into account all potential confounders.

The hypothesis that low serum selenium is an independent risk factor for lung cancer was not supported.

KEYWORDS: Alcohol use, epidemiology, lung cancer mortality, serum selenium, smoking

Selenium is an essential trace element with potentially anticarcinogenic properties and an association between serum selenium levels and risk of lung cancer has been suggested in the literature. The physiological role of the trace element selenium was established in 1973 [1, 2]. Selenium is an essential structural element of the enzyme glutathione peroxidase. This enzyme takes part in a system converting aggressive oxidation products, intracellular free radicals, into less reactive or neutral components [3].

As reviewed in two recent papers, the evidence for an association between selenium and lung cancer is inconsistent and predominantly based on nested case–control studies [4, 5]. None of these has found statistically significant associations between serum selenium levels and lung cancer risk. However, based on toenail measurements of selenium, VAN DEN BRANDT *et al.* [6] found a 50% decreased risk among those with the highest levels of selenium and HARTMAN *et al.* [7] found a significant inverse association between toenail selenium and lung cancer. In contrast, in the Nurses' Health Study of >60,000 participants, including 47 incident cases of lung cancer, GARLAND *et al.* [8] found a more than four-fold nonsignificantly increased risk of lung cancer comparing those in the highest tertile of toenail selenium with those in the lowest tertile. In their summary of the literature, ZHUO *et al.* [5] suggested a number of possible reasons for these inconsistencies: differences in exposure measurement, control selection, follow-up period, study populations or other differences in study design. Other problems could be a lack of conventional longitudinal cohort studies addressing the issue or even insufficient control for confounders.

In the Copenhagen Male Study (CMS), we have previously shown that a low serum selenium level is associated with increased risk of ischaemic heart disease during short-term follow-up [9]. In another more recent report from the CMS, we studied risk factors for lung cancer other than serum selenium [10]. As stated by NAVARRO SILVERA and ROHAN [4], additional prospective studies are needed. We agree with this; therefore,

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in a 16-yr follow-up, we tested the hypothesis that a low serum selenium concentration would be associated with an increased risk of lung cancer mortality.

MATERIAL AND METHODS

Patient characteristics

The CMS was set up in 1970–1971 as a prospective cardiovascular cohort study of 5,249 Caucasian males with a mean age of 48 yrs (range 40–59 yrs). The examination comprised a short interview based on a previously completed questionnaire from which information was obtained on lifestyle, including smoking habits [11, 12]. Based on information about education and job profile, the males were subdivided into five social classes as previously described [13].

In 1985–1986, a new baseline was established giving more comprehensive information about study participants. This baseline was used for the present study. All males from the 1970–1971 study were traced by means of the Danish Central Population Register. Between June 1985 and June 1986, all survivors (except 34 emigrants) from the original cohort were invited to take part in this study; 3,387 (75%) males agreed and gave informed consent; their mean age was 63 yrs (range 53–74 yrs). The 1985–1986 study took place as part of the Glostrup Population Studies at Glostrup Hospital (University of Copenhagen, Copenhagen, Denmark). Each subject was interviewed about a previously completed questionnaire and subjected to a clinical examination; a venous blood sample was taken for determination of serum selenium concentration. With respect to serum selenium and lung cancer mortality diagnoses, useful information was available for 3,333 males. The proportion of missing values did not exceed 3% for any other single variable.

Serum selenium determination

Serum selenium level was determined at Medisinsk Laboratorium (Oslo, Norway) using a graphite furnace atomic absorption spectrophotometric method after a simple dilution with a solution containing nickel in nitric acid [9]. The solutions were analysed for selenium at 196 nm with a deuterium background corrector after single injections into the graphite furnace and a standard curve of reference serum was used for the calibration. All samples were analysed in duplicate. The coefficient of variation was 5.5%.

As described in our previous report on serum selenium and ischaemic heart disease risk [9], it has been shown that at levels of selenium in whole blood >100 $\mu g \cdot L^{-1}$ and of plasma selenium >1.25 $\mu mol \cdot L^{-1}$, there is no noticeable increase in the glutathione peroxidase enzyme activity, indicating saturation. The indicated levels both correspond to ~ 1 $\mu mol \cdot L^{-1}$ of serum selenium. Almost one-third of the males in the present study had serum levels $\leqslant 1$ $\mu mol \cdot L^{-1}$. Accordingly, for analysis, we subdivided the population into three groups, *i.e.* into males with the lowest, potentially insufficient level of selenium ($\leqslant 1$ $\mu mol \cdot L^{-1}$) and those with higher levels were subdivided into two almost equally large groups.

Tobacco smoking habits

Subjects classified themselves as never-smokers, previous smokers or current smokers. Current tobacco consumption was calculated from information about the number of cigarettes, cheroots or cigars, or the weight of pipe tobacco smoked daily. One cigarette was taken as equivalent to 1 g tobacco, one cheroot as 3 g tobacco and one cigar as 4 g tobacco. As previously estimated by means of serum cotinine, the validity of tobacco reporting in the CMS was high [14]. Number of pack-years was calculated based on information about average total daily use of tobacco in grams multiplied by number of years as a smoker divided by 20.

Dietary factors

Salt and fat intake was crudely measured based on two simple questions: ''Do you use more salt in your food than others?'' and ''Do you try to avoid fatty foods?'' We have previously shown that both these dietary markers were associated with risk of lung cancer mortality, independently of tobacco history and other factors [10].

Alcohol consumption

Total weekly consumption of alcohol was calculated from questionnaire items about average alcohol consumption on weekdays and at weekends. Intakes of beer, wine and spirits were reported separately. One drink corresponded to 10–12 g ethanol.

Occupational exposures

Information on potentially relevant physical and chemical respirable occupational exposures was obtained from the questionnaire. Long-term exposure was defined as frequent occupational exposure for $\geqslant 5$ yrs. The question was phrased as follows: ''Have you at your present or previous work places often, *i.e.* several times per week or more, been exposed to dust? If yes, for how many years?''

End-points

Notification of death and causes of death within the period from 1985–1986 to the end of 2001 was obtained from the Danish Register of Causes of Death. The International Classification of Diseases (ICD) lung cancer mortality diagnoses used were codes ICD-8 162 and, from 1994, ICD-10 C34. Information on histological type of lung cancer was available for 128 out of the 170 lung cancer deaths.

Statistical analysis

All basic analyses, including unpaired t-test, Chi-squared analyses, Mann–Whitney rank-sum tests and regression analyses, were performed with the SPSS statistical software for Windows (IBM, Somers, NY, USA). Relative risks were estimated by $\exp(\beta)$, where β is the hazard coefficient for the variable of interest in Cox proportional hazards regression models following different adjustments. Assumptions for use of Cox proportional hazards were met. A two-sided probability value of $p \leqslant 0.05$ was *a priori* taken as significant.

Ethics

Each participant was informed that all personal data were confidential and gave written consent to participate. The study was approved by the Committee for Ethics in Medical Research of the County of Copenhagen (Copenhagen, Denmark).

TABLE 1 Lifestyle and other characteristics at baseline according to serum selenium level

	Serum selenium			p_{trend}[§]	p_{het}[f]
	Low[#]	Medium[¶]	High[+]		
Subjects n	965	1141	1227		
Smoking characteristics					
Exposure pack-yrs	32.4±28.4	28.5±24.0	24.5±23.4	<0.001	0.94
Current smokers	64.0	56.7	46.8	<0.001	<0.001
S-cotinine ng·mL^{-1}					
<100	38.9	46.8	57.5		
100–360	28.1	25.9	22.4	<0.001	<0.001
>360	33.0	27.3	20.1		
Smokers in 1970–1971	74.9	68.6	63.4	<0.001	<0.001
Never-smokers	8.2	11.3	13.3	<0.001	0.001
Alcohol use					
Alcoholic beverages per week					
0	10.6	9.8	12.7		
1–21	58.0	64.0	60.8	0.008	0.007
⩾22	31.4	26.2	26.4		
Beer drinkers	78.7	74.8	69.8	<0.001	<0.001
Beer beverages per week	12.9±11.3	10.5±8.3	10.5±8.7	<0.001	0.003
Wine drinkers	48.0	54.3	58.3	<0.001	<0.001
Wine beverages per week	7.4±6.9	7.7±7.8	7.4±6.2	0.92	0.51
Spirits drinkers	50.9	53.8	53.4	0.29	0.36
Spirits beverages per week	7.1±6.1	6.1±4.9	5.9±4.9	<0.001	0.14
Dietary factors					
Salt[##]	16.0	13.0	9.1	<0.001	<0.001
Fat[¶¶]	57.3	51.2	47.6	<0.001	<0.001
Occupational exposure					
Long-term dust exposure[++]	6.9	7.1	8.5	0.16	0.30
Other characteristics					
Chronic bronchitis	19.9	13.7	10.7	<0.001	<0.001
Peak flow L·min^{-1}	481±104	509±97	516±92	<0.001	0.006
Low social class[§§]	60.2	50.9	46.5	<0.001	<0.001
Age yrs	63.5±5.3	62.6±5.1	62.7±5.1	0.001	0.007

Data are presented as mean±SD or %, unless otherwise stated. p_{trend}: p-value for trend; p_{het}: p-value for heterogeneity. [#]: 0.4–1.0 μmol·L^{-1}; [¶]: 1.1–1.2 μmol·L^{-1}; [+]: 1.3–3.0 μmol·L^{-1}; [§]: Kendall's tau B or test for linearity in ANOVA; [f]: Chi-squared test (likelihood ratio) or test for deviation from linearity in ANOVA; [##]: uses more than others; [¶¶]: does not avoid fatty foods; [++]: ⩾5 yrs; [§§]: class IV–V.

TABLE 2 Lifestyle and other characteristics at baseline according to lung cancer mortality 1985–2001

	Lung cancer mortality		
	Yes	No	p-value[#]
Subjects n	170	3179	
Mean serum selenium μmol·L^{-1}			
All males	1.185	1.189	0.85
All smokers	1.185	1.185	0.46
Smokers with high cotinine[¶]	1.175	1.129	0.11
Smoking characteristics			
Exposure pack-yrs	36.4±21.6	27.6±25.4	<0.001
Current smokers	74.9	54.1	<0.001
S-cotinine level ng·mL^{-1}			
<100	24.4	49.7	
100–360	32.7	25.0	<0.001
>360	42.9	25.4	
Smokers in 1970–1971	87.6	67.5	<0.001
Never-smokers	4.8	11.5	0.003
Alcohol use			
Alcoholic beverages per week			
0	10.0	11.1	0.08
1–21	55.3	61.5	
⩾22	34.7	24.4	
Beer drinkers	78.7	73.9	0.15
Wine drinkers	55.6	54.0	0.68
Spirits drinkers	63.3	52.2	0.04
Dietary factors			
Salt[+]	20.0	11.9	0.003
Fat[§]	64.1	51.1	0.001
Occupational exposure			
Long-term dust exposure[f]	10.8	7.4	0.13
Other characteristics			
Chronic bronchitis	29.6	13.8	<0.001
Peak flow L·min^{-1}	470±109	505±97	<0.001
Low social class[##]	51.8	51.9	0.98
Age yrs	63.7±5.2	62.8±5.2	0.03

Data are presented as mean±SD or %, unless otherwise stated. [#]: unpaired t-test or Chi-squared test (likelihood ratio); [¶]: >360 ng·mL^{-1}; [+]: uses more than others; [§]: does not avoid fatty foods; [f]: ⩾5 yrs; [##]: class IV–V.

RESULTS

Overall, in the population eligible for study, 167 (5.1%) males died from lung cancer during the period from 1985–1986 to the end of 2001.

Baseline characteristics according to serum level of selenium

Table 1 shows univariate baseline characteristics stratified according to serum selenium level. With a few exceptions with respect to wine and spirits intake and occupational dust exposure, all lifestyle and other characteristics were clearly and statistically significantly associated with serum selenium level. The association with smoking variables was inverse for all variables presented. Total alcohol consumption was statistically significantly associated with selenium levels. However, the direction of the association depended both on the quantitative and qualitative weekly intake. Thus, an inverse association was found to beer intake and spirits intake (measured as units per week) and a positive association was found to wine intake (drinking wine or not).

Subjects who reported a high use of salt and those who did not avoid fatty foods were over-represented among males with low and medium serum selenium levels. Subjects with low peak flow values or chronic bronchitis were over-represented

among those with low selenium levels. This was the case also for subjects belonging to low social classes. A statistically significant but small inverse association was found with respect to age.

Table 2 shows lifestyle and other baseline characteristics of subjects who later died from lung cancer and subjects who did not. Subjects who died from lung cancer were statistically significantly more often current smokers, they had more pack-years of exposure, higher serum cotinine levels and only 4.8% had never smoked. Lung cancer cases had a slightly higher total alcohol consumption at baseline and a slightly higher intake of spirits.

Subjects using more salt than others died statistically significantly more often due to lung cancer and the same was the case for males who did not avoid foods high in fat. In addition, lung cancer cases were slightly more often exposed to occupational dust than others, but not statistically significantly so. Among lung cancer cases, the prevalence of chronic bronchitis was twice as high as among others, and they also had lower peak flow values. Overall, no association was found with social class. Lung cancer cases were slightly older. At baseline, mean serum selenium levels were the same among lung cancer cases and others.

Table 3 shows hazard ratios (HRs) for lung cancer and all-cause mortality according to serum selenium concentration. No association between serum selenium and lung cancer risk was found either with respect to crude incidence or after adjustment for relevant risk factors. A statistically nonsignificant higher risk with increasing serum selenium was found in the fully adjusted model (HR 1.43, 95% CI 0.96–2.14).

With respect to all-cause mortality, a statistically significant lower risk was found with increasing levels of serum selenium, when adjusted for age only and for the same factors included in the analysis of lung cancer risk.

Table 4 shows HRs for lung cancer mortality according to serum selenium concentration among all smokers at baseline, and among smokers with the lowest and highest levels of serum cotinine. Among all smokers, those with the medium and highest levels of serum selenium had a nearly statistically significantly increased risk of lung cancer mortality. Among smokers with high serum cotinine, those with the highest serum selenium levels had a statistically significant increased risk (HR 2.26, 95% CI 1.19–4.27) of lung cancer mortality. In contrast, no statistically significant association was found among smokers with the lowest serum cotinine levels. With respect to all-cause mortality, no associations were found among all smokers and smokers with high serum cotinine, but a slightly lower risk of all-cause mortality was found among smokers with low cotinine and medium selenium concentrations.

DISCUSSION

Overall, no association was found between baseline levels of serum selenium and subsequent risk of lung cancer mortality during a 16-yr follow-up and our hypothesis was not supported by the data presented. However, we found a statistically increased risk of lung cancer mortality among heavy smokers (those with cotinine levels above the mean among smokers) with high serum selenium. The finding of no association between serum levels and lung cancer in the whole cohort is in accordance with the results of nested case–control studies [4, 5] and one of the cohort studies previously

TABLE 3 Hazard ratios (HRs) for lung cancer and all-cause mortality according to serum selenium concentration following different adjustment criteria

	Serum selenium		
	Low#	Medium¶	High+
Subjects n	965	1141	1227
Lung cancer mortality			
Crude incidence %	5.0	5.1	5.1
HR (95% CI)			
Adjusted for age	1##	0.97 (0.66–1.43)	0.99 (0.68–1.45)
Adjusted for age and pack-years	1##	1.02 (0.69–1.51)	1.14 (0.78–1.69)
Adjusted for age, pack-years and spirits intake	1##	1.00 (0.68–1.48)	1.13 (0.68–1.48)
Adjusted for age, pack-years, spirits intake and dietary markers§	1##	1.04 (0.70–1.54)	1.21 (0.82–1.79)
Full model$	1##	1.17 (0.79–1.75)	1.43 (0.96–2.14)
All-cause mortality			
Crude incidence %	51.6	39.5	39.1
HR (95% CI)			
Adjusted for age	1##	0.75 (0.66–0.85)***	0.75 (0.66–0.86)***
Adjusted for age and pack-years	1##	0.77 (0.67–0.87)***	0.80 (0.71–0.92)***
Adjusted for age, pack-years and spirits intake	1##	0.77 (0.67–0.87)***	0.80 (0.70–0.91)***
Adjusted for age, pack-years, spirits intake and dietary markers§	1##	0.76 (0.67–0.87)***	0.80 (0.70–0.91)***
Full model$	1##	0.83 (0.73–0.95)**	0.90 (0.79–1.03)

Cox proportional hazards regression analyses with forced entry of variables. #: 0.4–1.0 μmol·L^{-1}; ¶: 1.1–1.2 μmol·L^{-1}; +: 1.3–3.0 μmol·L^{-1}; §: salt and fat intake; $: adjusted for age, pack-years, spirits intake, dietary markers (salt and fat intake), chronic bronchitis and peak flow; ##: reference group. **: p<0.01; ***: p<0.001.

TABLE 4 Hazard ratios (HRs) for lung cancer mortality according to serum selenium concentration following different adjustment criteria among all smokers at baseline and baseline smokers with the highest levels of serum cotinine, smokers with the lowest levels of cotinine and all smokers with cotinine >100 ng·mL^{-1}

	Serum selenium		
	Low[#]	Medium[¶]	High[+]
All smokers with serum cotinine >100 ng·mL^{-1}			
Subjects n	550	565	486
Crude mortality incidence %			
Lung cancer	6.0	8.5	7.8
All causes	56.6	46.6	47.5
HR[§] (95% CI)			
Lung cancer mortality	1[¶¶]	1.50 (0.95–2.37)	1.61 (0.99–2.62)
All-cause mortality	1[¶¶]	0.85 (0.72–1.01)	0.95 (0.79–1.13)
Smokers with high serum cotinine[f]			
Subjects n	294	287	230
Crude mortality incidence %			
Lung cancer	6.1	9.1	10.9
All causes	56.0	50.2	50.0
HR[§] (95% CI)			
Lung cancer mortality	1[¶¶]	1.77 (0.95–3.33)	2.26 (1.19–4.27)*
All-cause mortality	1[¶¶]	0.97 (0.77–1.23)	1.01 (0.79–1.30)
Smokers with low serum cotinine[##]			
Subjects n	256	278	256
Crude mortality incidence %			
Lung cancer	5.9	7.9	5.1
All causes	57.4	43.0	45.3
HR[§] (95% CI)			
Lung cancer mortality	1[¶¶]	1.32 (0.67–2.59)	1.07 (0.49–2.31)
All-cause mortality	1[¶¶]	0.74 (0.57–0.95)*	0.90 (0.70–1.17)

Cox proportional hazards regression analyses with forced entry of variables are shown. [#]: 0.4–1.0 μmol·L^{-1}; [¶]: 1.1–1.2 μmol·L^{-1}; [+]: 1.3–3.0 μmol·L^{-1}; [§]: adjusted for age, pack-years, spirits intake, dietary markers (salt and fat intake), chronic bronchitis and peak flow; [f]: >360 ng·mL^{-1}; [##]: 100–359 ng·mL^{-1}; [¶¶]: reference group. *: $p<0.05$.

published based on toenail measurements [8]. The only cohort study based on toenail measurements finding an increased risk of lung cancer associated with a low selenium level is the study by VAN DEN BRANDT *et al.* [6]. A probable explanation for the discrepancy between our study and that of VAN DEN BRANDT *et al.* [6] may be the complexity of the association of selenium levels with relevant lung cancer risk factors.

The other major result of the present study is the observation that serum selenium levels are associated with nearly all the risk factors for lung cancer previously identified in the CMS (table 1). The only exception from this was long-term occupational dust exposure. This may indicate that a methodological problem exists that may have affected data published to date, since low serum selenium *per se* is a marker of a clustering of lung cancer risk factors.

A third result of the present study is the finding that among smokers with high serum cotinine levels, surprisingly, risk of lung cancer increased with increasing levels of serum selenium. A plausible biological explanation for this observation is not presently available. A high serum selenium value should, theoretically, be protective against lung cancer in smokers, who place a heavy burden of oxidative stress on their cells, including those of the bronchial epithelium. It can be speculated that our result is analogous to the surprising results of a Finnish randomised intervention study on heavy smokers, where an increased risk of lung cancer was found among those who had received the highest supplements of the antioxidant β-carotene [15].

Strength and limitations

Several methodological challenges confront researchers attempting to find out whether a causal association exists between serum selenium level and risk of lung cancer. Most important among these are temporality (the exposure must precede the outcome), validity of the exposure assessment and validity of the outcome(s), and a sufficient confounder control to minimise residual confounding.

In this study, temporality was obtained. In addition, serum selenium must be considered a valid measure of selenium status in the body. In support of the validity of the selenium measure was its high ability to discriminate subjects with highly different lifestyles and other characteristics. Validity of the outcome must also be considered high, because Danish national registers have a high validity with respect to causes of

death [16, 17]. In particular, control for relevant confounders was possible in the present study.

The weaknesses of this study are that serum selenium was measured only at one time-point, and that only middle-aged and elderly Caucasian males were included.

Conclusion

The hypothesis that low serum selenium is an independent risk factor for lung cancer mortality did not gain any support from the present study.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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