

Prediagnostic Serum Selenium and Zinc Levels and Subsequent Risk of Lung and Stomach Cancer in Japan

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Abstract

Serum samples were collected in Hiroshima and Nagasaki, Japan, from 1970 to 1972 for 208 persons who in 1973–1983 developed stomach cancer; for 77 who in 1973–1983 developed lung cancer; and for controls matched for age, sex, city, and season of blood collection. Average serum levels of selenium and zinc were slightly (<5%) but not significantly lower among the cancer cases than among controls. Smoking-adjusted risks of lung cancer were elevated only among those in the lowest quartiles of serum selenium [odds ratio (OR) = 1.8] and zinc (OR = 1.3); the trends in risk of this cancer with decreasing serum levels were neither linear nor significant. Little or no excess risk of stomach cancer was observed among those with lowest levels of selenium (OR = 1.0) or zinc (OR = 1.2). These exploratory findings add to limited data available from other reports showing slightly increased risks of lung cancer associated with low blood levels of selenium, but suggest little association with either lung or stomach cancer across normal selenium or zinc ranges in this Japanese population.

Introduction

Selenium and zinc have been considered as potential inhibitors of cancer in human populations, although the evidence linking selenium with reduced cancer risk is somewhat inconsistent and data on the influence of zinc are sparse (1). Herein we report an assessment of the relationships between prediagnostic serum levels of selenium and zinc and subsequent risk of stomach and lung cancers. The data were derived from a 13-year follow-up of adults who were part of a fixed population of 20,000 atomic bomb survivors in Hiroshima and Nagasaki, Japan, that yielded some of the largest numbers of these cancers yet available for this type of analysis.

Subjects and Methods

The cohort of atomic bomb survivors followed by RERF² and the methods for the collection and storage of sera have been described in detail elsewhere (2). In brief, a cohort of approximately 20,000 atomic bomb survivors in Hiroshima and Nagasaki have been offered biennial clinical examinations since the 1960s. All cohort members examined during the 1970–1972 cycle, when blood samples were first stored, were cross-classified by city, sex, age at examination (in 4-yr categories), and year and month of blood collection. All cases of primary stomach or lung cancer during 1973–1983 were identified from routine RERF follow-up procedures, which include review of records from the Hiroshima and Nagasaki tumor and tissue registries and RERF mortality files. Because of the national vital statistics registration system in Japan, ascertainment of mortality was thought to be nearly 100% complete. From each cross-classified cell with at least one stomach and/or lung cancer case, the same number of controls as the number of cases (most cells had but one case) in the cell was randomly selected. Ineligible as controls were those who had died before the date of diagnosis of the earliest case in the cell. When controls were not available in a cell, they were selected from neighboring cells of the same sex and city.

Information on radiation dose received from the atomic bombs was available for the large majority of cohort members. Smoking status was obtained for most on the basis of surveys conducted in the late 1960s.

Serum samples, which had been kept frozen between –60 and –70°C except for a 4-day thaw in 1982, were retrieved, and those with volumes of at least 1.0 ml were selected for analysis. To determine the concentrations of selenium and zinc, NAA was performed (3). The assay procedure for NAA was developed to measure selenium and zinc simultaneously. To 0.2-ml serum samples, cesium was added as an internal standard. Suprasil-2 (Sin'etsu Sekiei Co., Ltd.) silica tubes of the same lot, which were cut and sealed under low temperature vacuum conditions with a hydrogen gas burner to eliminate contamination, were used to produce freeze-dried samples. Each freeze-dried serum sample, sealed in a silica tube, was then exposed for 256 h in reactor JRR-2 of the Japan Atomic Energy Research Institute (Tokai, Ibaraki, Japan) with a flux of thermal neutrons of about 10^{13} neutrons/cm²/s. The samples were measured for radioactivity with a γ -ray spectrometer for 3000–4000 s after being cooled for 3 weeks to eliminate interfering activities and placed in 46% hydrogen fluoride for 4 min to remove surface radioactivity. Repeat measurements ($n = 14$) showed the between-assay coefficients of variation for

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² The abbreviations used are: RERF, Radiation Effects Research Foundation; NAA, neutron activation analysis; OR, odds ratio; SOD, superoxide dismutase.

Table 1 Characteristics of stomach and lung cancer cases and controls

	Stomach cancer		Lung cancer	
	Cases	Controls	Cases	Controls
Number of subjects	202	226	77	120
Mean age ^a	60	59	56	56
Percent male	56	56	56	56
Percent Hiroshima resident	73	74	67	66
Percent smoker ^b	61	58	75	67
Male	90	93	98	84
Female	21	12	40	10

^a Age at blood collection in 1970–1972.

^b Percentage who ever smoked before blood collection.

selenium and zinc to be 6.7% or less. In a comparison of standard samples measured by atomic absorption analysis (for zinc) and fluorometry (for selenium), mean values from NAA and these methods did not differ more than 3.0% (4).

ORs were calculated as measures of the association between stomach and lung cancer risks and serum selenium and zinc levels. Estimates of the ORs and corresponding significance tests were obtained by conditional logistic regression analysis for matched case-control data (5). Consecutive integers for levels of ordered categories were used in tests for trends. The models included terms for atomic bomb radiation exposure (as a continuous variable) and cigarette smoking (categorized as nonsmoker, former smoker, or smoker). Adjusted mean differences between serum trace-element concentrations for cases and controls were calculated by linear regression analysis. Because of the skewed distribution of serum concentrations of zinc, values were normalized (log 10 transformed) in tests for statistical significance of differences between means for cases and controls, whereas selenium concentrations were used without transformation.

Results

The numbers and several characteristics of the cancer subjects and controls whose serum was assayed are summarized in Table 1. Excluded from the cases were six stomach and two lung cancer cases with abnormally high (>3000 mg/ml) zinc levels, which were thought to be due to hemolysis since zinc levels are known to be about 10-fold higher in RBC than in serum (6). The mean ages ranged from 56 to 60 years, with males outnumbering females. More than 67% were Hiroshima residents. The prevalence of smoking, predominantly a habit of men, before blood collection was slightly higher for stomach cancer and markedly higher for lung cancer in the cases than in the controls.

As shown in Table 2, in controls, mean selenium concentrations showed a decline with age, were higher in males than in females and higher in Nagasaki than in Hiroshima, and were lower in bloods collected between July and September than between January and March. No overall significant differences in mean selenium were found among controls by total radiation dose or smoking status. However, among males, mean levels of selenium were significantly lower in exsmokers (−17.4%; $P = 0.01$) and in current smokers (−11.7%; $P = 0.04$) than in nonsmokers. The patterns for zinc tended to be similar, with mean zinc levels among male controls lower in exsmokers (−13.0%) and current smokers (−9.4%) than in nonsmokers, although these differences did not attain statistical significance.

Case-control differences in mean selenium and zinc concentrations in the sera collected between 1970 and 1972 are shown in Table 3. The differences were adjusted for the matching factors (age, sex, city, and season of blood collection), as well as radiation dose and cigarette smoking. The mean levels of selenium and zinc were slightly lower in stomach and lung cancer cases than in their matched controls, with differences ranging from 0.1 to 5%, but there were no significant case-control differences in average serum concentrations for either selenium or zinc. As shown in the table, adjustment for smoking did not materially alter the results. We also examined case-control differences in serum selenium and zinc within categories of sex, age, city of residence, smoking status, and time between cancer diagnosis and blood collection. The lower levels for selenium in the lung cancer cases than controls were more pronounced among males (−6.2%; $P = 0.09$) than among females (−2.9%), particularly nonsmokers, but the number of subjects in this latter category was small. There was inconsistent and nonlinear variation in the case-control differences by number of years since blood collection. The largest differences (−24%) in selenium occurred for lung cancers diagnosed within 3 years of blood collection but levels were lower in lung cancer cases diagnosed 3–6 years (−8.4%), 6–9 years (−2.7%), and 9+ years (−17%) after the sera were obtained. For stomach cancer, selenium levels were reduced only among those diagnosed within 6 years of blood collection, while no temporal trends were noted in zinc levels.

Finally, Table 4 shows ORs of stomach and lung cancer according to quartile level of selenium and zinc. There was little evidence of increased risks of stomach cancer associated with low selenium or zinc but risks of lung cancer were highest in the lowest quartiles for both selenium (OR = 1.8) and zinc (OR = 1.3). The trends for lung cancer, however, were not monotone, since the lowest risks were in the mid quartiles, and not significant.

Discussion

The present results suggest that serum selenium and zinc are not strongly inversely related to risk of either lung or stomach cancer in this population whose serum selenium and zinc levels are relatively high. Smoking-adjusted mean pre-diagnostic levels of both elements were only slightly lower in the cancer cases than in the controls. Risks of lung cancer were highest among those with the lowest levels of selenium and zinc but the excesses were not significant; dose-response trends were not smooth and tended to be curvilinear.

Inhibitory effects of selenium on the carcinogenic process have been demonstrated in animal experiments (1, 7–9). An association between selenium status and cancer has also been suggested by ecological studies inversely correlating cancer mortality rates, including lung cancer, with selenium levels in crops (10). Wide variations in selenium content in individual foods have hindered evaluation of dietary selenium as a protective factor, but several studies in the United States and Europe have examined serum levels of selenium in relation to cancer risk. Serum selenium was inversely related to total cancer (all types combined) in some investigations (11–16) but not in others (17–21), with the strongest and most consistent associations from Scandinavian countries (particularly Finland, where forage levels of selenium used to be quite low). Only a few

Table 2 Mean serum selenium and zinc levels (in ng/ml) in controls according to age, sex, city of residence, and season of blood collection

	Mean (\pm SE) of serum selenium and zinc levels					P for difference
	30–39	40–49	50–59	60–69	70+	
Age (yr)						
Selenium	127.0 (5.8) ^{a)}	114.7 (2.8)	117.8 (2.3)	114.3 (1.9) ^{b)}	111.5 (2.3)	a) > b); P < 0.05
Zinc	934.5 (55.6)	826.7 (26.7) ^{b)}	893.9 (21.9) ^{a)}	900.7 (18.7)	847.6 (22.3)	a) > b); P < 0.05
Sex		Male		Female		
Selenium		119.1 (2.0)		112.2 (2.3)		P = 0.02
Zinc		905.3 (18.6)		858.2 (20.7)		P = 0.09
City of residence		Nagasaki		Hiroshima		
Selenium		129.0 (2.6)		110.1 (1.8)		P < 0.001
Zinc		993.6 (23.8)		834.7 (16.0)		P < 0.001
Season of blood collection	(Jan–Mar)	(Apr–Jun)	(Jul–Sep)	(Oct–Dec)		
Selenium	119.9 (3.0) ^{a)}	116.5 (3.3)	111.5 (3.0) ^{b)}	116.3 (3.0)		a) > b); P < 0.05
Zinc	948.4 (27.0) ^{a)}	885.9 (29.7)	870.8 (27.0) ^{c)}	870.8 (27.0) ^{b)}		a) > b); P < 0.05 and a) > c); P < 0.01

Table 3 Mean serum selenium and zinc concentrations in stomach and lung cancer cases

	Stomach cancer			Lung cancer		
	Mean (ng/ml)	Adjustment of smoking status ^{a)}	Difference from control (%) ^{b)}	Mean (ng/ml)	Adjustment of smoking status ^{a)}	Difference from control (%) ^{b)}
Selenium	117.4	Yes	-1.3 (P = 0.52)	113.0	Yes	-5.0 (P = 0.09)
		No	-1.1 (P = 0.59)		No	-4.4 (P = 0.16)
Zinc	888.3	Yes	-3.3 (P = 0.19)	899.0	Yes	-0.1 (P = 0.89)
		No	-2.6 (P = 0.30)		No	-0.8 (P = 0.86)

^{a)} Smoking status was classified into nonsmoking, exsmoking and current smoking.

^{b)} Differences adjusted for age, sex, city, season of blood collection, and radiation dose.

of these investigations have examined the relationship of serum selenium to the risk of specific cancers. In Finland, among 189 lung and 58 stomach cancers, Knekt *et al.* (16) found lung and stomach cancer risks 3–11-fold higher for men in the lowest quintiles of serum selenium than for men in the highest quintiles. Among women, the strongest association between selenium and cancer risk (a 4-fold difference) was for stomach cancer. Low selenium in this population was defined as a serum concentration <49 ng/ml and high as a concentration \geq 78 ng/ml. In the United States, where population levels of serum selenium typically exceeded 100 ng/ml, as in Japan, prediagnostic levels were mildly decreased in small series of lung cancer patients (11, 21); in a larger series (99 cases), Menkes *et al.* (18) found no evidence that the risk of lung cancer increased as selenium serum levels decreased (rather there was a modest positive correlation). Also, in a study of Japanese Americans in Hawaii (19), the first report on a Japanese population, no association of serum selenium concentrations with lung or stomach cancer was found, although in Japan serum selenium concentrations were significantly lower among families of lung cancer patients than among age-matched controls (22). We are not aware of other studies that had sufficient numbers of lung or stomach cancers to allow evaluation of the influence of serum selenium on risks. In a 3-year prospective follow-up in the Netherlands, rates of lung cancer were twice as high among those with low

than those with high quintile levels of toenail selenium, and there was a suggestive inverse association between risk of stomach cancer and toenail selenium among men (23, 24).

The data from the present study are consistent with the impression that low serum selenium may be associated with increased cancer risk of lung cancer, but once selenium exceeds an adequate level (about 100 ng/ml in our study) no further reduction in the risk of this cancer is attained with increasing serum selenium concentration. It is noteworthy that glutathione peroxidase activity, which may protect against oxidative stress, rises with increasing blood selenium level but also tends to plateau at higher (around 100 ng/ml or slightly less) selenium concentrations (25). In our data the association between selenium and lung cancer, although not significant in either sex, was slightly stronger for males than for females, now a consistent observation across multiple studies. Some investigations have detected interactive or synergistic effects (13, 17), with the influence of low selenium enhanced when accompanied by low vitamin E, but tocopherol in our stored sera was found to have been degraded too much for precise analysis.

With respect to zinc, epidemiological findings have been quite limited (1). Case-control studies (26–28) have shown lower serum levels of zinc in patients with lung and other cancers than in controls, although pathophysiological effects of cancer on zinc serum status could not be differentiated and cancer mortality rates in parts of the United

Table 4 ORs for stomach and lung cancer according to quartile level of serum selenium and zinc

Concentration quartile	Stomach cancer			Lung cancer		
	OR	95% CI ^a	Number of cases/controls	OR	95% CI	Number of cases/controls
Selenium						
1 (low) ^b	1.0	0.5–1.9	(64/56)	1.8	0.7–5.0	(30/27)
2	0.6	0.3–1.1	(34/56)	0.6	0.2–1.9	(12/31)
3	0.8	0.4–1.4	(48/56)	1.0	0.4–2.5	(20/30)
4 (high)	1.0 ^c		(55/54)	1.0 ^c		(15/30)
Zinc						
1 (low) ^b	1.2	0.6–2.3	(54/55)	1.3	0.4–4.3	(24/29)
2	1.4	0.8–2.7	(64/56)	0.8	0.3–2.5	(21/29)
3	0.9	0.5–1.8	(37/57)	0.4	0.1–1.3	(10/30)
4 (high)	1.0 ^c		(46/54)	1.0 ^c		(22/30)

^a CI, confidence interval.

^b Cutoff points for the quartiles were 99, 113, and 128 ng/ml for selenium and 704, 849, and 989 ng/ml for zinc on the basis of controls for the stomach cancer cases. Means for the four quartiles were 86, 106, 120, and 151 ng/ml for selenium and 600, 774, 914, and 1217 ng/ml for zinc. Cutoffs and means based on controls for the lung cancer cases were essentially the same for selenium and slightly higher for zinc.

^c Reference category. ORs are adjusted for age, sex, city, radiation dose, and smoking.

States were inversely correlated with blood zinc levels (29). In one preliminary examination of prediagnostic serum zinc, lower levels were found among 64 persons who subsequently developed cancer (all types combined) but the association was not significant (30).

As for biological mechanisms by which serum zinc might be inversely associated with cancer risk, there may be a role of SOD, especially copper-zinc-SOD (31). Zinc is known to be a structural element of copper-zinc-SOD which is intracellularly distributed in RBC and may act as a scavenger of active oxygen. Although it is not expected that serum zinc concentration is linearly related to copper-zinc-SOD activity, a reduction of the enzyme activity among zinc-deficient people is possible. Additional experimental studies suggest possible interactive effects between zinc and retinol in inhibiting cancer (32, 33).

However, the present analysis found no strong association between either lung cancer or stomach cancer and serum zinc. We found no evidence of effect modification by serum retinol level (data not shown). Variation of serum zinc has been reported according to time of blood sampling in the day, since serum zinc is known to have a circadian rhythm (34), but adjustment for time of blood sampling during the day, the records for which were available in Hiroshima (data not shown), did not alter the findings.

Since the incidence of stomach and lung cancer among atomic bomb survivors is related to radiation exposure (35), it is possible that glutathione peroxidase and SOD activities might be affected by free radicals induced by radiation exposure, which may in turn increase selenium and zinc requirements, respectively. However, no significant effects of radiation dose on 1970–1972 serum levels of selenium and zinc among controls were observed, although this possibility could not be denied for the period just after radiation exposure.

Thus, these findings from one of the largest series of lung and stomach cancers with prediagnostic serological data add to limited data available from other reports showing slightly increased risks of lung cancer associated with low blood levels of selenium, but suggest little association with either lung cancer or stomach cancer across normal selenium and zinc ranges in this Japanese population.

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BLOOD CANCER DISCOVERY

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