

Baseline Serum β -carotene Concentration and Mortality among Long-Term Asbestos-Exposed Insulators

Dana Hashim^{1,2,3}, Denise Gaughan^{1,2,3}, Paolo Boffetta^{1,2}, and Roberto G. Lucchini^{1,3,4}

Abstract

Background: Although interventional trials demonstrated that moderate-dose β -carotene supplementation increases lung cancer mortality in smokers and asbestos-exposed workers, differences in serum concentrations in absence of supplementation have not been studied in asbestos-exposed workers.

Methods: A mortality analysis was performed to assess the relationship of nonsupplemented serum β -carotene to all-cause and cancer mortalities using 1981 to 1983 serum β -carotene concentration measurements from 2,646 U.S. white male insulators (mean age, 57.7 years). Multivariable-adjusted Cox proportional hazard models that included terms for age, duration of asbestos exposure, smoking, season, and region were fitted to estimate mortality HRs and 95% confidence intervals (CI) according to serum β -carotene concentrations.

Results: Median follow-up was 12.8 years and 984 (33.8%) subjects died during the follow-up period, including 415

deaths from overall cancer and 219 deaths from lung cancer. The overall mortality HR for a serum β -carotene increase of 10 $\mu\text{g/dL}$ was 0.97 (95% CI, 0.96–0.99). Compared with the lowest quartile, HRs were 0.90 (95% CI, 0.76–1.07) for the second (38–65 $\mu\text{g/dL}$), 0.80 (95% CI, 0.67–0.96) for the third (66–104 $\mu\text{g/dL}$), and 0.63 (95% CI, 0.51–0.77) for the highest serum β -carotene quartile (≥ 105 $\mu\text{g/dL}$). There was no association between serum β -carotene and overall cancer mortality (HR, 1.00; 95% CI, 0.97–1.02) or lung cancer mortality (HR, 0.99; 95% CI, 0.96–1.02).

Conclusions: Higher nonsupplemented serum β -carotene concentrations were negatively associated with all-cause mortality among asbestos-exposed individuals.

Impact: Serum β -carotene can be a marker of one or more determinants of reduced mortality in asbestos-exposed workers. *Cancer Epidemiol Biomarkers Prev*; 24(3); 555–60. ©2014 AACR.

Introduction

Despite growing insight into β -carotene's influence on cellular physiology, its systemic effects on mortality are not fully elucidated. β -carotene exists naturally in green leafy vegetables and other orange-colored plant sources. It is the only provitamin A carotenoid that is metabolized by humans into vitamin A and, unmetabolized, also serves as a fat-soluble antioxidant, neutralizing free radicals that have potential to disrupt genetic integrity (1).

Although *in vitro* (2), *in vivo* (3, 4), and epidemiologic studies (5) have reported an inverse association between β -carotene intake and malignancy, three major interventional trials have had varied results. The β -Carotene and Retinol Efficacy Trial (CARET; ref. 6) in the United States and the Alpha-Tocopherol β -Carotene Lung Cancer Prevention Study (ATBC; ref. 7) in Finland have found lung cancer mortality to be significantly higher (46% and 8%, respectively) in groups receiving β -carotene than in

placebo-receiving groups. Both trials found the risk of adverse events to be higher in smokers, and CARET also found adverse associations with all-cause mortality. Another U.S. trial, the Physicians Health Study, studied a population of male physicians that included a smaller proportion of smokers and found no significant association between β -carotene supplementation and all-cause mortality (8). All three trials administered dosages of β -carotene 20 mg per day or higher, which raised serum β -carotene concentrations 10 times the normal range (9).

These interventional trials have reported a procarcinogenic effect of β -carotene at doses exceeding physiologic serum concentrations. However, the average daily nonsupplemented dose of β -carotene has remained at only a few milligrams since the 1980s (10, 11). When the three major interventional trials occurred, only about 35% of U.S. adults took vitamin supplements (12). This contrasts 2003 to 2006 NHANES data, which had reported an increase of vitamin supplementation to 54% in the same population. Of those, nearly half admitted to consuming >1 vitamin supplement (13). Therefore, understanding the influences of isolated nutrients on mortality is important for public health.

A legacy of the North American Insulator Cohort (NAIC; refs. 14–17) has been the establishment of a database, which recorded clinical examinations of asbestos-exposed insulators. Asbestos exposure has been shown to be associated with increased mortality as well as increased risk of lung cancer, mesothelioma, and cancers of other organs (14–17). The aim of this study was to investigate the association between serum β -carotene concentration and mortality in an asbestos-exposed population using archived data collected from a subset of the NAIC.

¹Icahn School of Medicine at Mount Sinai, New York, New York. ²Icahn School of Medicine at Mount Sinai, Institution of Translation Epidemiology, New York, New York. ³Icahn School of Medicine at Mount Sinai, Division of Occupational and Environmental Medicine, New York, New York. ⁴Division of Occupational Medicine, University of Brescia, Brescia, Italy.

Corresponding Author: Dana Hashim, Icahn School of Medicine at Mount Sinai, Department of Preventive Medicine, 17 E. 102nd Street, New York, NY 10029. Phone: 212-824-7002; Fax: 212-996-0407; E-mail: dana.hashim@mssm.edu

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Subjects and Methods

Study cohort

On January 1, 1967, all U.S. and Canadian white male members of the International Association of Heat and Frost Insulators and Asbestos Workers union ($n = 17,800$) were enrolled into a cohort that was observed through December 31, 1976. Details on the composition of this cohort, including classification by age, years since first exposure, and mortality, have been published (14, 17, 18).

Clinical examinations

In 1981, 5,355 members of this cohort, who were still alive in 1976 and had worked in asbestos insulation for at least 30 years, were invited for a comprehensive medical examination; 2,077 (38.8%) appeared and 446 who had met the same criteria before the November 15, 1981, examination start date were added (15). In addition, 384 white male asbestos insulation workers who had heard of the study and arrived were also examined, although some had not met the 30-year asbestos exposure criterion (14). Clinical examinations took place in 19 U.S. cities from November 1981 to November 1983. They encompassed chest radiography, pulmonary function, standard laboratory tests (19), and special serological studies (20) that included measurement of serum β -carotene concentration. Workers who had taken β -carotene supplements were excluded from study participation.

Of the 2,907 participants, the number of workers with complete data that included serum β -carotene concentrations and number of years worked in insulation was 2,646 (91.0%). Encompassing 6.5% of the missing numbers were 17 individuals in Anchorage, Alaska, none of whom had serum β -carotene concentrations drawn. Participants had been exposed to mixed-asbestos fiber types, predominantly chrysotile (21), and asbestos exposure was measured as the duration of insulation work. Although documentation of the original measurements was not available, serum β -carotene concentrations were presumed to be recorded in $\mu\text{g}/\text{dL}$ due to the range of the measurements (0 to 527; mean 75.5 ± 52.4 SD). Smoking status was defined as non (smokers of <1 cigarette per day average lifetime or <10 cigarettes per day for <6 months, or smoked only cigars and pipes without inhaling), former (smokers who exceeded nonsmoker levels and quit for at least 2 years), and current smokers (22–24). The years smoked and the number of cigarettes per day for current and past smokers were also tabulated. By time of clinical examination onset, 58.8% of the 886 smoking insulators had quit smoking (25).

Records from the union and state health departments provided birthdates, death dates, and death certificate diagnoses for each insulator (17). Occupational history, medical symptoms, and smoking history were obtained from participants by mail questionnaire (14). Causes of death as listed on death certificates (DC) were categorized into diseases by an experienced nosologist. Best-evidence (BE) diagnoses were then ascertained after requesting further clinical data, histological materials, and/or x-ray films from respective hospitals after death certificates had been completed (14, 17). In 10% of cases, when no clinical or histopathologic material was available, DC was recorded as BE (26). BE diagnoses were used to identify lung cancer deaths.

Statistical analysis

Median and interquartile ranges on demographic and occupational data were calculated on cohort at baseline. Packs per year of smoking were calculated from cigarettes per day and number of

years smoked. Seasons were defined as follows: autumn (September 16–December 15), summer (June 16–September 15), spring (March 16–June 15), and winter (December 16–March 15). U.S. geographical regions were defined by west, northeast, southwest, southeast, and midwest.

Mortality follow-up was conducted between the date of examination for each insulator and January 7, 1996. The number of person-years contributed by each insulator was calculated as the time interval between the date of the initial examination and the date of death or, for surviving study participants, January 7, 1996. Death rates were calculated as incidence densities (i.e., number of deaths divided by person-years) and there was no loss to follow-up.

Cumulative hazard curves for total cancer within serum β -carotene concentrations and quartiles were obtained from Kaplan–Meier estimates of mortality probabilities. Differences between the curves were tested using Mantel–Haenszel log-rank tests. Multivariable-adjusted Cox proportional hazard models that included terms for age, duration of asbestos exposure, and tobacco smoking were fitted to estimate mortality HRs and 95% confidence intervals (CI) according to serum β -carotene concentration. Models that included the addition of examination season and geographical region adjustment were also analyzed. A test of the proportionality assumption over time was conducted by including an interaction term between serum β -carotene concentration and logarithm of the variables. The presence of effect modification by baseline age, smoking status, insulation work duration, season, and U.S. geographical region was tested using the likelihood ratio test. Analyses were conducted using SAS statistical software, version 9.3.

The associations of baseline serum β -carotene were also assessed on the three most reported specific types of cancer determined by BE diagnosis at death. Serum β -carotene was analyzed continuously and also stratified by quartiles. Trends were determined using Cochrane–Armitage and linear trend tests where appropriate. HRs were computed for each of the quartiles by dividing the rates in the upper quartiles of intake by the rates in the lowest category of intake. For all statistical tests of significance, the 5% level was used as the cutoff point and CIs were set to 95%.

Results

Principal analysis

Basic demographic and vital status data of the 2,646 insulator workers overall and across high-risk subsets are represented in Table 1. Median follow-up of 12.8 years and the age-adjusted arithmetic mean of serum β -carotene was 75.5 ± 52.4 SD $\mu\text{g}/\text{dL}$.

Table 1. Demographic data and vital status of asbestos insulator cohort ($n = 2,646$), 1981 to 1996

	All insulators ($n = 2,646$)	
	Median, IQR	n (%)
Age (y)	57.7, 52.8–62.3	
Serum β -carotene ($\mu\text{g}/\text{dL}$)	75.5, 37–104	
Age at start working (y)	21.2, 18.0–25.0	2,638 (99.7%)
Age at death (y)	66.8, 61.0–72.6	984 (33.8%)
Total exposure time (y)	33.0, 29.0–36.0	
Past smokers	–	1,226 (46.3%)
Current smokers	–	886 (33.5%)
Nonsmokers	–	534 (20.2%)
All causes of death		984 (33.8%)
Lung cancer deaths		219 (8.28%)

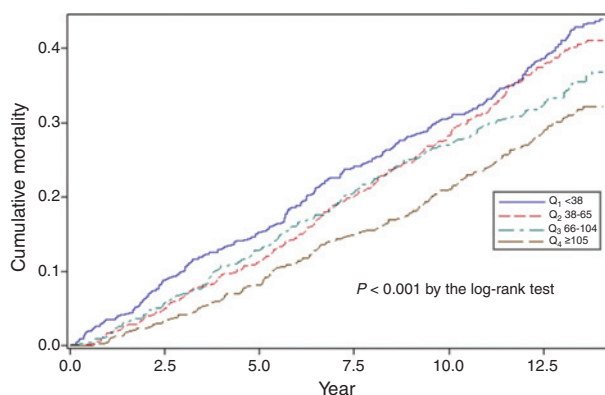


Figure 1.

Cumulative hazard of all-cause mortality over time by baseline serum β -carotene concentration quartile ($\mu\text{g}/\text{dL}$). Q₁: <38; Q₂: 38–65; Q₃: 66–104; Q₄: ≥ 105 .

A mortality test for heterogeneity revealed a significant association with prior serum β -carotene concentration (log-rank $P < 0.001$). The effect was also observed when serum β -carotene was divided into <37 (Q₁), 38 to 65 (Q₂), 66 to 104 (Q₃), and ≥ 105 (Q₄) quartiles (in $\mu\text{g}/\text{dL}$) by percentile distribution (Fig. 1).

Multivariable Cox proportional hazard analysis adjusted for age at clinical examination, years of asbestos-exposed insulation work, and smoking status revealed serum β -carotene was negatively associated with mortality for every 1 $\mu\text{g}/\text{dL}$ (HR, 0.998; 95% CI, 0.997–0.999) and for each 10 $\mu\text{g}/\text{dL}$ increase in serum β -carotene (HR, 0.981; 95% CI, 0.969–0.994). This association was also significant when models included season and U.S. geographical region (HR, 0.997; 95% CI, 0.996–0.999) for every 1 $\mu\text{g}/\text{dL}$ and HR of 0.97 (95% CI, 0.96–0.99) for every 10 $\mu\text{g}/\text{dL}$ increase in serum β -carotene. The Linear trend test demonstrated a dose-response effect for both models ($P < 0.001$).

Serum β -carotene was also analyzed in quartile ranges, using the lowest quartile as a reference group. Baseline parameters by serum β -carotene quartile for all insulation workers are shown in Table 2. Associations with all-cause mortality by serum β -carotene concentration quartile are shown in Table 3. Those with serum β -carotene concentrations in Q₄ had a 29% lower risk of all-cause mortality when adjusted for duration of asbestos exposure, smoking status, and age compared with those in Q₁. When season and geographical region were included in the models as well, there was a 37% lower risk of all-cause mortality for those in Q₄.

No effect modification of mortality HRs for all-cause outcomes was found in models examining serum β -carotene concentration by baseline age ($\chi^2 = 0.13$, $P = 0.72$), duration of asbestos insulation work ($\chi^2 = 0.59$, $P = 0.44$), smoking status ($\chi^2 = 1.40$, $P = 0.50$ across all smoking categories), or for each smoking status by current smokers ($\chi^2 = 1.37$, $P = 0.24$) and past smokers ($\chi^2 = 0.80$, $P = 0.37$). Nonsmokers also had no effect modification of mortality HRs ($\chi^2 = 0.41$, $P = 0.52$) when they were compared with past and current smokers. Effect modifications of mortality HRs examining serum β -carotene concentration in models that included season and geographic region were also not significant.

Serum β -carotene and mortality, adjusted for smoking pack-years

Among the 886 (33.5%) current smokers at baseline examination, there was a significant association of all-cause mortality with each 10 $\mu\text{g}/\text{dL}$ serum β -carotene concentration increase when adjusted for pack-years (HR, 0.967; 95% CI, 0.943–0.992). For past smokers, the effect of each 10 $\mu\text{g}/\text{dL}$ serum β -carotene concentration increase was not significant when adjusted for pack-years and years since quitting smoking (HR, 0.985; 95% CI, 0.968–1.003).

Serum β -carotene and mortality from specific cancers

Among the 984 total BE deaths identified, 415 (42.2%) were due to cancer. Of these all-site cancer deaths, 123 (29.6%) occurred in those in the Q₁ serum β -carotene concentration group and 71 (17.1%) occurred in Q₄. There were no statistically significant associations of serum β -carotene with cancer mortality as well as by specific cancer after adjustment for age, insulation work duration, and smoking status (Table 4). When region and season were also included in the models, HRs per 10 $\mu\text{g}/\text{dL}$ serum β -carotene concentration increase were 1.00 (95% CI, 0.97–1.02) for all-cause mortality, 0.98 (95% CI, 0.94–1.01) for lung cancer mortality, 1.00 (95% CI, 0.95–1.05) for mesothelioma mortality, and 0.72 (95% CI, 0.43–1.21) for colon cancer mortality. Because of the small number of observations for some cancers, we could not obtain stable HRs by serum β -carotene quartile.

Discussion

Our analysis showed an inverse association between nonsupplemented concentrations of serum β -carotene and all-cause mortality in asbestos-exposed workers. The highest magnitudes of association with mortality were demonstrated in participants with serum β -carotene concentrations within the carotene

Table 2. Baseline parameters by serum β -carotene quartile ($\mu\text{g}/\text{dL}$)

	Q ₁ (<38)	Q ₂ (38–65)	Q ₃ (66–104)	Q ₄ (≥ 105)	χ^2 or Z	P
N	673	666	651	654	0.58	0.57
n all deaths	288	265	227	202	4.79	<0.001
Mean age at exam (y)	57.1	57.8	57.6	58.2	135.6	<0.001
Mean pack-years ^a	14.5	14.6	14.7	11.3	2.15	0.14
Mean years since quit smoking ^b	15.8	15.6	9.54	13.2	12.3	<0.001
Mean insulation years worked	31.8	32.3	31.7	31.1	37.5	<0.001
Smoking status					76.4	<0.001
Non	116	120	121	177	71.3	<0.001
Past	282	261	331	352	22.3	<0.001
Current	275	285	200	126	71.3	<0.001

^aCurrent and former smokers at baseline.

^bFormer smokers at baseline.

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Table 3. Associations for all-cause mortality by serum β -carotene concentration quartile in asbestos-exposed insulators

β -carotene concentration quartile ($\mu\text{g/dL}$)	All-cause mortality events, <i>n</i>	HRs (95% CIs)	
		Model 1 ^a	Model 2 ^b
Q ₁ (<38)	288	1 (ref.)	1 (ref.)
Q ₂ (38–65)	265	0.87 (0.74–1.03)	0.90 (0.76–1.07)
Q ₃ (66–104)	227	0.83 (0.70–0.98)	0.80 (0.67–0.96)
Q ₄ (\geq 105)	202	0.71 (0.59–0.85)	0.63 (0.51–0.77)

^aModel 1: adjusted for age, duration of insulation work, and smoking status.^bModel 2: adjusted for variables in Model 1 in addition to season and region.

reference range of 50 to 300 $\mu\text{g/dL}$ (27). However, a dose-response effect was demonstrated across the entire range of serum β -carotene concentrations.

NAIC data had been collected during an era when vitamin supplementation was relatively uncommon in comparison with recent times (12, 13), offering an opportunity to examine below reference range serum β -carotene concentration effects in a population exposed to respiratory carcinogens, such as asbestos and smoking. To our knowledge, the only prospective trial which examined the effect of supplementation in a population with low dietary β -carotene was conducted in Linxian, China (28). In a study population that included individuals with an overall nutrient and calorie deficiency, results demonstrated a total mortality reduction in the β -carotene-selenium- α -tocopherol supplemented group. Furthermore, the total mortality reduction in this study arm had been attributed to a large proportion of reduced risk of stomach and esophageal cancers, although the effect of β -carotene had not been studied independently of the other two supplements.

It cannot be ruled out that the apparent favorable association of high baseline serum β -carotene concentrations with mortality was due to confounding lifestyle factors. Individuals consuming a β -carotene-rich diet may also be likely to consume a fruit-and-vegetable-rich diet (29). We did not have data on other nutrient serum concentrations, dietary habits, or other lifestyle-related parameters such as body mass index or cholesterol. However, because β -carotene-containing foods naturally also contain many other health-beneficial vitamins (30), disentangling the effects of one micronutrient from another is not possible when studying nonsupplemented serum β -carotene concentration. The increasing trend in serum β -carotene concentrations by region and season toward warm harvesting environments is a testament to β -carotene consumption trends.

High-dose interventional trials that detected a negative association with mortality, such as the ATBC trial, used the more bioavailable and less antioxidant-acting all-*trans* form of β -carotene, whereas dietary sources of β -carotene naturally contain both *trans* and *cis* isomers (31, 32). The explanation for the difference between our results and the results of these high-dose interventional trials may be that β -carotene's inverse effect on all-cause mortality was due to synergistic and vetting interaction with other micronutrients present in nonprocessed food sources.

A strength of the study was the utilization of the serum β -carotene concentrations as an assessment of β -carotene nutritional status. From a biologic perspective, serum β -carotene concentrations are a more relevant method than dietary dosage for assessing β -carotene's physiologic influence (10) while also being a useful biomarkers of fruit and vegetable intake (33). Serum β -carotene concentrations have also been demonstrated to be inversely related to tobacco smoking and alcohol intake (34–36), and thus serves as an indicator of nutritional status and overall healthy lifestyle. Whether the phenomenon of lower serum β -carotene concentrations in smokers and alcohol intake is due to low dietary intake of β -carotene or enhanced degradation of circulating antioxidants due to oxidative stress remains unclear (37).

A limitation of the study was that serum β -carotene concentration measurements were taken at one time only with no repeat measurements to assess possible dietary changes over the 12.8 years median follow-up. Because other studies from the same time period have shown that repeated serum β -carotene measurements over the course of many years were reproducible (38) and reliable (39), an assumption was made that serum β -carotene concentrations had remained consistent throughout the follow-up time.

Since the durational measurement of asbestos exposure had been already used as a means of assessing asbestos exposure in previous studies (14–19, 22) and because asbestos-exposed workers were insulators, an assumption was made that all had the same intensity of exposures at varying time intervals. However, because 75% of the NAIC had \geq 29 years of asbestos-exposure levels, with the lowest duration being 3 years, the dataset may not have been conducive for an accurate assessment of an effect modification between high and low levels of asbestos exposure and serum β -carotene. Moreover, β -carotene's mechanism of action has been shown to vary depending on low oxygen pressure and chronic oxidative stress (3, 4, 40). An investigation of whether asbestos exposure had activated the favorable effect of β -carotene on survival or whether this particular population incidentally had low background β -carotene concentrations in which the effect on mortality would be apparent is needed.

In conclusion, higher baseline concentrations of serum β -carotene concentrations were associated with decreased mortality in asbestos-exposed insulators. However, no associations were found for risk of all cancers combined, lung cancer, mesothelioma, or

Table 4. Associations between serum β -carotene concentration and mortality by commonest cancer sites^a

Cancer site	Per 10 $\mu\text{g/dL}$ unit increase HR (95% CI)	Q ₁ (<38) HR (95% CI)	Q ₂ (38–65) HR (95% CI)	Q ₃ (66–104) HR (95% CI)	Q ₄ (\geq 105) HR (95% CI)	χ^2	<i>P</i>
All cancers (<i>n</i> = 415)	1.00 (0.97–1.02)	1 (ref.)	0.98 (0.75–1.26)	1.18 (0.90–1.53)	1.03 (0.78–1.39)	2.17	0.54
Lung (<i>n</i> = 219)	0.99 (0.99–1.02)	–	0.87 (0.60–1.24)	0.96 (0.66–1.24)	0.88 (0.59–1.31)	0.81	0.85
Mesothelioma (<i>n</i> = 104)	1.02 (0.96–1.05)	–	1.38 (0.76–2.51)	0.96 (0.56–1.64)	1.23 (0.65–2.30)	2.13	0.55
Colon (<i>n</i> = 17)	0.69 (0.64–1.00)	–	1.86 (0.44–7.80)	0.72 (0.10–5.14)	0.08 (0.01–1.01)	5.35	0.15

^aAdjusted for baseline age, years worked in insulation, and smoking status.

colon cancer. Serum β -carotene can be a marker of one or more determinants of reduced all-cause mortality in this population.

Disclosure of Potential Conflicts of Interest

P. Boffetta has provided expert testimony for Edison Spa. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: D. Hashim, D. Gaughan, P. Boffetta

Development of methodology: D. Hashim, D. Gaughan

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Hashim, D. Gaughan, P. Boffetta

Writing, review, and/or revision of the manuscript: D. Hashim, D. Gaughan, P. Boffetta, R.G. Lucchini

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Hashim
Study supervision: P. Boffetta, R.G. Lucchini

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Dana Hashim, Denise Gaughan, Paolo Boffetta, et al.

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