Dietary vitamin A and prevalence of bronchial metaplasia in asbestos-exposed workers[1–3]

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ABSTRACT The purpose of this investigation was to examine the association between dietary intake of vitamin A in the form of retinol and provitamin A carotenoids and the prevalence of bronchial squamous metaplasia in a sample of asbestos workers from an industrial clinic. Bronchial biopsies were obtained from 49 asbestos workers. Pulmonary function testing was done and in-person interviews were conducted to estimate dietary intake of retinol and provitamin A carotenoids, tobacco exposure, and asbestos exposure. Results indicated that workers with metaplasia reported consuming a significantly lower intake of total vitamin A [2000 retinol equivalents (RE)/d] than did subjects without metaplasia (2710 RE/d, $P = 0.02$). Logistic regression analyses showed that higher intakes of retinol [odds ratio (OR): 0.31; 95% CI: 0.04, 2.44], provitamin A carotenoids (OR: 0.31; 95% CI: 0.03, 2.84), and total vitamin A (OR: 0.29; 95% CI: 0.03, 2.49) were associated with a nonsignificant reduction in the OR for metaplasia (highest quartile compared with lowest quartile, adjusted ORs). Current smoking (OR: 5.25; 95% CI: 0.50, 55.1) and former smoking (OR: 2.95; 95% CI: 0.31, 28.1) were associated with a nonsignificant increase in the OR for bronchial metaplasia compared with never smoking. Greater airway obstruction [decreased forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC)] was associated with an increased OR for metaplasia (OR: 2.86; 95% CI: 1.09, 7.69). These results suggest that a higher (ie, above the median) intake of vitamin A from foods decreases the risk of bronchial metaplasia in workers occupationally exposed to asbestos. *Am J Clin Nutr* 1998;68:630–5.

KEY WORDS Bronchial metaplasia, vitamin A, retinol, carotenoids, asbestos, adults, humans

INTRODUCTION

A large body of literature shows that smokers who consume greater quantities of dietary vitamin A from foods, particularly in the form of provitamin A carotenoids, have a lower risk for lung cancer (1). This observation led to several randomized, placebo-controlled trials designed to test the hypothesis that pharmacologic-level supplements of β-carotene—the most commonly ingested provitamin A carotenoid—retinol, or both reduce lung cancer risk. As reviewed elsewhere (2), the 2 largest lung cancer prevention trials involving β-carotene, with and without retinol, were completed with unexpected results. The first involved 29 133 men aged 50–69 y from Finland (3) who were heavy cigarette smokers at entry (average: 1 pack/d for 36 y). The study had a 2×2 factorial design with participants randomly assigned to receive supplemental β-carotene (20 mg/d), α-tocopherol (50 mg/d), both β-carotene and α-tocopherol, or placebo for 5–8 y. Unexpectedly, participants receiving the high doses of β-carotene (alone or in combination with α-tocopherol) had a lung cancer incidence 18% higher [relative risk (RR): 1.18; 95% CI: 1.03, 1.36] than that of participants receiving placebo.

The finding of an increased incidence of lung cancer in β-carotene–supplemented individuals has now apparently been replicated in another major trial, the Carotene and Retinol Efficacy Trial (CARET). CARET is a multicenter lung cancer prevention trial of high-dose, supplemental β-carotene (30 mg/d) plus retinol (25 000 IU/d) compared with placebo in smokers and asbestos workers (4). The intervention component of CARET was terminated nearly 2 y early because the interim results indicated that the supplemented group was developing more lung cancer, not less, a finding that was consistent with the results of the Finnish trial. Overall, lung cancer incidence increased by 28% in the supplemented subjects (RR: 1.28; 95% CI: 1.04, 1.57). For the 4050 asbestos workers in CARET, the risk for lung cancer with high-dose vitamin supplementation was even more marked (RR: 1.42; 95% CI: 1.07, 1.87).

CARET data suggest that high doses of β-carotene plus retinol from supplements may increase the incidence of lung cancer in asbestos workers and smokers. Similar results emerged recently in a lung cancer prevention trial using a premalignant endpoint. The Tyler (TX) Chemoprevention Trial randomly assigned 755 asbestos workers to receive high-dose β-carotene

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(50 mg/d) and retinol (25 000 IU every other day) or placebo to see whether the nutrient combination could reduce the prevalence of atypical cells in sputum (5). After a mean intervention period of 58 mo, there was no significant difference in the 2 groups in the prevalence of sputum atypia, although the supplemented group had more sputum atypia than the nonsupplemented group [odds ratio (OR): 1.24; 95% CI: 0.78, 1.96]. In contrast, a trial of smokers who were not occupationally exposed to asbestos showed that 14 wk of supplemental β-carotene (20 mg/d) significantly reduced micronuclei counts in sputum (6). Taken together, the results of these studies suggest that high-dose supplements of retinol and β-carotene do not help and may harm asbestos workers.

What effects, if any, do dietary vitamin A intakes have on the risk of lung cancer in asbestos workers? We were unable to locate any studies of dietary vitamin A and risk of lung cancer in asbestos workers, but identified one hospital-based case-control study of dietary habits and risk of malignant mesothelioma, an asbestos-associated cancer, in asbestos workers. Muscat and Huncharek (7) reported that subjects who consumed carrots (≥1/mo) had a risk of developing mesothelioma that was 80% lower than that in subjects who never consumed carrots.

Bronchial squamous metaplasia is considered to be part of the continuum from normal columnar epithelium to lung cancer. Because bronchial metaplasia is reversible, it has been used as an intermediate endpoint for several lung cancer prevention trials, some of which have included various retinoids (8–11).

The purpose of this investigation was to examine the association between dietary intake of vitamin A and the prevalence of bronchial metaplasia in a group of asbestos workers. We hypothesized that contrary to the results of intervention trials and similar to the results of observational studies of smokers, a higher intake of dietary vitamin A would be associated with a lower risk of lung cancer as measured by a lower prevalence of metaplasia.

SUBJECTS AND METHODS

Subjects

Subjects with a history of occupational exposure to asbestos were recruited from an occupational medicine clinic. This same clinic also served as one of the recruitment sites for asbestos-exposed workers for CARET, recruiting >1000 subjects. Clinic records were screened and workers were recruited from a group of individuals with abnormal chest radiographs indicating significant prior asbestos exposure. Volunteers were admitted to the Yale General Clinical Research Center whereupon informed written consent was obtained. During the first day, subjects underwent a physical examination and general medical history to ascertain that no condition existed that would preclude safe inclusion in the protocol. The occupational history was reviewed with each subject by a certified industrial hygienist. A smoking history, including age at the time the first cigarette was smoked, average pack-years (average number of packs of cigarettes smoked per day × the number of years smoked), and years since the last cigarette was smoked, was also obtained. Full pulmonary function tests were performed, including spirometry, static lung volume determination, and diffusing capacity for carbon monoxide by using a clinical reference laboratory (DSII Plus system; Collins, Braintree, MA). All studies were approved by the Yale Human Investigations Committee.

Collection and processing of biopsies

On the following morning, bronchoscopy was performed as described previously (12, 13). Briefly, the nose and upper airways were anesthetized with a topical anesthetic, and a fiberoptic bronchoscope was passed via the mouth. The airways were inspected carefully for abnormal lesions. If none were found, attempts were made to obtain 3–6 mucosal biopsy specimens at random from subsegmental branch points in the right lower lobe. Attempts were terminated when the operator determined that 3 visible pieces had been recovered.

Biopsies were fixed for 6 h in glutaraldehyde-paraformaldehyde fixative and embedded in paraffin, and 4-μm sections were cut and stained with hematoxylin and eosin. All biopsies were scored in blinded fashion by a pathologist who was unaware of the identity of study subjects. The biopsy material was scored with respect to the worst lesion of squamous metaplasia present, similar to the procedure used in the studies of Auerbach et al (14–16). Biopsies were judged to be adequate if mucosa were seen on cut tissue sections.

Dietary assessments

Dietary information was collected by a registered dietitian using an interviewer-administered food-frequency questionnaire. Subjects were asked to estimate their usual frequency of consumption in the past year of 86 food items that represent the major contributors to the intake of vitamin A in the United States. The questionnaire had 5 food categories (dairy products; fruit; vegetables; meat, fish, and poultry; and miscellaneous food items) and is available on request from the authors. Food models were used as appropriate to aid in the estimation of portion sizes.

To calculate nutrient intake, the reported frequency of consumption of each food item was converted to an estimated monthly frequency of consumption of a standard portion size of the food item. Nutrient intake was calculated as the weighted sum of the monthly frequencies of consumption of the food items that contained the nutrient of interest, for which the weights correspond to the nutrient content of the standard portion of the food items (17, 18). The nutrient database used is based on the US Department of Agriculture food-composition tables (17), and differentiates vitamin A ingested as retinol from vitamin A ingested in the form of provitamin A carotenoids. Data are presented as the daily dietary intake of total retinol equivalents (REs), REs from preformed vitamin A, and REs from provitamin A carotenoids.

Asbestos exposure assessment

At the time these workers were being exposed to asbestos, environmental sampling for asbestos was uncommon. Therefore, average and cumulative doses were estimated by using the relative scale proposed by Nicholson et al (19). Asbestos insulators and workers from highly dusty manufacturing jobs were given a score of 1 insulator-year for each year of employment. Other tradesmen and those in less dusty industries were given estimated values ranging from 0.1 to 0.5 insulator-year equivalents. Cumulative dose was estimated by summing the values over the entire span worked before institution of asbestos substitutes or major controls, which had generally occurred several years before the study began.

Lung function assessment

Measured values for total lung capacity (by helium dilution), forced vital capacity (FVC), forced expiratory volume in 1 s

(FEV_1), and diffusing capacity of the lung for carbon monoxide (D_LCO) were compared with the predicted values based on age and height. The equation of Gaensler and Wright (20) was used for predicted D_LCO, whereas the equation of Morris et al (21) was used for FVC. Predicted total lung capacity was derived by adding the residual volume using the equation of Goldman and Becklake (22). Values were scored as the percentage predicted for each of these major indexes.

Data analysis and exclusions

Subjects who were lacking information regarding bronchial metaplasia or dietary intake of vitamin A were excluded from further analysis. First, descriptive statistics were used to describe the study population. Then, subjects were stratified by metaplasia status, and demographic and risk-factor variables were compared between the 2 groups by using Student's *t* test or chi-square analysis. Because the dietary data were found to be skewed, they were log transformed before these analyses. Univariate and multivariate logistic regression were subsequently conducted to evaluate relations between dietary intake and metaplasia status, with other variables of interest controlled for. Analyses were done with SAS (Statistical Analysis System, Cary, NC) and EGRET (Statistics and Epidemiology Research Corporation, Seattle) statistical packages. ORs were calculated as an estimate of RR, and 95% CIs were also calculated. The ORs obtained from modeling continuous variables were calculated based on a difference corresponding to the interquartile range. For example, the ORs for pack-years reflect a comparison of the 75th percentile of exposure in the population with the 25th percentile of exposure.

RESULTS

Reports on a portion (50 asbestos workers) of the present study population were published previously (23–26), although data regarding dietary exposures were not included. Six additional subjects were recruited to this group, for a total of 56 subjects. Four subjects who were unable to be bronchoscoped were excluded, as were 3 individuals who failed to complete the dietary portion of the interview. Thus, 49 subjects were included in this analysis (88%). Demographic characteristics of the population are shown in **Table 1**. All asbestos workers were men, and their mean age was 60 y. Most of these men (n = 27) were exsmokers, having quit largely because of aggressive smoking cessation interventions in asbestos workers in general. Eight subjects had never smoked and 14 were current smokers.

Fifteen of the 49 subjects were found to have bronchial squamous metaplasia; demographic characteristics of the subjects by metaplasia status are summarized in **Table 2**. Subjects with metaplasia were found to have a significantly lower intake of total vitamin A than subjects without metaplasia (P = 0.02). Subjects with metaplasia were also found to have a significantly lower FEV_1/FVC (P = 0.03) than subjects without metaplasia. None of the other factors differed significantly, although subjects with metaplasia tended to have a lower intake of retinol (P = 0.06), tended to be current smokers (P = 0.3, chi-square test), and tended to have greater tobacco exposure than subjects without metaplasia (46 compared with 33 pack-years, P = 0.2).

It is possible that the association between dietary vitamin A intake and bronchial metaplasia was due to confounding; therefore, multivariate logistic regression analyses were done to evaluate this possibility. The results of logistic regression analyses of several potential confounders are shown in **Table 3**. FEV_1/FVC was significantly associated with metaplasia status. A decrease in this ratio, indicating a greater degree of airway obstruction, was associated with a 2.86-fold increase in the OR for metaplasia; the OR was based on a 13.3% decrease, corresponding to the interquartile range. A lower FEV_1/FVC remained a significant predictor of metaplasia status even after pack-years as well as other covariates were controlled for (adjusted OR: 2.79; 95% CI: 1.03, 7.58).

Although none of the other potential confounding variables were associated significantly with metaplasia status in the logistic regression analysis, the point estimates for several were notable. For example, being a former smoker was associated with a 3-fold increase (95% CI: 0.31, 28.1) and being a current smoker was associated with a 5-fold increase (95% CI: 0.50, 55.1) in the OR for metaplasia compared with never smokers. Estimated asbestos exposure was also associated with a 46% increase in the OR for metaplasia (95% CI: 0.68, 3.15) for a dif-

TABLE 1
Demographic characteristics of participants in the bronchial metaplasia study[1]

Variable	Mean	Median	Range
Age (y)	60	62	37–74
Smoking history (pack-years)	37	32	0–124
Cumulative asbestos dose (insulator-years)	14	13	3–34
Total lung capacity (% of predicted)	78	77	48–122
FVC (% of predicted)	75	72	46–105
FEV_1/FVC	75	76	55–92
Diffusing capacity for carbon monoxide (% of predicted)	79	79	27–142
Retinol (RE/d)	1190	890	110–4130
Vitamin A from carotenes (RE/d)	1300	1060	160–8060
Total vitamin A intake (RE/d)	2490	2070	440–12100

[1] n = 49. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RE, retinol equivalents.

TABLE 2
Demographic characteristics of participants in the bronchial metaplasia study, by metaplasia status[1]

Variable	No metaplasia (n = 34)	Metaplasia (n = 15)
Age (y)	61 ± 2	60 ± 2
Smoking history (pack-years)	33 ± 5	46 ± 10
Cumulative asbestos dose (insulator-years)	13 ± 1	15 ± 2
Total lung capacity (% of predicted)	78 ± 3	78 ± 5
Forced vital capacity (% of predicted)	74 ± 2	76 ± 5
FEV_1/FVC	77 ± 2	70 ± 2[2]
Diffusing capacity for carbon monoxide (% of predicted)	82 ± 3	72 ± 7
Retinol (RE/d)	1330 ± 170	890 ± 170
Vitamin A from carotenes (RE/d)	1380 ± 230	1110 ± 240
Total vitamin A intake (RE/d)	2710 ± 330	2000 ± 380[3]

[1] $\bar{x}$ ± SEM. Log-transformed data used for significance testing of dietary variables; untransformed data shown for ease of interpretation. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RE, retinol equivalents.

[2,3] Significantly different from no metaplasia (Student's *t* test): [2] P = 0.03, [3] P = 0.02.

TABLE 3
Risk factors for bronchial metaplasia in asbestos workers, from logistic regression analyses[1]

Variable	Odds ratio	95% CI	Interquartile range
Smoking status			
Never smokers	1.00	—	—
Former smokers	2.95	0.31, 28.1	—
Current smokers	5.25	0.50, 55.1	—
Age (y)	0.90	0.30, 2.70	8
Smoking history (pack-years)	1.86	0.70, 4.98	52.5
Years quit	1.01	0.52, 1.94	10
Years exposed to asbestos	1.11	0.43, 2.88	15
Cumulative asbestos dose (insulator-years)	1.46	0.68, 3.15	10.1
Age first exposed	0.84	0.44, 1.64	7
Total lung capacity (% of predicted)	1.02	0.46, 2.22	19.1
Forced vital capacity (% of predicted)	1.23	0.51, 2.99	21.2
FEV_1/FVC	2.86[2]	1.09, 7.69	13.3
Diffusing capacity for carbon monoxide (% of predicted)	0.52	0.21, 1.25	27.3

[1] All variables were modeled as continuous variables, except smoking status. Unadjusted odds ratios are shown, based on a differential corresponding to the interquartile range of exposure in the full population (75th percentile minus 25th percentile). Interquartile ranges for each of the continuous variables are shown. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.
[2] $P = 0.03$.

TABLE 4
Vitamin A intake (quartiles I–IV) and risk of bronchial metaplasia in asbestos workers[1]

Variable	Crude odds ratio	Adjusted odds ratio[2]
Retinol		
I (<650 RE/d)	1.00	1.00
II (≥650 and <890 RE/d)	0.35 (0.06, 1.90)	0.30 (0.04, 2.43)
III (≥890 and <1490 RE/d)	0.67 (0.13, 3.45)	0.85 (0.12, 5.84)
IV (≥1490 RE/d)	0.23 (0.04, 1.51)	0.31 (0.04, 2.44)
P for trend	0.20	0.37
Provitamin A carotenoids		
I (<780 RE/d)	1.00	1.00
II (≥780 and <1060 RE/d)	0.58 (0.11, 2.95)	0.55 (0.08, 3.84)
III (≥1060 and <1430 RE/d)	0.23 (0.03, 1.51)	0.10 (0.01, 1.33)
IV (≥1430 RE/d)	0.39 (0.07, 2.13)	0.31 (0.03, 2.84)
P for trend	0.17	0.14
Total Vitamin A		
I (<1670 RE/d)	1.00	1.00
II (≥1670 and <2070 RE/d)	0.83 (0.17, 4.06)	1.17 (0.15, 9.16)
III (≥2070 and <2680 RE/d)	0.23 (0.04, 1.51)	0.44 (0.05, 3.90)
IV (≥2680 RE/d)	0.23 (0.04, 1.51)	0.29 (0.03, 2.49)
P for trend	0.06	0.21

[1] 95% CIs in parentheses. RE, retinol equivalents; FEV, forced expiratory volume in 1 s; FVC, forced vital capacity.
[2] Adjusted for smoking status, age, pack-years, asbestos dose, and FEV_1/FVC.

ferential exposure of 10.1 insulator-years. Subjects at older ages tended to have a slightly lower OR for metaplasia, as did subjects with a higher percentage D_LCO and those first exposed to asbestos at older ages.

Relations between vitamin A intake and bronchial metaplasia, with and without adjustment for potential confounders, are shown in **Table 4**. Higher intake of total vitamin A, retinol, and provitamin A carotenoids reduced the OR for metaplasia by 71%, 69%, and 69%, respectively (highest quartile compared with lowest quartile, adjusted OR), although the tests for linear trend were not significant. Adjustment for these potentially confounding variables had little effect on the associations between dietary intake of vitamin A and metaplasia.

DISCUSSION

Food-frequency questionnaires are generally used to provide estimates of usual nutrient intake over some period in the past. Although food-frequency questionnaires may not accurately measure actual nutrient intake, they are thought to be useful for classifying relative intakes within a population (27). The purpose of this study was to determine whether or not asbestos workers with a higher reported intake of vitamin A had a lower prevalence of bronchial metaplasia than workers with lower reported intakes of vitamin A. As shown in the results, men with bronchial metaplasia had, on average, significantly lower intakes of vitamin A.

The recommended dietary allowance (RDA) for vitamin A is 1000 RE/d for men (28). Only 4 individuals in this population reported vitamin A intakes at or below the RDA. Thus, this population appeared to have more than an adequate intake of vitamin A. However, because this questionnaire was designed to capture all major dietary sources of retinol and provitamin A carotenoids, overestimation of vitamin A intake was likely. Overestimation of vitamin A intake with food-frequency questionnaires has been documented elsewhere (29). Potential overestimation did not affect the internal validity of this study, but may limit comparisons of dietary intakes with other populations.

The finding that men with metaplasia consumed significantly less vitamin A than those without metaplasia may have been due to confounding by other risk factors, such as tobacco use; therefore, multiple logistic regression analyses were done to assess the independent effects of vitamin A intake on the OR for metaplasia, after other variables (including smoking status, pack-years, cumulative asbestos exposure, age, and FEV_1/FVC) were controlled for. The point estimates indicate that higher dietary intakes of vitamin A, retinol, and provitamin A carotenoids were associated with a reduction in the OR for bronchial metaplasia, although the tests for linear trend showed no significance. These results are reassuring for asbestos-exposed workers who have been consuming more vitamin A–rich foods to reduce their risk of lung cancer. However, because the questionnaire was designed to capture all major sources of vitamin A in the diet but not all major sources of energy, adjustment of these results by energy intake was not possible.

Another potentially important finding of this study was that a greater degree of airway obstruction, as measured by a decreased FEV_1/FVC, was associated with a marked, significant increase in the OR for bronchial metaplasia. This was true even after tobacco exposure and other covariates were controlled for. This finding is consistent with those in the literature, suggesting that a greater degree of airway obstruction (decreased FEV_1/FVC) is associated with an increased risk of lung cancer (30–32), even after adjustment for smoking.

The participants recruited into this cross-sectional study had characteristics similar to those of the asbestos workers recruited into CARET. Although high-dose supplements of vitamin A

increased the risk of lung cancer in CARET participants, our results suggest that asbestos workers should be encouraged to continue to consume diets containing foods rich in vitamin A because higher consumption of vitamin A from foods was associated with a reduced OR for metaplasia. However, high-dose supplements of vitamin A and β-carotene should clearly be discouraged in this population.

What might account for the disparity in results seen in observational studies of smokers and asbestos workers, in which dietary vitamin A appears to be protective against lung cancer, compared with results seen in intervention trials, in which supplements appear to increase risk? One critical factor may be the dose. It is conceivable that high doses of β-carotene, alone or in combination with retinol, may produce unexpected and potentially harmful side effects, whereas dietary intakes may be beneficial. Alternatively, dietary sources of β-carotene, primarily fruit and vegetables, contain a diverse array of chemical substances, including several vitamins, minerals, fibers, and phytochemicals (33). More detailed speculations of the mechanisms involved in the apparent enhancement of lung carcinogenesis by supplements but not by dietary sources of β-carotene and retinol can be found in the literature (34, 35).

The major limitation of this study was the small sample size, a consequence of the invasiveness—and thus the nonnegligible risk to the participants—and the expense involved in obtaining bronchial biopsies from disease-free individuals. However, although the number of subjects was small, a strength of this study was the depth of information collected for each participant, providing a rather unique opportunity to link the biopsy information and the detailed assessments of pulmonary function with detailed exposure information on the key factors of interest, namely smoking, asbestos exposure, and dietary vitamin A intake. The associations between smoking status and asbestos exposure and metaplasia status were as expected. The fact that older subjects were somewhat less likely to have metaplasia than were younger subjects is consistent with findings from studies of lung cancer risk in asbestos workers, in whom risk increases up to a certain age and then declines thereafter (19). Thus, despite the small sample size of this study, the primary exposure variable (dietary vitamin A in those with metaplasia compared with that in those without metaplasia) was significant and the point estimates for others were in the direction anticipated.

In conclusion, this study found that asbestos workers with bronchial squamous metaplasia consumed significantly less total vitamin A than did asbestos workers without metaplasia. The prevalence of metaplasia was greatest for current smokers, followed by former smokers, and then never smokers. The OR for metaplasia increased with increasing occupational exposure to asbestos and with a greater degree of airway obstruction. The apparent protective effect of dietary vitamin A did not appear to be due to confounding. Thus, these data provide no evidence to suggest that higher dietary intakes of vitamin A are harmful to asbestos workers—rather, these data show evidence of protective effects of vitamin A in foods against lung cancer risk in this population.

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