



The Influence of Serum Vitamin A on Lung Cancer Risk

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Abstract: The objective of this study was to evaluate the association of serum level vitamin A with the incidence of lung cancer (LCa). An analysis, using a prospective study design, was conducted among a cohort of 3,086 men and women, ages 25 to 74 years, from the First National Health and Nutrition Examination Survey-Epidemiologic Follow-up Study. Using Cox proportional hazards regression analysis, inverse associations between serum vitamin A and LCa risk were observed in all models. These findings suggest that increased serum vitamin A may protect against LCa. Additional studies, addressing the limitations encountered in this analysis, are needed to validate the protective role vitamin A may play against LCa risk.

Keywords: Follow-up Studies, Incidence, Lung Neoplasms, Nutrition Surveys, Prospective Studies, Vitamin A

1. Introduction

Lung cancer (LCa) is one of the most significant malignant neoplastic diseases burdening the adult population in the United States (U.S.). Of the top ten cancers among men and women in the U.S., LCa remains in second place, with an age-adjusted invasive cancer incidence rate of 59.4 cases per 100,000 population [1]. In this same population, LCa remains the leading cause of cancer death, with an age-adjusted mortality rate of 43.4 deaths per 100,000 population [1].

Smoking has been established as the most significant risk factor in the onset of LCa [2, 3]. For this reason, smoking status is used as one of the main factors in guiding ongoing LCa screening and prevention strategies [4, 5]. However, observed racial [6, 7] and gender [8, 9] differences in LCa risk have not been entirely explained by individual smoking status. Furthermore, it is estimated that 10% of LCa deaths occur among non-smoking men, and among 20% of non-smoking women in the U.S. [10]. As such, these reports suggest that other factors may play a role in the development of LCa.

Over the past several decades, a significant amount of attention has been given to nutrition's significance in the etiology of cancer, with a specific focus on the role of vitamin intake [11, 12, 13, 14]. One of these being vitamin A [12, 13, 14]. Likewise, a series of experimental and observational studies have followed, examining the vitamin A-LCa relationship [15, 16]. Its role as a promoter of, or

protector against, LCa, however, remains unclear as some analyses suggest that vitamin A provides a protective effect against LCa [17, 18, 19, 20, 21], while others suggest no association [22, 23, 24], or even increase the risk of lung carcinogenesis [25, 26]. To gain a better understanding of the function vitamin A might play in the promotion of, or protection against, LCa, this study was conducted to examine the association of serum level vitamin A with the incidence of LCa in a cohort of adult men and women from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study [27].

2. Methods

2.1. The NHANES I Epidemiologic Follow-up Study

The NHANES I Epidemiologic Follow-up Study (NHEFS) is a national longitudinal study that was conducted to assess the associations of nutritional, behavioral, and clinical factors with subsequent morbidity, mortality, and risk factor changes [27]. The initial cohort for the NHEFS was comprised of 14,407 adults, aged 25-74 years, who completed a medical examination during the NHANES I. Follow-up for the NHEFS cohort consisted of four follow-up periods, with the first follow-up being conducted 1982-1984, and the fourth (and final) follow-up period in 1992 [27]. A total of 96% of the initial NHEFS cohort were successfully traced through the final follow-up wave in 1992. All NHEFS data files are de-identified and are available in the public domain [28, 29].

2.2. Study Participants

From the original NHEFS cohort, a total of 10,518 study participants, who reported not to have any known tumor or malignancy, were initially selected for the present analysis. Participants for the present analysis were further excluded if information regarding serum vitamin A, selected covariates, or incident LCa were not provided or missing. After applying this additional criteria, further exclusions due to missing serum vitamin A level ($n=3,444$), smoking status ($n=3,468$), and family history of LCa ($n=520$) were made, leaving a total of 3,086 study participants for the present analysis.

2.3. Serum Vitamin A

Specific procedures used in the NHANES I specimen allocation and analysis of serum vitamin A levels are explained in detail elsewhere [30]. Briefly, baseline serum vitamin A levels were obtained as a part of the NHANES I and were provided in micrograms per deciliter ($\mu\text{g}/\text{dl}$), for each study participant [30]. For the present analysis, subjects were categorized into quartiles of serum vitamin A, based on their respective quartile distribution of the analytic cohort.

2.4. Incident Lung Cancer

For this analysis, incident cases of LCa were determined initially by the use of follow-up interviews conducted during the four NHEFS follow-up periods [28]. Additional cases of LCa were identified using death certificates [28]. A total of 95 LCa cases were identified in the analytical cohort.

2.5. Covariates

Covariates that included age, gender, race, smoking status, physical activity and family history of LCa were evaluated as potential confounders of the vitamin A-LCa relationship. Age, gender, race, smoking status and physical activity were all ascertained at baseline during the NHANES I [28]. Smoking status was determined by asking subjects, "Have you smoked at least 100 cigarettes during your entire life?" [28]. Physical activity level was ascertained by asking subjects, "In your usual day, aside from recreation, how active are you?" [28] Study participant physical activity level was subsequently categorized as categorized as "very active," "moderately active" or "quite inactive" [28]. Finally, family history of LCa was derived from first-degree relatives during the 1982-1984 follow-up period.

2.6. Statistical Analysis

To estimate the relative risk (RR) of LCa with each quartile of serum vitamin A level, Cox proportional hazards regression analysis was used. An initial model was constructed, adjusting for age, gender and race. This was followed by the construction of a second model, additionally adjusted for smoking status, physical activity level, and family history of LCa. Resulting RR's and 95% confidence intervals (CI) were reported for each Cox regression model. A test for trend across quartiles of serum vitamin A level was conducted and subsequent P-values were reported. The

assumption of proportionality was tested by visually inspecting the log (-log) survival curves.

To estimate study participant follow-up time, the date from the baseline NHANES I exam, to the date of LCa incidence, or the date last known to be alive was used and provided in years. The mean follow-up time of study participants in the present analysis was 16.6 years. Statistical Package for Social Sciences (SPSS) Version 23.0® was used for all statistical analyses.

3. Results

Table 1 provides a summary of the analytic cohort characteristics by LCa status. Of the 3,086 study participants, approximately 3% ($n=95$) were diagnosed with LCa. A higher mean age was observed among LCa cases (59.0 years [standard deviation (SD) =10.0 years]), compared to study participants without LCa. By gender, approximately 65% ($n=62$) of incident LCa cases were seen among men. In an examination of race/ethnicity, just over 89% ($n=85$) of LCa cases were found among whites, compared to an estimated 10% ($n=9$) and 1% ($n=1$) among blacks and Aleut/Eskimo/Native Americans respectively (Table 1). With regard to smoking status, approximately 83% ($n=79$) of LCa cases reported smoking 100 or more cigarettes in their lifetime. An estimated 93% ($n=88$) of LCa cases reported engaging in at least a moderate level of physical activity, while only an estimated 8% reported having a family history of LCa. Finally, a lower mean serum vitamin A level was observed among LCa cases (57.0 $\mu\text{g}/\text{dl}$ [SD=15.3 $\mu\text{g}/\text{dl}$]), compared to study participants without LCa.

Table 1. Cohort Baseline Characteristics by Lung Cancer Status ($n=3,086$).

	Yes LCa (n=95)	No LCa (n=2,991)
Characteristic		
Age, mean years (SD)	59.0 (10.0)	50.0 (14.0)
Gender, %		
Male	65.3%	47.7%
Female	34.7%	52.3%
Race/Ethnicity, %		
White	89.5%	84.8%
Black	9.5%	14.2%
AS/PI	0.0%	0.7%
AL/ES/AI	1.1%	0.2%
Other	0.0%	0.3%
Smoking Status, %		
Yes	83.2%	56.0%
No	16.8%	44.0%
Physical Activity, %		
Quite Inactive	6.3%	9.8%
Moderately Active	46.3%	44.1%
Very Active	47.4%	46.1%
Family History of LCa, %		
Yes	8.4%	5.7%
No	91.6%	94.3%
Serum Vitamin A ($\mu\text{g}/\text{dl}$), mean (SD)	57.0 (15.3)	60.0 (18.1)

Abbreviations: AI, American Indian; AL, Aleut; AS, Asian; ES, Eskimo; LCa lung cancer; PI, Pacific Islander; SD, standard deviation; $\mu\text{g}/\text{dl}$, micrograms per deciliter

Table 2 presents the Cox regression analyses models

created for the analytical cohort. In the first model, initially adjusted for age, gender, and race, a 51% (RR 0.49, 95% CI= 0.27-0.86) and a 53% (RR 0.47, 95% CI= 0.27-0.85) decreased risk in LCa was observed among subjects with a vitamin A level between 58.2-69.2 µg/dl and \geq 69.3 µg/dl respectively, relative to subjects in the lowest serum vitamin A level quartile of \leq 47.2 µg/dl. In the second model, which was additionally adjusted for smoking status, physical activity level and family history of LCa, subjects with a vitamin A level between 58.2-69.2 µg/dl and \geq 69.3 µg/dl maintained a 49% (RR 0.51, 95% CI= 0.29-0.90) and 52% (RR 0.48, 95% CI=0.27-0.86) decreased risk of LCa respectively, relative to subjects in the lowest serum vitamin A level quartile. Significant trends across serum vitamin A quartiles were observed in each regression model (Table 2).

Table 2. Relative Risk of Lung Cancer Incidence by Serum Vitamin A Quartile.

	RR*	95% CI	RR**	95% CI
Vitamin A (µg/dl)				
\leq 47.2	1.00 (Reference)		1.00 (Reference)	
47.3-58.1	0.76	0.44-1.30	0.76	0.44-1.30
58.2-69.2	0.49	0.27-0.86	0.51	0.29-0.90
\geq 69.3	0.47	0.26-0.85	0.48	0.27-0.86
P for trend	006		007	

Abbreviations: CI, confidence interval; RR, relative risk; µg/dl, micrograms per deciliter

*Adjusted for age, gender, and race/ethnicity

**Adjusted for age, gender, race/ethnicity, physical activity, smoking and family history of LCa

4. Discussion

Several studies suggest vitamin A provides some protective effect against LCa. Goodman et al. found that study participants of the Beta-Carotene and Retinol Efficacy Trial, with a serum retinol level between 660-777 ng/ml, had a 41% decrease risk of LCa, relative to subjects with a serum retinol level of \leq 577 ng/ml [17]. In a case-control analysis, Epplein et al. observed a 70% decreased odds in LCa among subjects in the highest tertile of serum beta-carotene, compared to those in the lowest beta-carotene tertile [18]. Using a prospective design, Michaud et al. observed a 32% decreased risk of LCa among 46,924 men from the Health Professionals Follow-Up Study and 77,283 women from the Nurses' Health Study [19]. Holick et al. found that men in the highest quintiles of serum beta-carotene ($>$ 290 µg/liter) and a serum retinol ($>$ 684 µg/liter) had a 19% and 27% decreased risk of LCa respectively, compared to men in the lowest quintiles of serum beta-carotene ($<$ 99 µg/liter) and serum retinol ($<$ 484 µg/liter) [20]. Yet in another analysis, Yong et al. observed a 67% decrease risk of LCa among a cohort of men and women smokers, with a reported carotenoid intake of $>$ 2,289.87 international units (IU), compared to those reporting an intake of $<$ 206.20 IU [21]. Consistent with these findings, a statistically significant inverse association was also observed between serum vitamin A level and LCa incidence

in the present analysis.

The protective effect observed in previous investigations [17, 18, 19, 20, 21], as well as the present analysis, may have resulted from serum vitamin A acting as a regulator of host immune-surveillance and response. Leukocyte presence in the tumor microenvironment is one of the key hallmarks of cancer-related inflammation [31, 32, 33, 34, 35, 36]. Although not well understood, it is thought that the difference between tumor suppression or elimination, and tumor progression or escape, is based on the make-up of this inflammatory response. Specifically, is it posited that the primary mechanism by which tumor suppression or elimination is governed is dependent upon host T-lymphocyte response [33]. This response has been characterized by the up-regulation, or down-regulation, of innate and adaptive leukocytes that include both Natural Killer T-lymphocytes and CD8 cytotoxic T-lymphocytes [36]. Consistent with this process, previous reports suggest that T-lymphocyte proliferation [37, 38], as well as cytotoxicity [39], are in part, regulated by host serum vitamin A levels. Despite this evidence, no studies (to the author's knowledge) have evaluated T-lymphocyte response in relation to vitamin A levels and lung carcinogenesis. Therefore, additional studies are needed to elucidate the potential role T-lymphocyte proliferation, and cytotoxicity may play in the vitamin A-LCa relationship.

In stark contrast to the present study, however, some studies suggest that vitamin A has no association with LCa [22, 23, 24]. In a case-cohort analysis involving 939 LCa cases and a subcohort of 1,525 adult males, aged 55-69 years, from the Netherlands Cohort Study on Diet and Cancer, Voorrips et al. found no association between reported carotenoid and LCa risk [22]. Similarly, Shibata et al. found no association between reported beta-carotene intake and vitamin A supplementation with the risk of LCa in a cohort of 11,580 residents of Leisure World, Laguna Hills, California [23]. Friedman et al. also observed no significant association between serum vitamin A level and LCa in a case-control analysis, consisting of 151 cases and 302 controls [24]. It is possible that the statistically insignificant associations observed in these studies resulted from self-reported information used to estimate vitamin A intake [22, 23], as well as the lack of significant difference in mean serum retinol values between cases (82.17 µg /dl) and controls (82.37 µg /dl) [24].

To a lesser extent, some reports even suggest that the risk of LCa increases, in relation to increasing vitamin A levels [25, 26]. In Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, which involved 29,133 male smokers from Finland, an 18% increase in LCa cases was observed among subjects receiving an intervention of 20 mg/day beta-carotene, compared to the group receiving no intervention [25]. During the Beta-Carotene and Retinol Efficacy Trial (CARET), investigators found that subjects receiving a combined intervention of 30 mg of beta-carotene and 25,000 IU retinyl palmitate had a 28% increased risk of LCa compared to subjects in the placebo group [26].

Collectively, these findings yield a couple of hypotheses. First, high-dose beta-carotene supplementation in active smokers may promote, and even accelerate, lung tumor progression [40, 41, 42, 43, 44]. Second, it is possible that the specific source of vitamin A intake may promote, or protect against, lung cancer. Unlike the negative outcomes observed with vitamin A supplement intake during the ATBC and CARET studies, Holick et al. found that participants with the highest fruit and vegetable consumption quintile had a 27% decreased risk of LCa (RR 0.73, 95% CI=0.62-0.86) [20]. Additionally, an inverse association was observed between baseline serum beta-carotene and LCa risk in all participants of the CARET [26]. A similar protective effect of baseline measures, including baseline beta-carotene dietary intake, was also observed among participants of the ATBC Cancer Prevention Study [25]. These observations, however, were limited to the control group of the ATBC [25]. Despite the significance of these findings, associations between preformed vitamin A, provitamin carotenoids, and resulting LCa risk could not be evaluated in the present analysis, as these specific derivatives of vitamin A were not ascertained during the NHANES I NHEFS. To address these shortfalls, future studies, assessing the vitamin A-LCa relationship, should evaluate differences in LCa risk, based on the specific sources of vitamin A intake.

Significant strengths of this study included its large sample size, prospective design, and use of objective measures of individual vitamin A level. Despite these strengths, results of this study should be interpreted with caution as several limitations were encountered. First, the majority of LCa cases were determined by self-report. Although the predictive value and sensitivity of self-reported LCa diagnosis are relatively robust [45, 46], it is possible that overestimation, or underestimation, of LCa risk, resulted due to self-reporting bias. Second, it could not be determined if study participant serum vitamin A levels varied over time, as only baseline measures of serum vitamin A level were obtained [30]. Finally, it is possible that the protective effect observed between serum vitamin A level and LCa incidence were confounded by one or more other risk factors, not accounted for in this study. Other significant risk factors for LCa such as, exposure to radon [47] and exposure to second-hand smoke [3], were not able to be assessed as potential confounders, as they were not ascertained during the NHANES I NHEFS.

5. Conclusion

The role that vitamin A serves in critical human physiological functions are well known [48]. Its function as a chemopreventive agent against LCa, however, remains unclear. For this reason, this analysis sought to better understand the vitamin A-LCa relationship. In this study, an inverse association between serum vitamin A and LCa risk was observed among a sample of 3,086 men and women from the NHANES I NHEFS. These findings, in conjunction with previous reports, suggest that increased serum vitamin

A may provide some protective effect against LCa. As such, diets high in fruit and vegetable intake should be, and remain, a part of any strategy aimed at reducing LCa risk. Nevertheless, additional studies, addressing the limitations encountered in this analysis, are needed to validate the protective role vitamin A may play against LCa risk.

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