The Impact of Food-Based Composite Dietary Antioxidant Intake and Lung Cancer Risk: Findings from the Singapore Chinese Health Study

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Abstract

Background. The protective effect of a balanced diet on lung cancer risk has been well established in the literature. However, a limited amount of research exists on the role of food-based antioxidant intake on lung cancer risk, especially among an Asian population.

Methods. The Singapore Chinese Health Study (SCHS) is an ongoing prospective cohort study with 61,321 participants aged 47-74 years old at baseline. Using this data, we evaluated the association between the Composite Dietary Antioxidant Index (CDAI) and lung cancer risk. A Cox proportional hazard regression model was used to estimate hazard ratio (HR) and the corresponding 95% confidence interval (CI) for lung cancer risk in relation to CDAI scores, after adjusting for confounders.

Results. In the SCHS cohort, 2,008 participants developed lung cancer after an average of 17.5 years of follow-up. No significant association between CDAI score and lung cancer cases. After stratification histologic subtype, smoking status, alcohol consumption, BMI, and diabetes history, we found a significant association between the fourth quartile range of CDAI scores and increased lung squamous cell carcinoma risk among never smokers (HR=6.17; 95% CI: 1.27-30.0; P_{trend}=0.06). Further analyses into the association between CDAI scores and lung cancer risk by second-hand smoke exposure stratification did not reveal significant results.

Conclusion. Additional work in this area of research needs to be done among the Asian population to clearly define this association. The public health relevance of the issue is evident

given the limited used of the CDAI as a predictor of lung cancer risk. As more conclusive research is conducted, lung cancer prevention recommendations for the general public, specifically on the effect food-based antioxidant intake on lung cancer risk, can be revised.

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1.0 Introduction

Lung cancer has consistently been a leading cause of mortality in the United States (US) and globally. In 2020, there were 2.2 million new lung cancer cases and 1.8 million lung cancer deaths, accounting for 18% of all cancer deaths worldwide.[1] Lung cancer incidence rates are particularly high among both men and women in Eastern Asia, largely due to the persistence of the tobacco epidemic in these countries.[1] In Singapore, lung cancer is the third most common cancer diagnosis in males and females.[2] Lung cancer accounted for 26.4% of cancer deaths for men, and 15.7% for women in Singapore from 2014 to 2018.[2] The rate of lung cancer deaths in the US was 34.8 per 100,000 population, far surpassing mortality rates for any other type of cancer in 2018.[3] Recent studies have shown that lung cancer incidence is rising in women globally, particularly among never smokers. The disparity in lung cancer incidence between men and women suggests genetic and hormonal variations impact lung cancer development as well.[4]

A variety of factors can increase lung cancer risk; however, the most notable risk factor is smoking. Approximately 80% of lung cancer deaths have resulted from smoking or having a history of smoke exposure.[5] Lung cancer among never smokers was found to be responsible for 30-50% of all lung cancers in Southeast and East Asia.[6,7] Environmental and occupational determinants of lung cancer risk are exposure to radon, asbestos, and other cancer-causing agents such as arsenic.[5,8–10] Suspected factors that have been attributed to the increase in lung cancer incidence among Asian women specifically were indoor cooking with coal (a known carcinogen) and the prevalence of infectious diseases such as human papillomavirus (HPV) and tuberculosis (TB); both of which have been associated with lung cancer development.[4] Evidence has also shown that asthma is a risk factor for lung cancer, specifically the small-cell and squamous cell carcinoma

histological subtypes, because it is a prevalent chronic disease and is majorly exacerbated by smoking and secondhand smoke exposure.[11–13] Lung cancer continues to have a substantial impact on Asian men and women, and research must continue to be done in order to establish concrete risk factors and prevention measures for the disease.

Dietary antioxidants act as an important factor in lung cancer prevention. Several studies, both experimental and observational, have evaluated antioxidant intake in relation to lung cancer risk.[11] However, the antioxidant intake and lung cancer association largely depends on the stratification by smoking status, as antioxidants can have different effects when interacting with the materials that make up cigarette and tobacco products.[14] A meta-analysis of 35 relevant studies published through 2012 sought to systematically investigate the effects of dietary flavonoids on the risk of smoking-related cancer in observational studies, assessing these effects separately rather than using a composite score.[15] In relation to lung cancer, the authors found that flavonoids, specifically quercetin and kaempferol, were significantly associated with reduced lung cancer risk.[15] A case-cohort study called the Netherlands Cohort Study on diet and cancer yielded comparable results, and also provided detailed differences in antioxidant intake among smokers versus non-smokers. After adjusting for covariates, the researchers found that lutein, zeaxanthin β-cryptoxanthin, folate, and vitamin C intake rendered statistically significant protective effects on the risk of lung cancer.[16] Additionally, they reported that antioxidant intake was the lowest among those who were current smokers and highest among participants who had never smoked.[16] In a prior analysis of data from the Singapore Chinese Health Study (SCHS) population, similar results regarding the protective effect of high β-cryptoxanthin intake on lung cancer risk was observed.[17] However, in light of these findings it is important to consider how the method of

assessing multiple antioxidants in relation to lung cancer can lead to correlation between the antioxidant variables, which is not ideal.[14]

The lack of a complete analysis of individual and combined assessments of antioxidant intake on lung cancer risk led a group of investigators to develop the Composite Dietary Antioxidant Index (CDAI).[14] To test this nuanced method of assessing antioxidant intake as a whole and its ability to predict lung cancer risk, Wright et al.[14] performed a prospective cohort analysis of a double-blinded randomized control trial, known as the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. The study population for the prospective cohort analysis included 27,111 men who resided in Finland, were between the ages of 50-69 years old, smoked five or more cigarettes a day, and had complete baseline dietary information. Wright et al.[14] developed the CDAI score by ranking an individual's antioxidant intake compared to characteristics of the population using statistical modeling. Previously conducted observational studies have been limited by the range of antioxidants examined and often led to correlations between individual antioxidant assessments.[18,19] Hence, a comprehensive index considers the biologic and statistical interactions that tend to occur between antioxidants and provides an overall impact of antioxidant intake on health outcomes, such as lung cancer. The main groups of antioxidants included in the CDAI were vitamins A, C, and E; manganese, selenium and zinc. In the study by Wright et al.,[14] reduced risk of lung cancer was observed across the quintiles of CDAI compared to the lowest quintile (HR=1.0 [0.87-1.14], 0.91 [0.79-1.05], 0.79 [0.68-0.92], and 0.84 [0.72-0.98], p_{trend}=0.02 for second, third, fourth, and fifth quintiles). Additionally, the investigators revealed that the CDAI predicted lung cancer incidence better than previous methods of assessing antioxidants separately or using a summation of the nutrients after adjustment for energy intake,

age, number of cigarettes smoked per day, number of years of smoking, body mass index, and educational level.

1.1 Gaps in Knowledge

Given the recent negative or insignificant observational and clinical research findings on the effects of supplement intake and lung cancer risk by varying smoking status, we are not evaluating the effect of antioxidant supplements on lung cancer risk. For example, in the previously mentioned ATBC study, a double-blind, randomized, placebo-controlled trial, 20mg/day β-carotene supplementation was found to significantly increase lung cancer risk by 25% among current male smokers.[20] Another randomized placebo-controlled trial called the Women's Health Initiative (WHI) aimed to evaluate the association between vitamin D and calcium supplement intake and lung cancer risk. The results from the WHI study showed a higher risk of lung cancer among smokers with calcium/vitamin D supplementation and a high vitamin A intake.[21] Adversely, the Carotene and Retinol Efficacy Trial (CARET) case-cohort study found a 62% significant reduction in lung cancer risk among current smokers who had a high intake of vitamin A and vitamin D supplements.[22] Data from experimental and observational studies show that a number of antioxidant supplements can increase lung cancer risk, and the effect of food-based antioxidant intake on lung cancer risk has been understudied.

Since it has been shown that using the CDAI instead of separately analyzing each antioxidant was more efficient,[14] it will be used to evaluate its effect on analyzing a reduced risk of lung cancer with stratification by smoking status in our study population. Other studies have acknowledged the utility of the CDAI as a method to estimate risk for specific conditions. Various

disease outcomes have been assessed using CDAI as the exposure variable, such as HPV, atherosclerosis, and cervical cancer.[23–25] Each of these studies modified the CDAI to work for their specific outcome, illustrating the versatility of the CDAI as well. However, data on the CDAI and lung cancer association is limited in Asian populations; hence, the current analysis was conducted to fill this gap of knowledge. We offer a timely updated investigation into this topic, as well as representative insight into an Asian population, with both sexes, and the confounding effect of smoking status on both lung cancer risk and food-based antioxidant intake.

In the current analysis, we aimed to evaluate the association between dietary-derived CDAI and lung cancer risk in an ongoing prospective cohort study among more than 61,000 men and women in Singapore, the Singapore Chinese Health Study (SCHS). We expect to observe an inverse association between CDAI score and lung cancer risk; as the CDAI score increases, the lung cancer risk decreases.

2.0 Methods

2.1 Study Population

The present analysis used data from the SCHS that has been previously described in detail elsewhere.[17] Briefly, the SCHS is an on-going prospective population-based cohort study comprised of 61,321 Chinese men and women. Participants enrolled in the study were aged 45 to 74 years old at baseline (April 1993 and December 1998), belong to either Hokkien or Cantonese dialect groups, and resided in government-built housing estates between April 1993 and December 1998. The Hokkiens and Cantonese originated from the Fujian and Guangdong provinces in Southern China, respectively, and are the main dialect groups among the Chinese population living in Singapore. Participants were interviewed at baseline by trained interviewers at their place of residence in order to gather demographic information, such as current physical activity, body weight and height, lifetime use of tobacco, reproductive history, occupational exposures, medical history, and family history of cancer. All of the study participants were provided written informed consent. The SCHS has been approved by the Institutional Review Boards (IRBs) of the National University of Singapore and the University of Pittsburgh.

2.2 Ascertainment of Lung Cancer Cases

The International Classification of Diseases-Oncology 2nd Edition Code-C34 was used to identify lung cancer cases.[26] To identify incident lung cancer cases and cause-specific deaths, the

Nationwide Singapore Cancer Registry and the Birth and Death Registry were used via annual record linkage analysis for all surviving cohort participants. To date, only 56 (<0.1%) of the cohort were lost to follow-up due to moving out of Singapore or other reasons.

2.3 Dietary Assessment

A food frequency questionnaire (FFQ) comprised of 165 food items and food groups commonly consumed by Chinese in Singapore was used to obtain information on the current diet and consumption of beverages among the study population. Study participants were asked how frequently (in 8 categories: ranging from "*never or hardly ever*" to "*two or more times a day*") they consumed the food or food group followed by a question on the portion size, which was assisted with photographs showing three portion sizes (i.e., small, medium, and large). Average daily intake of approximately 100 nutrients and non-nutrient compounds was calculated for each study participant using the Singapore Food Composition Database.[27] The FFQ was validated against selected biomarker studies conducted on random subsets of cohort participants and a series of 24-hour dietary recall (24-HDR) interviews.[27] To evaluate the validity of the FFQ, two 24-HDRs, one on a weekday and the other on a weekend approximately two months apart were conducted in a random sample of 810 participants of the SCHS.[28,29] The correlation coefficients calculated between the FFQ and the 24-HDR for most of the calorie-adjusted nutrients ranged from 0.24 to 0.79.[27]

2.4 Assessment of Other Covariates

Relevant covariates were included in the interviews or questionnaires as previously discussed. In addition, tobacco smoking was recorded into three categories: current smokers, never smokers or ever smokers. In the questionnaire, physical activity obtained by asking, "On average, during the last year, how many hours in a week did you spend in the following activities?" Physical activity was recorded by a continuous scale from 0 to 8: never, 0.5-1, 2-3, 4-6, 7-10, 11-20, 21-30, and 31 hours or more on a weekly basis including three common physical activities (i.e., 1) strenuous sports – jogging, cycling on hills, tennis, swimming, tennis, or aerobics; 2) vigorous work – moving heavy items, shoveling, or related labor work; and 3) moderate activities – walking, cycling on flat ground, Tai Chi, and Chi Kung).[30] Participants who responded "never" to all activities were categorized as "no", all other responses were categorized as "yes". Alcohol drinking was categorized into heavy drinker or non-heavy drinker. A heavy drinker is defined by alcohol consumption ≥15 drinks/week for men and ≥8 drinks/week for women, following the definition from the United States Centers for Disease Control and Prevention (CDC).[31] As of medical history, we captured the pre-existing of type 2 diabetes mellitus as well as family history of lung cancer.

2.5 CDAI Scores

The CDAI was developed to reduce the number of correlated variables in antioxidant assessments, capture data variability, and better predict cancer risk compared to the individual assessment of antioxidants.[14] The antioxidants included in the CDAI were vitamins A, C, and E; manganese, selenium and zinc. For the purpose of this study, we will focus on the food-based

components of the CDAI rather than the supplemental antioxidants, because dietary supplements tend to confound associations with different kinds of cancer.

The development of CDAI was described previously,[14,23–25] and validated using 10 serum anti-inflammatory makers (urinary F2-isoprostanes [15-F2$_t$-IsoP]; urinary F2-isoprostane metabolites [15-F2$_t$-IsoPM]; urinary prostaglandin E2 metabolite [PGEM]; C-reactive protein [CRP]; interleukin-1beta [IL-1β]; interleukin-6 [IL-6]; tumor necrosis factor-alpha [TNF-α]; soluble TNF-receptor 1 [sTNF-R1]; soluble TNF-receptor 2 [sTNF-R2]; and soluble GP130 [sGP130]) in the Shanghai Women's Health Study (SWHS), a prospective cohort study.[32] Rounds of analysis were performed throughout the development of the CDAI as well to find the optimal composite model with a number of select components. For each individual subject, the CDAI was calculated by summing consumption of six antioxidants (*i)* including vitamins A, C and E, manganese, selenium, and zinc from food sources only (i.e., dietary supplements were excluded) as follows:

$$CDAI = \sum_{i=1}^{6} \frac{x_i - \mu_i}{S_i}$$

Here, x_i was the daily intake of antioxidant *i;* μ_i was the mean of x_i over the entire cohort for antioxidant *i*; S_i was the standard deviation for μ_i. It is also noted that less than 4% of the SCHS participants took dietary supplements of antioxidants (i.e., 2.1% of vitamin A, 3.9% of vitamin C, 3% of vitamin E, 0.5% of selenium, and 1.4% of zinc)(Data not shown). We did not collect such information for manganese; however, it was anticipated that the proportion of dietary supplements of this element should be similar to that of other antioxidants in the SCHS. For this reason, the association between dietary supplements of CDAI and lung cancer risk is not informative.

2.6 Statistical Analysis

Means and standard deviations (SDs) were computed for continuous variables while counts and proportions were calculated for categorical variables. An ANOVA test was used to compare the distributions of continuous and categorical variables, respectively, between cases and non-cases as well as across different quartiles of the CDAI. Cox proportional hazards regression models were used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) to evaluate the association between CDAI quartiles and lung cancer risk. Potential confounders adjusted for in the models were age, sex, dialect group (Hokkien or Cantonese), level of education (no formal education, primary school, secondary or higher education), year of enrollment (1993-1995 and 1996-1998), number of years smoking, number of cigarettes per day (i.e., never-smokers, 1-12, 13-22, or ≥23), duration of quitting smoking, fried meat consumption (in quartiles),[33] soy intake (in quartiles),[34] β-cryptoxanthin,[17] and total energy intake (Kcal/d). The smoking-related variables (number of years smoking, number of cigarettes per day, and duration of quitting smoking) were appropriately standardized to use for a lung cancer risk analysis in the SCHS, and consequently controlled for the confounding effects of smoking on the outcome. The Cox proportional hazards model was also stratified by lung cancer risk factors including histologic subtypes (i.e., adenocarcinoma vs. squamous cell types), smoking status (never, former, current), alcohol consumption (heavy vs. non-heavy drinker), BMI ($<23 mg/m^2$ vs $\geq 23 mg/m^2$), and diabetes history (with vs. without) to understand differences in the association between CDAI quartiles and lung cancer risk by risk factor. The linear trend was tested for both continuous values and quartile in ordinal values (1, 2, 3, and 4) with the risk of lung cancer. To test the proportional hazard assumption, Schoenfeld residuals test and a graph for residuals over time were performed and no violation was found.

An interaction term between CDAI and diabetes, BMI, smoking status, or family history of lung cancer was included in the multivariable Cox regression models. The log-likelihood ratio statistics were used to evaluate if the interaction term significantly improved the model fitting over the one without the interaction term. We also performed sensitivity analysis after excluding lung cancer cases and person-years observed within the first two years of observation post-enrollment.

Additionally, we performed stratified analysis by histologic subtype examining the joint effects of childhood exposure (<18 years of age), adulthood exposure (≥ 18 years of age), and both childhood and adult exposure to understand the role of second-hand smoking among never smokers on the association between CDAI and the risk of lung cancer.

All statistical analyses were performed using the computing software SAS version 9.4 (SAS Institute Inc., Cary, NC). *P*-values below 0.05 were considered being statistically significant, and all *P*-values were two-sided.

3.0 Results

After a mean (SD) follow-up of 17.5 (6.4) years, we identified 2,008 lung cancer cases among 61,321 participants who were free of cancer at baseline. The mean (SD) age of participants at enrollment was 60.6 (7.4) and 56.3 (8.0) years old for lung cancer cases and non-cases, respectively.

The baseline characteristics of the study participants are shown in **Table 1**. Overall, the average age of the study participants was 56.4 years (8.0), with a higher proportion of younger participants in the highest CDAI quartile (54.6 ± 7.5) than in the lowest CDAI quartile (58.6 ± 8.2) (*P*<.0001). Those in the highest CDAI quartile were more likely to be men, Cantonese, having primary education, never smokers, non-heavy drinkers, having no weekly physical activity, not having a history of diabetes or lung cancer, and having both childhood and adult second-hand smoking exposure, compared to the lowest CDAI quartile (all *P*'s<0.001).

Lung cancer cases in the SCHS were more likely to be female, Hokkien, and have primary school education compared to non-cases (all *P*'s<0.001). In regard to health history, cases were more likely to not have a family history of cancer (*P*<0.001) or type 2 diabetes (*P*=0.0019) than non-cases. Cases were more likely to engage in risk behaviors such as smoking (*P*<0.001), heavy drinking (*P*<0.001), not participating in weekly physical activity (*P*=0.0019), and a lower average β-cryptoxanthin mean intake (*P*<0.001) compared to cases. Non-cases had a higher BMI on average than cases (SD=3.2; *P*<0.001), but interestingly, no significant difference in total energy intake was detected between cases and non-cases (**Supplementary Table 1**).

No significant association was found between lung cancer cases and CDAI scores (**Table 2**). Among lung cancer cases, compared with the lowest CDAI quartile, the HRs and 95% CIs of

lung cancer for CDAI quartiles two, three, and four were 1.01 (0.89-1.16), 0.96 (0.82-1.13), and 0.97 (0.77-1.21), respectively (P_{trend}=0.65).

Next, we explored the association between CDAI score and lung cancer cases by histologic type, after stratification by smoking status, alcohol consumption, BMI, and diabetes history and adjustment for possible confounders (**Table 3**). Among never smokers, we found a significant association between the fourth quartile range of CDAI scores (58.5, 1.0) and increased risk of lung squamous cell carcinoma (HR=6.17; 95% CI: 1.27-30.0; P_{trend}=0.06).

In the stratified analysis by secondhand smoking status (i.e., childhood exposure, adulthood exposure, or both), we observed that there was no association between CDAI and lung cancer risk among different stratum: no exposure to secondhand smoking in both childhood and adulthood, exposure to secondhand smoking in childhood only, exposure to secondhand smoking in adulthood only, and exposure to secondhand smoking in both childhood and adulthood (**Table 4**).

In the sensitivity analysis by excluding incident cases and person-years observed in the first two years of enrollment among lung cancer cases and non-cases, the null association between CDAI and lung cancer risk remained the same to the analysis in the entire cohort (**Supplementary Table 2**).

4.0 Discussion

The present analysis of the large population-based prospective cohort study of 61,321 study participants in Singapore showed that low CDAI scores were not associated with the increased risk of lung cancer. Adversely, we found increased risk of lung squamous cell carcinoma among never smokers in the highest CDAI quartile after adjusting for confounders. In further stratified analysis, we also did not observe an association between CDAI and lung cancer risk among those exposed to secondhand smoking and those who were not exposed to secondhand smoking. We also did not find this association among study participants who were never-smokers. However, although not statistically significant, a trend was observed where an increase in CDAI score led to an increase in lung cancer risk among never smokers with childhood smoke exposure. A very limited number of studies have used the CDAI score as a predictor for disease outcomes thus far, therefore, our study provides novel results to add to the current literature on lung cancer risk and food-based antioxidant intake.

The method of analyzing antioxidants separately rather than using a composite score has been well documented in comparison to studies conducted using composite antioxidant indices, specifically the CDAI. As previously discussed, a major limitation of the individual assessment of antioxidant intake and association with cancer risk is the correlation between antioxidants. For example, a case-control study evaluating lung cancer risk in Hawaii had high correlations between multiple antioxidants in the analyses, with correlation coefficients ranging from 0.05 to 0.78.[19] To further elucidate the strengths of using the CDAI compared to assessing antioxidants in relation to cancer risk individually, a study that evaluated lung cancer risk and the intake of vitamins A, C, and E found no additional protective effect on lung cancer risk when analyzed separately. When

the vitamins were examined in combination, a significantly strong protective effect was observed for those in the higher quartiles compared to the lowest quartile (RR=0.32, 95% CI: 0.14-0.74, P_{trend}=0.0004).[18] However, our results contradict those found by Wright et al., where an increase in CDAI quintile led to a 13-16% decrease in lung cancer risk compared to the lowest quintile. On account of these results, the CDAI appears to be a promising method to determine associations between antioxidant intake and lung cancer, but more studies using the CDAI composite score compared to individually assessing the effect of antioxidant intake on lung cancer risk are warranted.

A number of studies have shown that high antioxidant intake demonstrates beneficial "anticancer" effects.[35] These aforementioned effects include but are not limited to reduced initiation, promotion, progression, and metastases of cancer cells and reduced oxidative damage to DNA proteins and lipids.[36] Given that lung cancer prevention is mostly limited to the modification of individual behaviors and the etiology of the disease is unknown, lowering the risk of lung cancer by using supplements as a way to intake more antioxidants could initially appear as a viable risk prevention behavior. However, the use of antioxidant supplements instead of prioritizing the intake of antioxidants via food is inconclusive. Notably, β-carotene, vitamin E, and B vitamin (B6, B12) supplementation has been most commonly found to increase lung cancer risk.[11,20,37–40] Therefore, the exclusion of supplemental antioxidant intake in the calculation of the CDAI score contributes more clear and meaningful results to the literature on this topic.

To our knowledge, antioxidant intake has only been investigated as a putative predictor of lung cancer risk in Western populations; therefore, limited data exists on this association in an Asian population. Given that the diet in Asian countries differs significantly compared to the United States, a look into the effect of a food-based composite dietary index, such as the CDAI, is

warranted and offers novel results in this respect. A large population based cohort study conducted in 2016 reported that the traditional Asian dietary culture consists of high intake of fish, soy-based foods, and rice, and less consumption of red meat and dairy products.[41] A meta-analysis of observational studies reported that the summary relative risk of lung cancer for highest versus lowest red meat intake categories was 1.34 (95% CI: 1.18-1.52). Moreover, the investigators found that high red meat intake specifically increased the risk of lung adenocarcinoma (RR=1.23; 95% CI: 1.04-1.46).[42] For these reasons, the role of diet as an exposure in an Asian population appears not to be as critical of a factor in assessing lung cancer risk as it may be in a Western population.

The findings from this study should be interpreted with certain strengths and limitations. The strengths of this study include a large sample size, prospective study design, and long-term (average 17.5 years) quality follow-up data. The prospective design provides quality primary exposure data, reducing the possibility of bias and misclassification. A large sample size for the study population increases the power of the study, and the long and complete follow-up reduces the probability of loss of follow-up bias. Additionally, the use of data among participants with no prior tobacco smoke exposure allowed us to elucidate the association between the primary exposure of interest and the outcome of lung cancer risk, without the strong confounding effect of smoking. The use of a composite dietary index to measure antioxidant intake in this population is also a considerable strength because it increases data variability and lowers the chance of correlation between the antioxidant variables if they were to be used in the analyses separately. Furthermore, the focus on food-based antioxidants rather than supplemental antioxidants eliminates the confounding effects of supplement intake on the lung cancer risk association. A limitation of this study is the potential self-reporting and recall bias due to how the dietary

information was obtained. However, sufficient steps were taken to validate FFQ and 24-HDR data to substantially reduce these biases in the study.

In conclusion, the current study exhibits promising results in our attempt to better understand the role of food-based antioxidant intake on lung cancer risk. More research on the association between food-based dietary antioxidant intake and lung cancer risk among an Asian population is needed to corroborate our results and to add more conclusive evidence to this area of research.

Table 1 Distributions of Baseline Characteristics among Study Participants.

	Total # Subjects	Composite Dietary Antioxidant Index[c]				P-value*
		Q1 (-13.3, -4.9)	Q2 (-4.9, -2.3)	Q3 (-2.3, 1.0)	Q4 (1.0, 58.6)	
Number of subjects	61,321	15,330	15,330	15,331	15,330	
Mean age (±SD)[a], years	56.4 (8.0)	58.6 (8.2)	56.7 (7.9)	55.6 (7.8)	54.6 (7.5)	**<0.001**
Sex (%)						
Male	27,293 (44.5)	4,953 (32.3)	6,091 (39.7)	7,376 (48.1)	8,873 (57.9)	**<0.001**
Female	34,028 (55.5)	10,377 (67.7)	9,239 (60.3)	7,955 (51.9)	6,457 (42.1)	
Dialect						
Cantonese	28,325 (46.2)	5,571 (36.3)	6,860 (44.8)	7,626 (49.7)	8,268 (53.9)	**<0.001**
Hokkien	32,996 (53.8)	9,759 (63.7)	8,470 (55.2)	7,705 (50.3)	7,062 (46.1)	
Highest level of education (%)						
No formal education	16,661 (27.2)	6,592 (43.0)	4,428 (28.9)	3,284 (21.4)	2,357 (15.4)	**<0.001**
Primary school	27,224 (44.4)	6,269 (40.9)	7,033 (45.9)	7,164 (46.7)	6,758 (44.1)	
Secondary school or higher	17,436 (28.4)	2,469 (16.1)	3,869 (25.2)	4,883 (31.9)	6,215 (40.5)	
Mean body mass index-BMI (±SD), Kg/m^2	23.1(3.3)	23.0 (3.2)	23.1 (3.3)	23.1 (3.3)	23.2 (3.3)	0.41
Smoking status (%)						
Never smoker	42,583 (69.4)	10,812 (70.5)	10,913 (71.2)	10,655 (69.5)	10,203 (66.6)	**<0.001**
Former smoker	6,681 (10.9)	1,334 (8.7)	1,516 (9.9)	1,737 (11.3)	2,094 (13.7)	
Current smoker	12,057 (19.7)	3,184 (20.8)	2,901 (18.9)	2,939 (19.2)	3,033 (19.8)	
Alcohol consumption						
Heavy drinker	1,007 (1.6)	195 (1.3)	185 (1.2)	257 (1.7)	379 (2.4)	**<0.001**
Non-heavy drinker	60,314 (98.4)	15,135 (98.7)	15,145 (98.8)	15,074 (98.3)	14,960 (97.6)	
Weekly physical activity[b]						
No	41,083(67.0)	11,920 (77.8)	10,668 (69.6)	9,726 (63.4)	8,769 (57.2)	**<0.001**
Yes	20,238(33.0)	3,410 (22.2)	4,662 (30.4)	5,605 (36.6)	6,561 (42.8)	

Table 1 (continued)

Diabetes history (%)						
No	55,852 (91.1)	13,764 (89.8)	13,949 (91.0)	14,055 (91.7)	14,084 (91.9)	**<0.001**
Yes	5,469 (8.9)	1,566 (10.2)	1,381 (9.0)	1,276 (8.3)	1,246 (8.1)	
Family history of lung cancer (%)						
No	59,972 (97.8)	15,082 (98.4)	15,015 (98.0)	14,960 (97.6)	14,915 (97.3)	**<0.001**
Yes	1,349 (2.2)	248 (1.6)	315 (2.0)	371 (2.4)	415 (2.7)	
β-cryptoxanthin intake (mcg), mean (SD)	164.1 (209.6)	115.7 (181.2)	157.5 (204.9)	177.8 (217.6)	205.4 (231.3)	**<0.001**
Second-hand smoking exposure						**<0.001**
None	9,140 (17.9)	2,105 (17.4)	2,277 (17.8)	2,351 (18.0)	2,407 (18.3)	
Childhood exposure	3,538 (6.9)	641 (5.3)	821 (6.4)	991 (7.6)	1,085 (8.2)	
Adulthood exposure	5,917 (11.6)	1,809 (15.0)	1,595 (12.5)	1,324 (10.2)	1,189 (9.0)	
Both childhood & adulthood exposure	32,453 (63.6)	7,524 (62.3)	8,070 (63.2)	8,379 (64.2)	8,480 (64.4)	

[a]SD, standard deviation
[b]Including strenuous physical activity and/or vigorous work
[c]Antioxidants were derived from food only
*Derived from ANOVA test.

Table 2. Association between CDAI quartiles and lung cancer risk in the Singapore Chinese Health Study population, 1993-2015.

CDAI Quartiles	Person years (case)	Hazard Ratio (95% CI)	*P-value*
Q1 (-13.3, -4.9)	259,993 (581)	1.00	-
Q2 (-4.9, -2.3)	270,206 (519)	1.01 (0.89-1.16)	0.85
Q3 (-2.3, 1.0)	263,717 (465)	0.96 (0.82-1.13)	0.62
Q4 (1.0, 58.6)	277,813 (443)	0.97 (0.77-1.21)	0.79
P_{trend}	0.65		

*Derived by Cox proportional hazard ratios, and adjusted for age, sex, dialect group, education, year of recruitment, years of smoking, number of cigarettes per day, duration of quitting, beta-cryptoxanthin, fried meat consumption (in quartiles), soy intake (in quartiles), and total energy intake (continuous).

Table 3. Association between CDAI quartiles and lung cancer risk in the Singapore Chinese Health Study population, 1993-2015, stratified by histologic subtypes, smoking status, alcohol consumption, BMI, and diabetes history.

	Total		Adenocarcinoma		Squamous cell carcinoma	
	Person years (case)	**Hazard Ratio (95% CI)**	**Person years (case)**	**Hazard Ratio (95% CI)**	**Person years (case)**	**Hazard Ratio (95% CI)**
Overall						
Q1 (-4.9, -13.3)			259,993 (205)	1.00	259,993 (98)	1.00
Q2 (-2.3, -4.9)			270,206 (180)	0.94 (0.75-1.17)	270,206 (102)	1.18 (0.86-1.60)
Q3 (1.0, -2.3)			273,717 (201)	1.07 (0.84-1.37)	273,717 (88)	1.09 (0.75-1.59)
Q4 (58.5, 1.0)			277,813 (207)	1.12 (0.79-1.57)	277,813 (72)	0.96 (0.56-1.65)
P_{trend}			0.42		0.98	
By Smoking Status						
Never Smoker						
Q1 (-4.9, -13.3)	192,837 (164)	1.00	192,837 (93)	1.00	192,837 (11)	1.00
Q2 (-2.3, -4.9)	200,977 (178)	1.25 (0.99-1.59)	200,977 (102)	1.13 (0.83-1.55)	200,977 (11)	1.78 (0.68-4.65)
Q3 (1.0, -2.3)	197,431 (147)	1.18 (0.88-1.58)	197,431 (97)	1.14 (0.78-1.64)	197,431 (7)	1.79 (0.51-6.32)
Q4 (58.5, 1.0)	191,477 (135)	1.37 (0.87-1.98)	191,477 (91)	1.14 (0.68-1.92)	191,477 (11)	**6.17 (1.27-30.0)**
P_{trend}	0.27		0.59		0.06	
Former Smoker						
Q1 (-4.9, -12.0)	19,959 (65)	1.00	19,959 (16)	1.00	19,959 (15)	1.00
Q2 (-2.3, -4.9)	23,597 (71)	1.06 (0.74-1.53)	23,597 (16)	0.99 (0.47-2.06)	23,597 (18)	1.00 (0.48-2.07)
Q3 (1.0, -2.7)	28,089 (65)	0.94 (0.60-1.45)	28,089 (24)	1.44 (0.66-3.12)	28,089 (12)	0.54 (0.22-1.32)

Table 3 (continued)

Q4 (40.9, 1.0)	35,629 (67)	0.96 (0.53-1.75)	35,629 (28)	1.63 (0.58-4.57)	35,629 (15)	0.49 (0.15-1.64)
P_{trend}	0.77		0.26		0.14	
Current Smoker						
Q1 (-4.9, -13.0)	47,197 (352)	1.00	47,197 (96)	1.00	47,197 (72)	1.00
Q2 (-2.3, -4.9)	45,362 (270)	0.89 (0.74-1.06)	45,362 (62)	0.72 (0.51-1.01)	45,362 (73)	1.17 (0.81-1.69)
Q3 (1.0, -2.3)	48,196 (253)	0.89 (0.72-1.09)	48,196 (80)	0.96 (0.66-1.39)	48,196 (69)	1.23 (0.79-1.90)
Q4 (46.4, 1.0)	50,707 (241)	0.87 (0.65-1.18)	50,707 (88)	1.06 (0.62-1.78)	50,707 (46)	0.88 (0.45-1.70)
P_{trend}	0.33		0.72		0.89	
$P_{heterogeneity}$	0.15		0.72		0.60	
By Alcohol Drinking Status						
Heavy Drinker						
Q1 (-4.9, -13.3)	3,017 (14)	1.00	3,017 (9)	1.00	3,017 (1)	1.00
Q2 (-2.3, -4.9)	2,794 (15)	1.22 (0.56-2.66)	2,794 (1)	0.10 (0.01-0.81)	2,794 (5)	5.73 (0.53-61.6)
Q3 (1.0, -2.3)	4,182 (21)	1.17 (0.50-2.74)	4,182 (9)	0.52 (0.15-1.81)	4,182 (3)	1.81 (0.13-25.3)
Q4 (58.5, 1.0)	6,263 (17)	0.83 (0.26-2.69)	6,263 (6)	0.24 (0.04-1.57)	6,263 (3)	1.03 (0.04-29.1)
P_{trend}	0.86		0.23		0.68	
Non-heavy Drinker						
Q1 (-4.9, 11.3)	256,977 (567)	1.00	256,977 (196)	1.00	256,977 (97)	1.00
Q2 (-2.3, -4.9)	267,412 (504)	1.01 (0.89-1.16)	267,412 (179)	0.99 (0.79-1.23)	267,412 (97)	1.12 (0.82-1.54)
Q3 (1.0, -2.2)	269,535 (444)	0.96 (0.81-1.13	269,535 (192)	1.11 (0.86-1.43)	269,535 (85)	1.06 (0.72-1.57)
Q4 (46.8, 1.0)	271,550 (426)	0.99 (0.79-1.25)	271,550 (201)	1.21 (0.85-1.72)	271,550 (69)	0.93 (0.53-1.63)

Table 3 (continued)

P_{trend}	0.75		0.26		0.92	
$P_{heterogeneity}$	0.43		0.10		0.96	
By BMI Status						
BMI<23mg/m²						
Q1 (-4.9, -13.0)	118,368 (327)	1.00	118,368 (114)	1.00	118,368 (55)	1.00
Q2 (-2.3, -4.9)	128,840 (307)	1.07 (0.90-1.27)	128,840 (112)	1.10 (0.83-1.46)	128,840 (65)	1.23 (0.83-1.83)
Q3 (1.0, -2.3)	133,274 (278)	1.07 (0.87-1.32)	133,274 (118)	1.27 (0.91-1.76)	133,274 (49)	0.97 (0.59-1.57)
Q4 (58.5, 1.0)	135,611 (257)	1.09 (0.81-2.46)	135,611 (121)	1.43 (0.91-2.26)	135,611 (43)	0.83 (0.41-1.65)
P_{trend}	0.58		0.10		0.54	
BMI≥23mg/m²						
Q1 (-4.9, -13.2)	141,625 (254)	1.00	141,625 (91)	1.00	141,625 (43)	1.00
Q2 (-2.3, -4.9)	141,366 (212)	0.95 (0.78-1.17)	141,366 (68)	0.77 (0.54-1.07)	141,366 (37)	1.12 (0.68-1.85)
Q3 (1.0, -2.3)	140,443 (187)	0.86 (0.67-1.09)	140,443 (83)	0.89 (0.61-1.29)	140,443 (39)	1.36 (0.75-2.46)
Q4 (55.1, 1.0)	142,202 (186)	0.87 (0.61-1.23)	142,202 (86)	0.84 (0.49-1.42)	142,202 (29)	1.29 (0.54-3.09)
P_{trend}	0.28		0.62		0.40	
$P_{heterogeneity}$	0.27		0.86		0.42	
By History of Diabetes						
Without Diabetes History						
Q1 (-4.9, -13.3)	239,048 (549)	1.00	239,048 (192)	1.00	239,048 (92)	1.00
Q2 (-2.3, -4.9)	250,455 (484)	1.00 (0.87-1.15)	250,455 (170)	0.95 (0.76-1.19)	250,455 (96)	1.17 (0.85-1.61)
Q3 (1.0, -2.3)	255,624 (431)	0.94 (0.79-1.10)	255,624 (189)	1.08 (0.83-1.39)	255,624 (79)	1.02 (0.69-1.51)

Table 3 (continued)

Q4 (58.5, 1.0)	258,574 (404)	0.92 (0.73-1.16)	258,574 (185)	1.07 (0.75-1.54)	258,574 (66)	0.88 (0.50-1.56)
P_{trend}	0.39		0.54		0.71	
With Diabetes History						
Q1 (-4.9, -12.1)	20,945 (32)	1.00	20,945 (13)	1.00	20,945 (6)	1.00
Q2 (-2.3, -4.9)	19,751 (35)	1.25 (0.74-2.11)	19,751 (10)	0.83 (0.35-1.97)	19,751 (6)	1.17 (0.34-4.08)
Q3 (1.0, -2.3)	18,093 (34)	1.40 (0.77-2.55)	18,093 (12)	1.08 (0.43-2.67)	18,093 (9)	2.05 (0.53-7.93)
Q4 (37.2, 1.0)	19,239 (39)	1.97 (0.88-4.41)	19,239 (22)	2.06 (0.68-6.21)	19,239 (6)	2.28 (0.33-15.7)
P_{trend}	0.12		0.22		0.28	
$P_{heterogeneity}$	0.03		0.05		0.41	

*Derived by Cox proportional hazard ratios, and adjusted for age, sex, dialect group, education, year of recruitment, years of smoking, number of cigarettes per day, duration of quitting, beta-cryptoxanthin, fried meat consumption (in quartiles), soy intake (in quartiles), and total energy intake (continuous), if applicable.

Table 4. Association between CDAI quartiles and the risk of lung cancer among never smokers in the Singapore Chinese Healthy Study, 1993 – 2015, stratified by second hand smoking status.

	Never Smokers	
	Person years (cases)	**Hazard Ratio (95% CI)**
None		
Q1 (-4.9, -12.0)	33,257 (27)	1.00
Q2 (-2.3, -4.9)	35,184 (18)	0.61 (0.32-1.17)
Q3 (1.0, -2.3)	35,493 (20)	0.64 (0.31-1.31)
Q4 (55.1, 1.0)	35,551 (25)	0.74 (0.28-1.95)
P_{trend}	0.45	
Childhood exposure (<18 yrs)		
Q1 (-4.9, -11.3)	8,140 (2)	1.00
Q2 (-2.3, -4.9)	11,567 (10)	4.32 (0.88-21.3)
Q3 (1.0, -2.3)	13,729 (10)	4.33 (0.76-24.8)
Q4 (58.5, 1.0)	14,236 (9)	4.87 (0.57-41.6)
P_{trend}	0.25	
Adulthood exposure (≥ 18 yrs)		
Q1 (-4.9, -13.3)	29,580 (17)	1.00
Q2 (-2.3, -4.9)	26,295 (20)	1.66 (0.80-3.45)
Q3 (1.0, -2.3)	21,879 (19)	2.04 (0.83-5.01)
Q4 (31.1, 1.0)	18,372 (13)	1.89 (0.52-6.87)
P_{trend}	0.22	
Both childhood & adulthood exposure		
Q1 (-4.9, -12.4)	97,776 (63)	1.00
Q2 (-2.3, -4.9)	107,815 (93)	1.42 (0.99-2.03)
Q3 (1.0, -2.3)	108,499 (66)	1.04 (0.66-1.64)
Q4 (54.3, 1.0)	105,414 (50)	0.85 (0.44-1.63)
P_{trend}	0.55	
$P_{heterogeneity}$		

*Derived by Cox proportional hazard ratios, and adjusted for age, sex, dialect group, education, year of recruitment, years of smoking, number of cigarette per day, duration of quitting, beta-cryptoxanthin, fried meat consumption (in quartiles), soy intake (in quartiles), and total energy intake (continuous), if applicable.

Supplemental Table 5. Baseline Characteristics of Study Participants with Lung Cancer and Subjects Without Lung Cancer, the Singapore Chinese Health Study, 1993-2016.

Characteristics	Lung Cancer		*P-value*
	Cases (n=2008)	**Non-cases (n=59,313)**	
Age (years), mean (SD)[a]	60.6 (7.4)	56.3 (8.0)	**<0.001**
Sex			
Female	1,342 (66.8)	25,951 (43.8)	**<0.001**
Male	666 (33.2)	33,362 (56.2)	
Highest Level of Education			**<0.001**
No formal education	606 (30.2)	16,055 (27.1)	
Primary school	1,035 (51.5)	26,189 (44.1)	
Secondary school or higher	367 (18.3)	17,069 (28.8)	
Dialect			**<0.001**
Cantonese	830 (41.3)	27,495 (46.4)	
Hokkien	1,178 (58.7)	31,818 (53.6)	
Weekly Physical Activity[b]			**0.0096**
Yes	609 (30.3)	19,629 (33.1)	
No	1,399 (69.7)	39,684 (66.9)	
Smoking Status			**<0.001**
Never Smoker	624 (31.1)	41,959 (70.7)	
Former smoker	268 (13.3)	6,413 (10.8)	
Current Smoker	1,116 (55.6)	10,941 (18.4)	
Alcohol Consumption			**<0.001**
Heavy Drinker	1,941 (96.7)	58,373 (98.4)	
Non-heavy Drinker	67 (3.3)	940 (1.6)	
History of Type 2 Diabetes			**0.0019**
Yes	140 (7.0)	5,329 (9.0)	
No	1,868 (93.0)	53,984 (91.0)	
Family History of cancer			**<0.001**
Yes	216 (10.8)	8,260 (13.9)	
No	1,792 (89.2)	51,053 (86.1)	
BMI (Kg/m), mean (SD)	22.4 (3.2)	23.2 (3.3)	**<0.001**
Total Energy Intake (kcal/day)	1562.9 (582.0)	1556.4 (565.7)	0.61
β-cryptoxanthin intake (mcg), mean (SD)	142.6 (213.6)	164.8 (212.0)	**<0.001**
Second-hand smoking exposure			**<0.001**
None	180 (12.9)	8,960 (18.0)	
Childhood exposure	90 (6.5)	3,448 (6.9)	
Adulthood exposure	129 (9.3)	5,788 (11.7)	
Both childhood & adulthood exposure	993 (71.3)	31,460 (63.4)	

[a]SD, standard deviation

[b]Including strenuous physical activity and/or vigorous work

Supplemental Table 6. Baseline characteristics in lung cancer cases and non-cases after excluding incident cases and person-years observed in the first two years post-enrollment.

CDAI Quartiles	Person years (case)	Hazard Ratio (95% CI)	*P-value*
Q1 (-4.9, -13.3)	229,731 (523)	1.00	-
Q2 (-2.3, -4.9)	239,782 (484)	1.02 (0.89-1.17)	0.77
Q3 (1.0, -2.3)	243,272 (435)	0.95 (0.81-1.12)	0.54
Q4 (58.5, 1.0)	247,302 (409)	0.92 (0.72-1.16)	0.46
P_{trend}	0.39		

*Derived by Cox proportional hazard ratios, and adjusted for age, sex, dialect group, education, year of recruitment, years of smoking, number of cigarettes per day, duration of quitting, beta-cryptoxanthin, fried meat consumption (in quartiles), soy intake (in quartiles), and total energy intake (continuous), if applicable.

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