HHS Public Access

Author manuscript

Eur J Cancer Prev. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Eur J Cancer Prev. 2021 May 01; 30(3): 275–281. doi:10.1097/CEJ.0000000000000660.

The Association Between Dietary Vitamin B_{12} and Lung Cancer Risk: Findings from a Prospective Cohort Study

Hung N. Luu[1,2], **Renwei Wang**[1], **Aizhen Jin**[3], **Woon-Puay Koh**[3,4], **Jian-Min Yuan**[1,2]

[1]Division of Cancer Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA

[2]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

[3]Health Services and Systems Research, Duke-NUS Medical School Singapore, Singapore

[4]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Abstract

Background.—Since previous epidemiological studies reported inconsistent associations between dietary vitamin B_{12} intake and lung cancer risk, more studies are warranted to clarify this association in different populations.

Methods.—The association between dietary B_{12} intake and lung cancer risk was examined in the Singapore Chinese Health Study, an ongoing prospective cohort study of 63,257 Singaporean Chinese men and women, 45–74 years of age at enrollment during 1993–1998 and were followed up for incidence of lung cancer for up to 25 years. Dietary vitamin B_{12} intake was derived from a validated food frequency questionnaire. Cox proportional hazard regression method was used to estimate hazard ratio (HR) and 95% confidence interval (CI) of lung cancer associated with dietary vitamin B_{12} intake with adjustment for multiple potential confounders.

Results.—After a mean follow-up of 17.64 years, 2,001 study participants developed lung cancer. High levels of vitamin B_{12} intake were associated with significantly increased risk of lung cancer (P_{trend}= 0.03). Compared with the lowest quintile, HRs (95% CIs) of lung cancer for quintile 2, 3, 4, and 5 of vitamin B_{12} intake were 1.09 (0.95–1.25), 1.11 (0.96–1.28), 1.11 (0.97–1.29) and 1.18 (1.03–1.35), respectively. This positive association was more apparent in men than in women, in adenocarcinoma patients, or in participants with equal or less than 2 years follow-up than those with longer duration of follow-up.

Conclusion.—Higher intake of dietary vitamin B_{12} was associated with increased risk of lung cancer. This highlights the potential harmful effect of vitamin B_{12} supplementation for lung cancer.

Keywords

Dietary Vitamin B_{12}; Lung Cancer

Corresponding Authors: Hung N. Luu, M.D., Ph.D., Division of Cancer Control and Population Sciences, University of Pittsburgh Hillman Cancer Center, UPMC Cancer Pavilion, 5150 Centre Avenue, Suit 4C, Room 466, Pittsburgh, PA 15232, USA, Phone: 412-623-3386, luuh@upmc.edu.

INTRODUCTION

Lung cancer is one of the most common cancers worldwide, accounting for more than 2 million new cases and 1.8 million deaths in 2018.[1] In the US, it is estimated that there are 228,220 new lung cancer cases and 135,720 deaths due to lung cancer in 2020, which accounts for 23% of all cancer deaths.[2] The 5-year survival for patients after diagnosis of lung cancer in the US was approximately 20% and is even lower globally.[2] This stresses the importance of having a better prevention and treatment program to reduce both morbidity and mortality of lung cancer. Established risk factors for lung cancer include tobacco smoking, exposures to radon, secondhand smoking, asbestos, and certain metals (i.e., chromium, cadmium, arsenic[1]), as well as genetic susceptibilities (e.g., 5p15, 6p21, 15q25).[3] Novel risk modifiers would help understand the lung carcinogenesis and develop more effective prevention strategy against the development of lung cancer.

It is well known that aberrant DNA methylation plays a pivotal role in cancer development and progression.[4,5] DNA methylation requires a methyl donor which is mainly provided by the metabolites in the one-carbon metabolism pathway.[6] Indeed, one-carbon metabolism is involved with various factors, including several B vitamins such as vitamins B_6, B_9 (folate) and B_{12} that serve as cofactors for the specific enzymes in biochemical reactions to produce methyl donors.[7] The disruption of one-carbon metabolism pathway may alter DNA methylation and cause genomic instability, both of which may enhance malignant transformation of cells, leading to the development of lung cancer.[8]

Prior epidemiological studies reported inconsistent associations between vitamin B_{12} and lung cancer risk. For instance, two large randomized, placebo-controlled trials of B_{12} vitamin supplementation [(i.e., 1) oral treatment with folic acid-0.8 m/d plus and vitamin B_{12}-0.4 m/d and vitamin B_6-40 mg/d; 2) oral treatment with folic acid-0.8 m/d plus and vitamin B12–0.4 m/d; 3) oral treament with vitamin B_6-40 mg/d alone; and 4) placebo] in Norwegian population showed that the risk of overall cancer, primarily driven by lung cancer, was increased among those who received both vitamins B_{12} and folic acid.[9] Results from the Vitamins and Lifestyle (VITAL) cohort study also showed that lung cancer risk was increased among men who had high amount of vitamins B_6 and B_{12} supplementation.[10] More recently, the Lung Cancer Cohort Consortium (LC3) project reported that higher levels of blood vitamin B_{12} was significantly associated with increased risk of lung cancer.[11] However, several large population-based cohort studies did not find a positive or inverse-association between dietary vitamin B_{12} intakes and risk of lung cancer in various populations such as in Australia,[12] China,[13] European countries,[14,15] and the US.[16] Most of these studies were conducted in Caucasians or African-Americans[9,10,12,14,15,16] which have different dietary habits than Asians.

To further elucidate the role of dietary vitamin B_{12} in lung cancer, we examined this association, using data from a population-based prospective cohort of Chinese in Singapore enrolled in 1990s with more than 25 years of follow-up.

METHODS

Study Population

We used data from the Singapore Chinese Health Study (SCHS) for the current analysis which was described in details elsewhere.[17] Briefly, the SCHS is an population-based prospective cohort study that enrolled 63,257 Chinese men and women, aged 45–74 years old from two main dialect groups of Chinese in Singapore (i.e., the Hokkiens and the Cantonese) during the period of April 1993 and December 1998. They were originated from Fujian and Guangdong provinces in southern China, respectively, who resided in the government-built housing estates. All study participants provided written informed consent. The SCHS has been approved by the Institutional Review Boards of the National University of Singapore and the University of Pittsburgh.

At the recruitment, study participants were interviewed in-person by trained interviewers, using a structured questionnaire. The questionnaire included information on demographics, body weight and height, current physical activity, lifetime use of tobacco (cigarettes and water-pipe), occupational exposure, medical history, family history of cancer, and for women, menstrual and reproductive history. Body mass index (BMI) was calculated as the current weight in kilograms divided by height in meters squared.

Dietary Assessment

Dietary assessment in SCHS was conducted using a semi-quantitative food frequency questionnaire (FFQs), which was validated against a series of 24-hour dietary recall interviews[18] and selected biomarker studies on random subsets of cohort participants.[19,20] The FFQ contained 165 food items and food groups that were commonly consumed by Chinese in Singapore. 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 and followed by a question on the amount of food consumed, using photographs to choose from three portion sizes (i.e., small, medium, large). Average daily intake of approximately 100 nutrients and non-nutrient compounds, including vitamin B_{12} per 100 g of edible food for each food item in the FFQ, was computed for each study participant using the Singapore Food Composition Database.[18] The two 24-hour dietary recalls, one on a weekday and the other on a weekend, approximately two month apart, were conducted in a random sample of 810 participants of the SCHS to assess the validity of the FFQ used. The correlation coefficients of the majority of calorie-adjusted nutrients between the FFQ and the 24-hour dietary recall surveys ranged from 0.24 to 0.79.[18]

Ascertainment of Lung Cancer Cases

The Nationwide Singapore Cancer Registry and the Birth and Death Registry were used to identify incident cases of lung cancer and cause-specific deaths via annual record linkage analysis for all surviving cohort participants. We used International Classification of Diseases-Oncology 2nd Edition Code-C34 to determine lung cancer cases.[21] Both the Nationwide Singapore Cancer Registry and the Birth and Death Registry have had high completion rate for all incident cases of cancer and deaths. To date, only 56 (<0.1%) cohort participants were lost to follow-up due to migration out of Singapore, making our follow-ups be virtually complete for the ascertainment of incident cancer cases and deaths.

Statistical Analysis

The present analysis included 61,321 participants who were free of cancer at the enrollment, after excluding 1,585 subjects with a history of cancer. After up to 20 years of follow-up, 2,001 participants developed lung cancer by 31 December 2015. For each participant, we calculated person-years at risk from the date of baseline interview to the date of lung cancer diagnosis, death, migration out of Singapore, or December 31, 2015, whichever occurred first.

Means and standard deviations (SDs) were calculated for continuous variables while counts and proportions were calculated for categorical variables. The *t* and χ^2 tests were used to compare the distributions of continuous and categorical variables, respectively, between cases and non-cases as well as across quintiles of dietary vitamin B_{12} intake. Cox proportional hazard regression method was used to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for lung cancer associated with vitamin B_{12} intake. The linear trend was performed by treating the categorical variable of vitamin B_{12} intake as an ordinal variable. We used Schoenfeld residuals test to evaluate proportional hazard assumption and found no violation for vitamin B_{12} intake. Covariates included in all multivariable Cox proportional hazards models were: age, sex, dialect group (Hokkien or Cantonese), level of education (i.e., no formal education, primary school, secondary or higher education), enrollment period (i.e., 1993–1995, 1996–1998), BMI (i.e., <20, 20-<24, 24-<28, ≥28), years of smoking, average number of cigarette per day (i.e., never-smokers, 1–12, 13–22, or ≥23), number of years since last smoked for quitters (i.e., <1, 1–4, 5–19 or ≥20), and daily intake of total calories. A separate Cox regression model was conducted to additionally adjust for dietary beta-cryptoxanthin (g/day),[17] and caffeine intake[22] because these dietary variables were found to be associated with lung cancer risk and/or contributors to vitamin B_{12}.

The sensitivity analyses were performed in subgroups stratified by smoking status (i.e., never smoker, former smoker, and current smoker), sex, histological subtypes (i.e., adenocarcinoma, squamous cell, and other/unknown cell types) and follow-up period (i.e., ≤2 years versus >2 years). The likelihood ratio test was used to evaluate the differential associations for dietary vitamin B_{12} intake with the risk of lung cancer between the subgroups. We also examined the potential interactions between the vitamin B_{12} intake and each of the stratifying variables on lung cancer risk by introducing a product term of the two in the Multivariable regression models. All statistical analyses were carried out using the computing software SAS version 9.4 (SAS Institute Inc., Cary, NC). All *P* values presented are two-sided. *P* values below 0.05 was considered being statistically significant.

RESULTS

There were 2,001 incident cases of lung cancer out of 61,321 participants who were free of any cancer at baseline (i.e., 814 adenocarcinoma, 374 squamous cell carcinoma, and 813 others/unknown cell types) after a mean 17.6 years of follow-up. The mean (±SD) age at the cancer diagnosis of all lung cancer patients was 72.0 (±7.9) years. The median time interval from the date of enrollment to the date of lung cancer diagnosis was 11.26 years (range 3 months to 22.41 years).

There were higher proportions of men, Hokkien, current smokers, consumers of ≥7 alcoholic drinks/week, among lung cancer cases than among non-cases. In contrast, we observed lower proportions of secondary school or higher education, having a history of diabetes and any weekly physical activity in non-cases than in lung cancer cases. Among dietary factors, participants who developed lung cancer had significantly lower intake of dietary beta-cryptoxanthin, higher intake of caffeine, and similar levels of vitamin B_{12}, total energy intake and fried meat intake as compared with non-cases (Table 1).

Table 2 shows characteristics of participants by category of dietary vitamin B_{12} intake. Compared to the lowest quintile, those in the highest quintile of dietary vitamin B_{12} intake were more likely to be women, Hokkien, no formal education, and having a history of diabetes. They were, however, less likely to be smoker and lower daily intake of total energy, beta-cryptoxanthin, fried meat intake and caffeine (all *P's*<0.001).

Higher intake of vitamin B_{12} was associated with increased risk of lung cancer (Table 3). There was a statistically significant 18% increased risk of lung cancer per g of vitamin B_{12} after adjustment for age, sex, education, cigarette smoking, and total energy intakes (P_{trend}=0.02). Compared with the lowest quintile, the HRs (95% CIs) of lung cancer for vitamin B_{12} intake in quintiles 2, 3, 4, and 5 were 1.09 (0.95–1.26), 1.12 (0.97–1.29), 1.12 (0.97–1.29) and 1.18 (1.03–1.36), respectively. Further adjustment for potential dietary confounders including beta-cryptoxanthin, and caffeine did not alter the association between dietary vitamin B_{12} and lung cancer risk (Table 3).

In stratified analysis, a similar positive association between dietary vitamin B_{12} and lung cancer risk was observed in men, in adenocarcinoma patients and in early follow-up period (within ≤2 years) post enrollment (Table 4). For example, within ≤2 years of follow-up, the HRs (95% CIs) of lung cancer for vitamin B_{12} in quintiles 2, 3, 4, and 5 were 1.49 (0.82–2.68), 1.77 (1.00–3.13), 1.84 (1.04–3.26), and 234 (1.36–4.04), respectively (P_{trend}= 0.002). The associations between dietary vitamin B_{12} intake and lung cancer risk was not statistically significant in women, other subgroups stratified by smoking status, or those with >2 years of follow-up. We did not find differential associations between vitamin B_{12} and risk of specific histological subtype lung cancer of squamous cell and other histological subtypes ($P_{heterogeneity}$=0.166) (Table 4).

DISCUSSION

In the present analysis of the population-based prospective cohort study of 61,321 individuals with an average follow-up of 17.64 years, we found that increasing dietary vitamin B_{12} intake was associated significantly with increased risk of lung cancer in dose-response manner. This positive association was more apparent in men than women, adenocarcinoma patients than squamous cell or other histologic sub-type paients, or in earlier (≤2 years) than later (>2 years) period of follow-up.

Our finding on the positive association between dietary vitamin B_{12} intake and increased risk of lung cancer is consistent with a study by Ebbing et al.[9] in two large randomized controlled trials of B vitamin supplementation, including folic acid (B_9), B_6, and B_{12} in a Norwegian populations with 6,837 participants. They reported that the risk of overall cancer, mainly lung cancer, was increased among those who received both vitamins B_{12} and folic acid (B_9).[9] Our finding that this association was more apparent in men is also consistent with the finding from a recent study of the Vitamins and Lifestyle (VITAL) cohort of 77,118 study participants aged 50–76 years old, in which Brasky et al.[10] showed that that lung cancer risk was increased among men who had high amount of vitamins B_6 and B_{12} supplementation. Accordingly, men who consumed vitamin B_{12} supplementation in the highest quintile, in comparison to the lowest quintile, had an HR of 1.33 (95% CI: 1.00–1.76) for lung cancer.[10] An important point to note is that in our study, we examined the vitamin B_{12} from food sources whereas vitamin B_{12} intake of the VITAL study and the clinical trial described above was derived from vitamin supplements with higher daily doses.[9,10] Taken together, our study and those prior large cohort studies[9,10] showed a robust positive association of vitamin B_{12} with lung cancer risk regardless of the sources of vitamin B_{12}.

In the current analysis, we did not find a statistically significant association between dietary vitamin B_{12} intake and the risk of developing lung cancer in women. Our finding is consistent with the results from the Shanghai Women's Health Study,[13] a prospective cohort study of more than 71,000 women in Shanghai, China. The respective HRs and 95% CIs of lung cancer for quartiles 2, 3 and 4 were 0.80 (0.61–1.04), 0.95 (0.72–1.25), and 0.76 (0.55–1.05), respectively, compared with the lowest quartile (P_{trend}=0.19).[13]

Our overall findings on the positive association between vitamin B_{12} and lung cancer risk is inconsistent with those in the Southern Community Cohort Study (SCCS)[16] and two other nested case-control studies (i.e., one from EPIC cohort[14] and the other from ATBC cohort[15]. This inconsistency might be explained by the difference in dietary vitamin B_{12} intake or sources of vitamin B_{12} (i.e., dietary in our study versus serum concentration in EPIC cohort[14] and ATBC cohort[15]).

We also found that the positive association between dietary vitamin B_{12} and lung cancer risk was significant among participants with less than 2 years follow-up. Our finding is inconsistent with prior result found in the VITAL cohort[10] in which longer supplementation of vitamin B_{12} (>55 µg/d) increased lung cancer risk; HR of lung cancer was 1.98 (95% CI: 1.32–2.97) for participants with an average 10 years of vitamin B_{12} supplementation compared with non-users. One possible mechanism is that vitamin B_{12} may be a cancer promoter or people changed their dietary habit when they are close to lung cancer manifestation. Another potential explanation is that the regression dilution phenomenon, meaning the longer the follow-up the more misclassification occurs when only baseline exposure is used; which might a potential limitation of the current study. Further studies are thus warranted to elucidate these potential mechanisms.

It is also noted that we have reported prior that both fried meat intake[25] and fish intake[26] were associated with lung cancer risk in the Singapore Chinese Health Study. In our cohort, two main sources of dietary vitamin $B_{12,}$ red meat and fish accounts for 57% of total vitamin B_{12}; thus finding from our current analysis reassured that overall vitamin B_{12} is, indeed, associated with increased risk of lung cancer.

Understanding the biological mechanism of vitamin B_{12} as one of the one-carbon metabolism nutrients, as aforementioned, would be useful to provide dietary recommendation in terms of timing and dosage for those who are in deficient status. Excessive use of vitamin B_{12} may be harmful as it was shown in the PRevention Of Osteoporotic Fractures (B-PROOF) study that long-term daily supplementation of vitamin B_{12} and folic acid was associated with changes in DNA methylation due to the activation and deregulation of four specific genes (i.e., *DIRAS3, DMR*, *NODAL*, and *HOXB7),* leading to carcinogenesis[23].

Strengths of the current study include prospective study design, low intake of vitamin B_{12}, compared with other studies in Europe or in the US, and in the area where vitamin supplementation, including vitamin B_{12} was uncommon; large sample size allowing for robust estimates of lung cancer risk, long-term and complete follow-up that reduced potential bias due to loss of follow-up. Additional strength is that estimates obtained from the longitudinal study design would reflect the true estimate with minimal possibility of reverse causation.

As aforementioned, our finding is consistent with the recent result of the Lung Cancer Cohort Consortium, showing that circulating vitamin B_{12} level was associated with increased risk of lung cancer, which was subsequently confirmed by the Mendelian randomization approach.[24] Our study is also part of the Lung Cancer Cohort Consortium as we contributed 800 cases and 800 matched controls. Dietary vitamin B_{12} intake in our cohort was strongly correlated with the serum vitamin B_{12} concentration ($P_{PersonCorr}$=0.004).

One possible limitation in our study was the misclassification of dietary exposure, as present in any observational study. However, our validation study[19,20] shown that the comprehensive dietary questionnaire used showed good reproducibility in multiple 24-hour dietary recall surveys. Another limitation might be the generalizability of our findings to other population as SCHS has lower intake of dietary vitamin B_{12} whereas this intake is much higher in Europe or in the US. Our study, however, can be generalizable to East Asian populations who have similar patterns of sources and consumption of vitamin B_{12}.

In summary, the current study shows a dose-dependent association between the dietary vitamin B_{12} intake and higher risk of lung cancer development. This association is more present among men, in adenocarcinoma patients and those who are equal or less than 2 year follow-up. This finding, together with results from large cohort studies in vitamin B_{12} supplementation,[9,10] highlights the importance message that high-dose or high level of vitamin B12 are not useful in lung cancer prevention program, instead it might be harmful particularly to men.

ACKNOWLEDGEMENTS

We thank the Singapore Cancer Registry for the identification of incident cancer cases among participants of the Singapore Chinese Health Study. We also thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study.

Funding: The Singapore Chinese Health Study was supported by R01 CA144034 and UM1 CA182876 the United States National Institute of Cancer (NCI). W-P Koh is supported by the National Medical Research Council, Singapore (NMRC/CSA/0055/2013). HN Luu is partially supported by the University of Pittsburgh Medical Center Hillman Cancer Center start-up grant.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. [PubMed: 30207593]
2. American Cancer Society. Cancer Facts & Figures 2020. Atlanta, GA: American Cancer Society, 2020.
3. Brennan P, Hainaut P, Boffetta P. Genetics of lung-cancer susceptibility. Lancet Oncol 2011;12:399–408. [PubMed: 20951091]
4. Baylin SB. DNA methylation and gene silencing in cancer. Nat Clin Pract Oncol 2005;2 Suppl 1:S4–11. [PubMed: 16341240]
5. Klutstein M, Nejman D, Greenfield R, Cedar H. DNA Methylation in Cancer and Aging. Cancer Res 2016;76:3446–50. [PubMed: 27256564]
6. Newman AC, Maddocks ODK. One-carbon metabolism in cancer. Br J Cancer 2017;116:1499–504. [PubMed: 28472819]
7. Kim Y-I. Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2004;13:511–9.
8. Ham M-S, Lee J-K, Kim K-C. S-adenosyl methionine specifically protects the anticancer effect of 5-FU via DNMTs expression in human A549 lung cancer cells. Mol Clin Oncol 2013;1:373–8. [PubMed: 24649178]
9. Ebbing M, Bønaa KH, Nygård O, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, Njølstad I, Refsum H, Nilsen DW, Tverdal A, Meyer K, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 2009;302:2119–26. [PubMed: 19920236]
10. Brasky TM, White E, Chen C-L. Long-Term, Supplemental, One-Carbon Metabolism-Related Vitamin B Use in Relation to Lung Cancer Risk in the Vitamins and Lifestyle (VITAL) Cohort. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:3440–8.
11. Fanidi A, Carreras-Torres R, Larose TL, Yuan J-M, Stevens VL, Weinstein SJ, Albanes D, Prentice R, Pettinger M, Cai Q, Blot WJ, Arslan AA, et al. Is high vitamin B12 status a cause of lung cancer? Int J Cancer 2019;145:1499–503. [PubMed: 30499135]
12. Bassett JK, Hodge AM, English DR, Baglietto L, Hopper JL, Giles GG, Severi G. Dietary intake of B vitamins and methionine and risk of lung cancer. Eur J Clin Nutr 2012;66:182–7. [PubMed: 21878960]
13. Takata Y, Cai Q, Beeghly-Fadiel A, Li H, Shrubsole MJ, Ji B-T, Yang G, Chow W-H, Gao Y-T, Zheng W, Shu X-O. Dietary B vitamin and methionine intakes and lung cancer risk among female never smokers in China. Cancer Causes Control CCC 2012;23:1965–75. [PubMed: 23065072]
14. Johansson M, Relton C, Ueland PM, Vollset SE, Midttun Ø, Nygård O, Slimani N, Boffetta P, Jenab M, Clavel-Chapelon F, Boutron-Ruault M-C, Fagherazzi G, et al. Serum B vitamin levels and risk of lung cancer. JAMA 2010;303:2377–85. [PubMed: 20551408]
15. Hartman TJ, Woodson K, Stolzenberg-Solomon R, Virtamo J, Selhub J, Barrett MJ, Albanes D. Association of the B-vitamins pyridoxal 5’-phosphate (B(6)), B(12), and folate with lung cancer risk in older men. Am J Epidemiol 2001;153:688–94. [PubMed: 11282797]

16. Takata Y, Shu X-O, Buchowski MS, Munro HM, Wen W, Steinwandel MD, Hargreaves MK, Blot WJ, Cai Q. Food intake of folate, folic acid and other B vitamins with lung cancer risk in a low-income population in the Southeastern United States. Eur J Nutr 2019;
17. Yuan J-M, Stram DO, Arakawa K, Lee H-P, Yu MC. Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2003;12:890–8.
18. Hankin JH, Stram DO, Arakawa K, Park S, Low SH, Lee HP, Yu MC. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer 2001;39:187–95. [PubMed: 11759279]
19. Seow A, Shi CY, Franke AA, Hankin JH, Lee HP, Yu MC. Isoflavonoid levels in spot urine are associated with frequency of dietary soy intake in a population-based sample of middle-aged and older Chinese in Singapore. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 1998;7:135–40.
20. Seow A, Shi CY, Chung FL, Jiao D, Hankin JH, Lee HP, Coetzee GA, Yu MC. Urinary total isothiocyanate (ITC) in a population-based sample of middle-aged and older Chinese in Singapore: relationship with dietary total ITC and glutathione S-transferase M1/T1/P1 genotypes. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 1998;7:775–81.
21. Parkin DM, Whelan S, Ferlay J, Teppo L, Thomas D, eds. Cancer incidence in five continents. Vol. 8: Cancer incidence in five continents ; Vol. 8. Lyon: IARC Press, 2002. 781p
22. Seow WJ, Koh W-P, Jin A, Wang R, Yuan J-M. Associations between tea and coffee beverage consumption and the risk of lung cancer in the Singaporean Chinese population. Eur J Nutr 2019;
23. Kok DEG, Dhonukshe-Rutten RAM, Lute C, Heil SG, Uitterlinden AG, van der Velde N, van Meurs JBJ, van Schoor NM, Hooiveld GJEJ, de Groot LCPGM, Kampman E, Steegenga WT. The effects of long-term daily folic acid and vitamin B12 supplementation on genome-wide DNA methylation in elderly subjects. Clin Epigenetics 2015;7:121. [PubMed: 26568774]
24. Fanidi A, Carreras-Torres R, Larose TL, Yuan J-M, Stevens VL, Weinstein SJ, Albanes D, Prentice R, Pettinger M, Cai Q, Blot WJ, Arslan AA, et al. Is high vitamin B12 status a cause of lung cancer? Int J Cancer 2018;
25. Butler LM, Montague JA, Koh W-P, Wang R, Yu MC, Yuan J-M. Fried meat intake is a risk factor for lung adenocarcinoma in a prospective cohort of Chinese men and women in Singapore. Carcinogenesis 2013;34:1794–9. [PubMed: 23568952]
26. Butler LM, Montague JA, Koh WP, Wang R, Yu MC, Yuan J-M. Fish intake and lung cancer risk among Singapore Chinese. Cancer Res 72:Abstract nr 677. doi:1538–7445.AM2012–677.

Table 1.

Distributions of Baseline Characteristics among Study Participants, The Singapore Chinese Healthy Study, 1993 – 2015

Characteristics	Cases (n=2,001) n, %	Non-cases (n=59,313) n, %	P-value
Mean age (±SD), years	60.6 (7.7)	56.3 (8.0)	<0.0001
Gender (%)			<0.0001
Male	1,337 (66.8)	25,951 (43.7)	
Female	664 (33.2)	33,362 (56.3)	
Dialect)[a]			
Cantonese	827 (41.3)	27,495 (46.4)	<0.0001
Hokkien	1,174 (58.7)	31,818 (53.6)	
Highest level of education (%)			
No formal education	603 (30.2)	16,055 (27.1)	<0.0001
Primary school	1,031 (51.5)	26,189 (44.1)	
Secondary school or higher	367 (18.3)	17,069 (28.8)	
Mean body mass index (±SD), Kg/m^2	22.4 (3.1)	23.2 (3.3)	<0.0001
Smoking status (%)			
Never smoker	621 (31.0)	41,959 (70.7)	<0.0001
Former smoker	266 (13.3)	6,413 (10.8)	
Current smoker	1,114 (55.7)	10,941 (18.5)	
Number of cigarettes per day (±SD)	19.0 (11.6)	17.1 (11.4)	<0.0001
Number of smoking years (±SD)	39.0 (8.7)	32.5 (11.7)	<0.0001
Alcohol consumption (%)			
Non-drinkers	1,526 (76.3)	48,119 (81.1)	<0.0001
1 to <7 drinks/week	296 (14.7)	8,475 (14.3)	
≥7 drinks/week	180 (9.0)	2719 (4.6)	
Diabetes (%)			
No	1,861 (93.0)	53,984 (91.0)	0.0019
Yes	140 (7.0)	5,329 (9.0)	
Any weekly physical activity * (%)			
No	1,393 (69.6)	39,684 (66.9)	0.0096
Yes	608 (30.4)	19,629 (33.1)	
Mean total energy intake (±SD), Kcal	1,563.0 (582.5)	1,556.4 (565.7)	0.61
Vitamin B_{12} (±SD), μg /d	2.39±1.34	2.34±1.27	0.15
Dietary beta-cryptoxanthin (g/day)	221.7±334.4	254.3±324.3	<0.0001
Caffeine intake (Mean±SD)	178.1±120.3	147.3±108.6	<0.0001

* The weekly physical activity was defined as any moderate or vigorous activity, or strenuous sports lasting at least 30 minutes

Table 2.

Distributions of Baseline Characteristics among Study Participants by Dietary Vitamin B12 Intake, the Singapore Chinese Health Study, 1993–2015

	Total # Subjects (61,321)	1st Quintile 12,264 (20%)	2nd Quintile 12,264 (20%)	3rd Quintile 12,265 (20%)	4th Quintile 12,264(20%)	5th Quintile 12,264 (20%)	*P*-value
Vitamin B_{12} intake (μg/d), Mean±SD	2.33±0.89	1.19±0.43	1.89±0.12	2.28±0.11	2.70±0.14	3.61±0.71	
Mean age (±SD), years	61,321	56.49±7.91	56.730±8.04	56.51±8.07	56.34±7.95	55.91± 7.95	<0.0001
Gender (%)							
Male	27,293 (44.5)	7,094 (57.8)	5,294 (43.2)	4,912 (40.1)	4,760 (38.8)	5,233 (42.7)	<0.0001
Female	34,028 (55.5)	5,170 (42.2)	6,970 (56.8)	7,353 (59.9)	7,504 (61.2)	7,031 (57.3)	
Dialect							
Cantonese	28,325 (46.2)	6,399 (52.2)	5,712 (46.6)	5,522 (45.0)	5,336 (43.5)	5,356 (43.7)	<0.0001
Hokkien	32,996 (53.8)	5,865 (47.8)	6,552 (53.4)	6,743 (55.0)	6,928 (56.5)	6,908 (56.3)	
Highest level of education (%)							
No formal education	16,661 (27.2)	2,891 (23.6)	3,455 (28.2)	3,581 (29.2)	3,486 (28.4)	3,248 (26.5)	<0.0001
Primary school	27,224 (44.4)	5,748 (46.9)	5,426 (44.2)	5,321 (43.4)	5,446 (44.4)	5,283 (43.1)	
Secondary school or higher	17,436 (28.4)	3,625 (29.5)	3,383 (27.6)	3,363 (27.4)	3,332 (27.2)	3,733 (30.4)	
Mean body mass index (±SD), Kg/m^2	23.1 (3.3)	23.1 (3.2)	23.1 (3.2)	23.1 (3.2)	23.2 (3.3)	23.2 (3.3)	0.0006
Smoking status (%)							
Never smoker	42,583 (69.4)	7,866 (64.1)	8,708 (71.0)	8,748 (71.3)	8,754 (71.4)	8,507 (69.4)	<0.0001
Former smoker	6,681 (10.9)	1,775 (14.5)	1,276 (10.4)	1,256 (10.2)	1,155 (9.4)	1,219 (9.9)	
Current smoker	12,057 (19.7)	2,623 (21.4)	2,280 (18.6)	2,261 (18.4)	2,355 (19.2)	2,538 (20.7)	
Second hand smoking exposure*							
None	9,140 (17.9)	2,033 (19.8)	1,888 (18.4)	1,796 (17.7)	1,738 (17.0)	1,685 (16.6)	<0.001
Childhood exposure (<18 yrs)	3,538 (6.9)	830 (8.1)	666 (6.5)	702 (6.9)	678 (6.6)	662 (6.5)	
Adulthood exposure (≥ 18 yrs)	5,917 (11.6)	951 (9.3)	1,222 (11.9)	1,308 (12.9)	1,258 (12.3)	1,178 (11.6)	
Both childhood & adulthood exposure	32,453 (63.6)	6,446 (62.8)	6,498 (63.2)	6,342 (62.5)	6,557 (64.1)	6,610 (65.2)	
Alcohol consumption (%)							
Non-drinkers	49,650 (81.0)	9,652 (78.7)	10,018 (81.7)	10,214 (83.3)	10,044 (81.9)	9,722 (79.3)	<0.0001
1 to <7 drinks/week	8,772 (14.3)	1,871 (15.3)	1,700 (13.9)	1,550 (12.6)	1,718 (14.0)	1,933 (15.8)	
≥7 drinks/week	2,899 (4.7)	741 (6.0)	546 (4.4)	501 (4.1)	502 (4.1)	609 (4.9)	
Diabetes (%)							
No	55,852 (91.1)	11,398 (92.9)	11,263 (91.8)	11,166 (91.0)	11,106 (90.6)	10,919 (89.0)	<0.0001

	Total # Subjects (61,321)	1st Quintile 12,264 (20%)	2nd Quintile 12,264 (20%)	3rd Quintile 12,265 (20%)	4th Quintile 12,264(20%)	5th Quintile 12,264 (20%)	*P*-value
Yes	5,469 (8.9)	866 (7.1)	1,001 (8.2)	1,099 (9.0)	1,158 (9.4)	1,345 (11.0)	
Any weekly physical activity (%)							
No	41,083 (67.0)	7,857 (64.1)	8,269 (67.4)	8,393 (68.4)	8,458 (69.0)	8,106 (66.1)	<0.0001
Yes	20,238 (33.0)	4,407 (35.9)	3,995 (32.6)	3,872 (31.6)	3,806 (31.0)	4,158 (33.9)	
Mean total energy intake (±SD), Kcal	1,556.6 (566.2)	1,768.1 (569.5)	1,458.7 (507.0)	1,416.2 (506.6)	1,447.4 (506.8)	1692.7 (635.4)	<0.0001
Dietary beta-cryptoxanthin (g/day) (Mean±SD)	253.6 (334.7)	282.2 (395.9)	263.1 (320.3)	252.5 (292.8)	236.1 (281.5)	231.9 (316.6)	<0.001
Caffeine intake (±SD)	148.3 (108.9)	161.1 (112.2)	148.3 (107.3)	144.8 (106.9)	141.4 (104.8)	145.4 (113.0)	<0.0001

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Association Between Dietary Vitamin B12 Intake and Lung Cancer Risk in the Singapore Chinese Health Study, 1993–2015

	Person-years	Number of cases	HR (95% CI)[a]	HR (95% CI)[b]
Continuous Variable	1,081,732	2,001	**1.07 (1.01–1.12)**	**1.05 (1.01–1.12)**
Quintile Variable				
Q1 (lowest)	216,518	391	1.00	1.00
Q2	216,993	399	1.09 (0.95–1.26)	1.09 (0.95–1.25)
Q3	215,624	396	1.12 (0.97–1.29)	1.11 (0.96–1.28)
Q4	216,917	400	1.12 (0.97–1.29)	1.11 (0.97–1.29)
Q5 (highest)	215,740	416	**1.18 (1.03–1.36)**	**1.18 (1.03–1.35)**
P_{trend}			**0.02**	**0.03**

[a]Adjusted for age, sex, education, and dialect group. year of enrollment, cigarette smoking (number of years smoking, number of cigarettes per day, number of years since last smoked), total energy intakes (calories)

[b]Adjusted for age, sex, education, dialect group, year of enrollment, cigarette smoking (number of years smoking, number of cigarettes per day, number of years since last smoked), dietary beta-cryptoxanthin, caffeine intake, total energy intakes (calories)

Table 4.

Association Between Dietary Vitamin B12 Intake and Lung Cancer Risk among Participants Stratified by Selected Characteristics in the Singapore Chinese Health Study, 1993–2015[a]

	Person-years	Number of cases	HR[a] (95% CI)
By Smoking Status[a]			
Never Smoker			
Q1 (lowest)	144,612	115	1.00
Q2	159,836	122	0.98 (0.74–1.24)
Q3	160,557	141	1.15 (0.90–1.49)
Q4	161,126	130	1.07 (0.83–1.39)
Q5 (highest)	156,591	116	1.03 (0.80–1.34)
P_{trend}			0.52
Former Smoker			
Q1 (lowest)	29,370	58	1.00
Q2	20,504	55	1.24 (0.85–1.80)
Q3	19,718	59	1.36 (0.94–1.96)
Q4	18,331	49	1.23 (0.83–1.81)
Q5 (highest)	19,351	47	1.20 (0.81–1.77)
P_{trend}			0.36
Current Smoker			
Q1 (lowest)	42,532	220	Ref.
Q2	36,631	224	1.11 (0.92–1.33)
Q3	35,350	195	1.00 (0.82–1.21)
Q4	37,438	222	1.08 (0.88–1.30)
Q5 (highest)	39783	255	1.19 (0.99–1.42)
P_{trend}			0.12
$P_{interaction}$			0.565
By Gender[b]			
Male			
Q1 (lowest)	121,397	282	1.00
Q2	89,158	268	1.17 (0.99–1.39)
Q3	81,032	252	1.16 (0.98–1.38)
Q4	79,683	244	1.12 (0.94–1.33)
Q5 (highest)	86,825	295	**1.28 (1.09–1.51)**
P_{trend}			**0.01**
Female			
Q1 (lowest)	95,117	110	1.00
Q2	127,813	133	0.89 (0.68–1.14)
Q3	134,591	143	0.94 (0.73–1.22)
Q4	137,212	157	1.02 (0.79–1.31)

	Person-years	Number of cases	HR[a] (95% CI)
Q5 (highest)	128,900	123	0.91 (0.70–1.18)
P_{trend}			0.97
$P_{heterogeneiry}$			0.130
By Sub-types[a]			
Adenocarcinoma			
Q1 (lowest)	216;514	150	1.00
Q2	216;972	142	1.04 (0.83–1.32)
Q3	215;624	158	1.20 (0.96–1.51)
Q4	216;895	177	**1.34 (1.07–1.67)**
Q5 (highest)	215;725	166	**1.25 (1.00–1.57)**
P_{trend}			**0.006**
Squamous cell carcinoma			
Q1 (lowest)	216;514	68	1.00
Q2	216;972	82	1.35 (0.97–1.87)
Q3	215;624	77	1.28 (0.92–1.79)
Q4	216;895	65	1.08 (0.76–1.52)
Q5 (highest)	215;725	66	1.04 (0.74–1.47)
P_{trend}			0.71
Others			
Q1 (lowest)	216;514	174	1.00
Q2	216;972	177	1.04 (0.84–1.29)
Q3	215;624	160	0.97 (0.77–1.20)
Q4	216;895	158	0.95 (0.76–1.18)
Q5 (highest)	215;725	186	1.16 (0.94–1.43)
P_{trend}			0.37
$P_{heterogeneity}$			0.166
By Follow-up Period[a]			
≤2 years of follow-up			
Q1 (lowest)	24,377	19	1.00
Q2	24;342	28	1.49 (0.82–2.68)
Q3	24;309	34	**1.77 (1.00–3.13)**
Q4	24;315	34	**1.84 (1.04–3.26)**
Q5 (highest)	24;299	42	**2.34 (1.36–4.04)**
P_{trend}			**0.002**
>2 years of follow-up			
Q1 (lowest)	192;137	374	1.00
Q2	192;629	373	1.07 (0.93–1.24)
Q3	191,314	361	1.08 (0.93–1.25)
Q4	192;581	367	1.08 (0.93–1.25)
Q5 (highest)	191;426	376	1.12 (0.97–1.29)

	Person-years	Number of cases	HR[a] (95% CI)
P_{trend}			0.15
$P_{interaction}$			0.168

[a]Adjusted for age, sex, education, dialect group, year of enrollment, cigarette smoking (number of years smoking, number of cigarettes per day, number of years since last smoked), dietary beta-cryptoxanthin, caffeine intake, fried meat intake total energy intakes (calories)

[b]Adjusted for age, education, dialect group, year of enrollment, cigarette smoking (number of years smoking, number of cigarettes per day, number of years since last smoked), dietary beta-cryptoxanthin, caffeine intake, total energy intakes (calories)