


Association of various dietary habits and risk of lung cancer: an updated comprehensive literature review

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Abstract

Lung cancer remains the leading cause of cancer death in both men and women worldwide. Tobacco smoking remains the single most important factor. Recent research has focused on the role of nutrition and dietary habits on lung tumorigenesis. With many individual reports on separate dietary aspects, no single review is available in the literature that summarizes the updated studies. To our knowledge, this is the first review that comprehensively reviews the updated literature on the effect of dietary habits on lung cancer. This review was concluded in February 2019 and included all meta-analyses, systematic reviews, and literature reviews. Thirty studies were retrieved in total. Items in the diet that offer a protective effect on lung parenchyma are fruits, vegetables, fish, nuts, soy, B vitamins, vitamin D, vitamin E, vitamin C, and zinc. Changing dietary habits to decrease the risk of lung cancer can be performed in parallel with smoking cessation programs. There is a need for future studies with large sample sizes to accurately evaluate some aspects of nutrition and their effect on lung cancer risk. Physicians are encouraged to provide nutritional advice to their patients.

Keywords

Epidemiology and prevention, hematology–oncology, thoracic oncology

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Introduction

Lung cancer continues to be the leading cause of cancer death in both men and women, claiming 1.59 million lives worldwide in 2012.^{1–3} The estimated number of new lung cancer cases in 2018 is 234,030 in the United States alone and it is projected that lung cancer remains the second most common cancer in men, after prostate cancer, and women, after breast cancer.⁴ Lung cancer is divided into 2 major histologic subtypes: non-small cell lung cancer, around 85% of cases, and small cell lung cancer, around 15% percent of cases.⁵ The different geographical patterns and increasing incidence rates vary for men and women and this reflects historical, regional, and cultural differences. The risk factors known to be associated with lung carcinogenesis include demographic, genetic, environmental, and behavioral ones.^{3,6}

Because of the lung's direct contact with the environment, it remains a major target organ for injuries arising from environmental pollution. The use of tobacco-containing products remains the single most important risk factor

in the development of lung cancer. Tobacco consumption burns no less than 60 different carcinogens, which in turn produce a large number of free radicals capable of inflicting gene damage. The outcome of this oxidative stress is damage to the DNA such as single- and double-stranded breaks and alterations in genomic processing.^{7,8}

Recent research has focused on the role nutrition plays in preventing or altering the risk of developing cancer. Dietary habits play an important role in lung cancer development and maintenance. Research has found that high intake of fruits, vegetables, and fish reduces risk of lung

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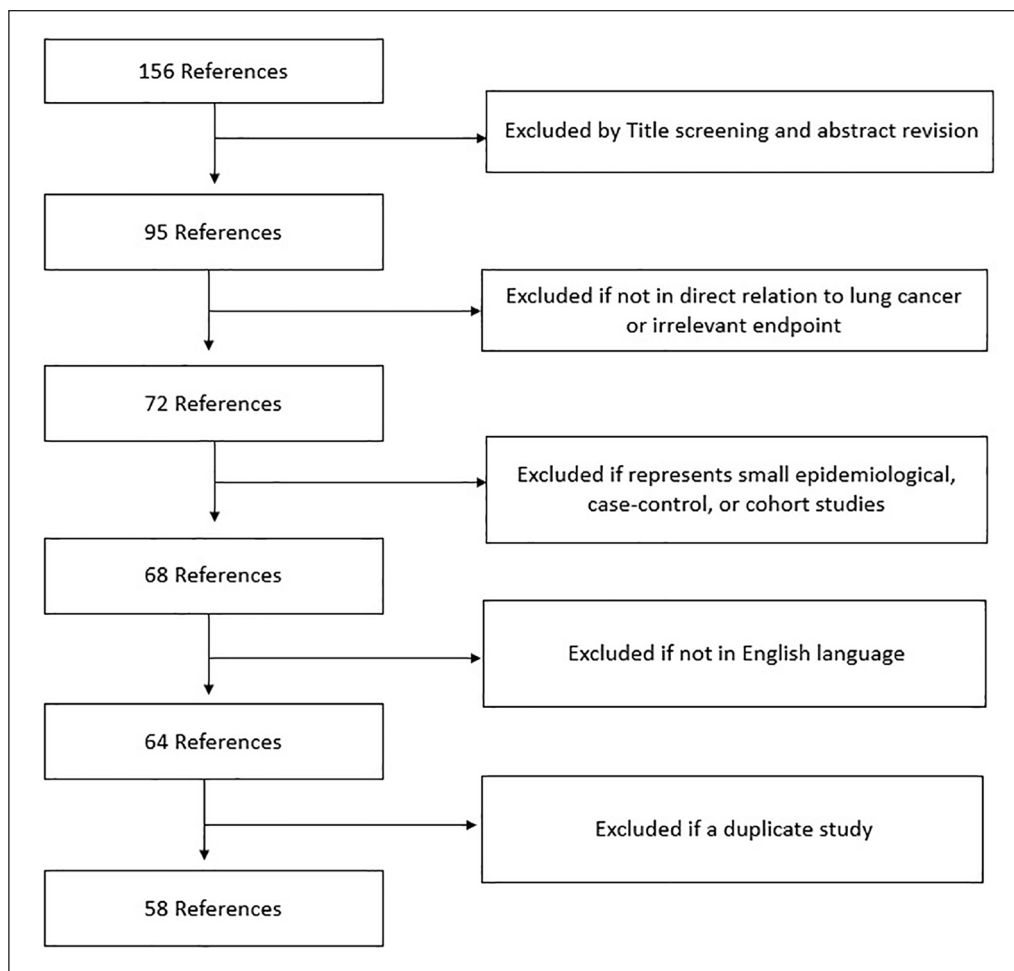


Figure 1. Literature review flow chart.

cancer, whereas intake of red meat and processed foods increases it.⁹⁻¹¹ Results have been inconsistent, with some clinical trials testing the effect of vitamins and other supplements failing to prove the existence of a protective effect on the lungs.^{12,13} Research has published data reviewing a few aspects of the diet and their association with lung cancer risk. To our knowledge, no data have been published that comprehensively review the updated literature for all aspects of nutrition and their relation to reducing or increasing lung cancer risk.

Methods

This review was conducted in February 2019. The search was conducted in accordance with the checklist of the Association of American Medical Colleges for review articles. The literature review is up to date and articles were critically appraised for validity and relevance. A comprehensive search was conducted in PubMed, Medline, and Google Scholar for the presence of gray literature. Articles were included if they were published in the English language and reported on the correlation between lung cancer

and all items of nutrition or diet. No limitations were made on year of publication or country of origin. The search strategy consisted of 2 concepts. The first concept regarding lung cancer was searched using MeSH terms and keywords for the following: lung cancer, lung tumor, lung oncology, lung adenocarcinoma, lung neoplasm, or non-small cell. The second concept was regarding diet and was searched using the following terms: diet, nutrition, food, fruit/s, vegetable/s, vitamin/s, meat/s, fish, fat, fatty, dairy, mineral/s, legume/s, bean/s, nut/s, phytochemical/s, phytoestrogen/s, and soy. Studies published for every aspect of nutrition were categorized separately. Priority was given to meta-analyses, systematic reviews, and literature reviews for every aspect. When those were unavailable, pooled data and large prospective studies were analyzed instead (Figure 1).

Results

The following is an item-by-item description of the medical literature that evaluated the effect of specific dietary elements on the risk of developing lung cancer.

Table 1. Systematic reviews and meta-analyses on food and outcome measures.

Authors, year	Variable	Outcome measure, 95% CI	Conclusion
Wu et al., 2013 ¹⁶	Cruciferous vegetables	RR: 0.75, 0.63–0.89	Decreased risk
Wang et al., 2015 ¹⁰	Vegetables	RR: 0.90, 0.84–0.96	Decreased risk
	Fruits	RR: 0.84, 0.79–0.90	Decreased risk
Wang et al., 2015 ¹⁷	Vegetables	RR: 0.74, 0.67–0.82	Decreased risk
	Fruits	RR: 0.80, 0.74–0.88	Decreased risk
Vieira et al., 2016 ¹⁸	Vegetables	RR: 0.92, 0.87–0.97	Decreased risk
	Fruits	RR: 0.82, 0.76–0.89	Decreased risk
Yang et al., 2012 ²¹	Red meat	RR: 1.35, 1.08–1.69	Increased risk
	Fish	RR: 1.01, 0.96–1.07	No effect
	Total white meat	RR: 1.06, 0.82–1.37	No effect
	Poultry	RR: 0.89, 0.84–0.95	Decreased risk
Xue et al., 2014 ²³	Red meat	RR: 1.44, 1.29–1.61	Increased risk
	Processed meat	RR: 1.23, 1.10–1.37	Increased risk
Gnagnarella et al., 2018 ²⁴	Red meat	RR: 1.24, 1.01–1.51	Increased risk
	Fish	RR: 0.92, 0.73–1.15	No effect
	White meat	RR: 1.04, 0.74–1.46	No effect
Song et al., 2014 ¹¹	Fish	RR: 0.79, 0.69–0.92	Decreased risk
Yu et al., 2016 ³³	Total dairy	RR: 0.96, 0.89–1.03	No effect
	Milk-only	RR: 0.95, 0.76–1.15	No effect
Yang et al., 2016 ³⁴	Total dairy	RR: 1.05, 0.84–1.31	No effect
	Milk-only	RR: 1.08, 0.80–1.46	No effect
	Cheese-only	RR: 0.83, 0.62–1.12	No effect
	Yogurt-only	RR: 0.88, 0.62–1.25	No effect
Yang et al., 2017 ⁴⁸	Total fat	HR: 1.07, 1.00–1.15	Increased risk
	Saturated fat	HR: 1.14, 1.07–1.22	Increased risk
	PUFA	HR: 0.92, 0.87–0.98	Decreased risk
	PUFA	RR: 0.91, 0.78–1.06	No effect
Zhang et al., 2014 ⁴⁷	PUFA	HR: 0.85, 0.73–1.00	Decreased risk
Luu et al., 2018 ⁴⁹	Saturated fat	HR: 1.00, 0.85–1.17	No effect
Yang et al., 2012 ⁵⁵	Phytoestrogens	RR: 0.83, 0.72–0.96	Decreased risk
Yang et al., 2011 ⁵³	Soy	RR: 0.77, 0.65–0.92	Decreased risk

CI: confidence interval; HR: hazard ratio; PUFA: polyunsaturated fatty acids; RR: relative risk.

Fruits and vegetables

Recent data have hypothesized that intake of fruits and vegetables can modify the risk for cancer development through enhancing the effect of detoxifying enzymes such as glutathione-S-transferases. In 2007, early reports from the World Cancer Research Fund (WCRF) published raw data suggesting a probable protective effect of fruits with limited data on the role of vegetables.¹⁴ The European Prospective Investigation into Cancer (EPIC) closely studied the relationship between lung cancer and fruit and vegetable consumption. In smokers, the risk of squamous cell carcinoma of the lung was slightly reduced but residual confounding from smoking was not ruled out. EPIC reported that there is an inverse relationship between consuming a variety of fruits and vegetables and lung cancer risk.¹⁵ Numerous systematic reviews and meta-analyses were published to further quantify the accumulated data.^{10,16–18} The data from these meta-analyses point to the fact that consumption of fruits and/or vegetables confers a protective effect on lung parenchyma (Table 1).

Meat

Global meat consumption has more than doubled in the last 2 decades, mostly due to an expanding population and increasing demands on food supplies. Historically, high intake of red meat has been linked to increased incidence of cardiovascular diseases, diabetes, and cancer. Red meat has been classified as Group 2A (probably carcinogenic) and processed meat has been classified as Group 1 (carcinogenic).¹⁹ It has been hypothesized that the cooking process of meat releases heterocyclic amines and polycyclic aromatic hydrocarbons, both of which have the ability to cause mutagenesis. In relation to red meat consumption, the hypothesis was that red meat contains high quantities of heme iron that acts as a prooxidant and catalyzes lipid peroxidation and expedites DNA damage. In addition, nitroso-related compounds are found in most types of processed meats and have been linked to increased incidences of cancer through prooxidant genetic alteration.²⁰ WCRF concluded that the positive association between intake of red meat and processed meat with lung cancer risk is only suggestive but

not sufficient while other cohort studies reported positive associations.^{14,21,22} Multiple reports from meta-analyses concluded that red meat and processed meat consumption increased the risk of lung cancer^{21,23,24} (Table 1).

Fish

Research examining the link between lung cancer risk and fish consumption dates to the late 1990s. Compared with never-consumers, data show that consumption of 60 g or more of fish per day is associated with a 12% decrease in all-cause mortality.²⁵ Fish and fish oil have abundant levels of N-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid, and docosahexaenoic acid. These molecules are known to exert inhibitory effects on carcinogenesis by inhibiting angiogenesis and damaging mitochondrial DNA of tumor cells.²⁶ Zhang et al.²⁷ reported an inverse relationship between fish consumption and the risk of lung cancer in men as well as a decreased mortality from lung cancer. Takezaki et al.²⁸ reported a statistically significant decreased risk for men and women with adenocarcinomas (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.31–0.84; and OR, 0.48; 95% CI, 0.24–0.94, respectively). As such, the evidence shows that a diet rich in fish decreases the risk of lung cancer, a link further confirmed by a recent meta-analysis¹¹ (Table 1).

Whereas data are sufficiently present regarding red and processed meat, the relationship of white meat and lung cancer has not been widely reported. White meat (poultry and fish) has been proposed, in earlier epidemiologic studies, to decrease the risk of lung cancer. This has been speculated mostly because of the lower heme iron content and the presence of long-chain omega-3 polyunsaturated fatty acids abundant in fish.²¹ The WCRF concluded that the evidence of white meat in relation to lung cancer is too limited to draw any conclusion in its regard.¹⁴ Combined data from meta-analyses revealed that poultry decreased the risk of lung cancer while other categories of white meat did not^{21,24} (Table 1).

Dairy products

Dairy products are nutrient-rich foods containing fatty acids, vitamins, minerals, and bioactive constituents that can influence cancer initiation and maintenance.²⁹ In its report in 2007, the WCRF concluded that there is insufficient evidence to link calcium, milk, and other dairy products to lung cancer risk.¹⁴ Milk was historically known for its beneficial effect on the body, but earlier studies reported conflicting results on its ability to increase overall mortality and lung cancer risk.^{30–32}

Earlier studies found conflicting results on the effect of milk, cheese, or yogurt on lung tumorigenesis. The effects of the constituents of dairy products on human health remain controversial. On one hand, some epidemiologic

studies reveal a protective effect of dairy on lung cancer risk. On the other hand, other studies argue that the high content of lactose in milk specifically can promote oxidative stress which, in turn, leads to chronic inflammation and tissue injury. Earlier prospective studies and the 2 meta-analyses found that the intake of dairy products in general or milk, cheese, or yogurt individually was not significantly associated with lung cancer risk^{33,34} (Table 1).

Legumes

A diet rich in legumes is diverse and includes beans, lentils, peanuts, and peas, among others. Their ability to incur protective cardiovascular and respiratory effects stems mostly from their high concentration of soluble fibers.³⁵ Moreover, legumes have high levels of vitamins, minerals, and selenium, all of which have potential anticancer and anti-inflammatory properties. High legume intake was recently linked to reduced levels of interleukin-6 and C-reactive protein.³⁶ While numerous studies have examined the link between a legume-rich diet and the risk of many cancers, little evidence is present regarding the risk of lung cancer. One large multicenter case-control study reported similar findings, where the OR for high consumers of legumes was 1.1 (95% CI, 0.9–1.3) as compared to low-to-never consumers.³⁷ A large cohort study in the early 2000s did not report a significant association between legume intake and lung cancer risk. The reported OR for high consumers was 1.12 (95% CI, 0.69–1.82).³⁸ No systematic reviews or meta-analyses have been published on this link to date. From the available literature, it seems that a diet rich in legumes does not add protective benefits on the lungs.

Nuts

Nuts are known for their antioxidant and anti-inflammatory effects. There is growing evidence on their protective effects on numerous chronic diseases by affecting the production of cytokines and protecting against oxidative DNA damage, but only limited data exist on nut consumption and lung cancer risk.^{39–41} In the Environment and Genetics in Lung Cancer Etiology (EAGLE) study, individuals with the highest intake of nuts had a statistically significant 26% lower risk of developing lung cancer (OR, 0.74; 95% CI, 0.57–0.95).⁴² Moreover, in the American Association of Retired Persons (AARP) study, individuals who consumed the highest amount of nuts had a statistically significant 14% lower risk to develop lung cancer (OR, 0.86; 95% CI, 0.81–0.91).⁴³ This has been further affirmed by a large case-control study in 2019 where it was reported that increased total nut intake is related to a significantly reduced risk of small cell carcinoma in men, after controlling for smoking.⁴¹ It seems reasonable that the evidence demonstrates the beneficial effect of nut intake on lung cancer risk.

Fat-rich foods

PUFA are known to be important in maintaining cell functions, homeostasis, cell growth, and viability. Early studies have demonstrated that PUFA have antineoplastic activities especially in lung cancer cell cultures.¹¹ Evidence on fish oil showed that supplements may be inversely associated with lung cancer development.⁴⁴ In 1994, it was established that plant-derived fat intake was associated with 30%–40% lower incidence of lung cancer (relative risk [RR], 0.6; 95% CI, 0.4–0.9).^{45,46} Data from the 3 meta-analyses confirm the advantage PUFA have on lung parenchyma in contrast to saturated fats^{47–49} (Table 1).

Phytochemicals

Dietary phytochemicals, including flavonoids and phytoestrogens, are plant-derived compounds with natural estrogen-like and antioxidant activities. They are present in a variety of dietary sources such as soy products, tea, chickpeas, spinach, broccoli, grains, and carrots.⁵⁰ The proposed mechanism for their role in cancer prevention is that parenchymal lung cells and tumor cells express estrogen receptors and upon binding of normal estrogen, cell proliferation is triggered. The binding of estrogen-like molecules competes with estrogen and antagonizes its effect.⁵¹ While numerous epidemiologic studies have supported the active role phytoestrogens play in preventing breast and prostate cancers, data on lung cancer risk are very limited. A recent case-control study by Schabath et al.⁵² reported that consumption of phytoestrogens was statistically significantly higher in healthy patients than in patients with lung cancer (OR, 0.54; 95% CI, 0.42–0.70). This has been further replicated in the Shanghai Women's Health Study, where the authors reported that intake of phytoestrogens was associated with a 40% decrease in the risk of lung cancer in non-smoking women (HR, 0.63; 95% CI, 0.44–0.90) as well as improved survival.^{53,54} The accumulated evidence was further supported by 2 meta-analyses that concluded that soy food intake reduces the risk of lung cancer^{53,55} (Table 1).

Vitamin A

Beta-carotenes and vitamin A derivatives are natural retinoids that exist in eggs, butter, grains, and highly pigmented vegetables such as carrots and squash. Retinoid molecules exhibit antiproliferative traits such as cell growth arrest and promotion of differentiation and were historically used to treat lung diseases.^{56,57} The Alpha-tocopherol, Beta-carotene Cancer Prevention study (ATBC) provided early evidence that supplementation with beta-carotene did not prevent lung cancer.⁵⁸ With the growth of the substantial interest in the role vitamin A plays in preventing lung carcinogenesis, 3 meta-analyses were published on the subject, with only one of them

demonstrating a beneficial effect of vitamin A intake on reducing the risk of lung cancer.^{13,59,60} While the precise mechanisms that can explain the discrepancy in the results have yet to be elucidated, the overall conclusion was that the association between beta-carotene or vitamin A intake and lung cancer risk was strong enough to confer a beneficial effect on lung cancer risk (Table 2).

Vitamin B

B vitamins are a class of water-soluble vitamins that play vital roles in cell metabolism. Found abundantly in meat, they are also found in legumes, whole grains, bananas, and vegetables.⁶¹ Previous studies have ascertained the fact that smokers have lower levels of circulating folate and vitamin B₆ and that intake of B vitamins could reverse metaplasia.^{12,62} In the EPIC study, a lower risk for lung cancer was seen for patients with elevated serum levels of vitamin B₆ (OR, 0.44; 95% CI, 0.33–0.60), and folate (OR, 0.68; 95% CI, 0.51–0.90).⁶³ This has been replicated in the ATBC and the Lung Cancer Cohort Consortium (LC3) studies, which confirmed the protective effect of high serum folate and B₆ versus dietary intake on lung cancer development.^{64,65} Without systematic reviews and meta-analyses, it is difficult to fully understand the effect of B vitamins on protecting against lung cancer. However, from the available literature, it is reasonable to believe that the higher the serum levels of vitamin B₆ and folate, the lower the risk of lung cancer.

Vitamin D

Vitamin D is a group of fat-soluble steroids responsible for a wide variety of biological processes including bone metabolism, immune system modulation, angiogenesis, and regulation of cell proliferation. Early studies have supported the beneficial effect of vitamin D on lung cancer prevention.^{66,67} Five meta-analyses were published between 2015 and 2018 to further clarify the accumulated evidence (Table 2). The overall conclusion is that a high serum vitamin D level as well as high intake of vitamin D can reduce the risk of lung cancer with a strong dose–response association. In addition, incremental increase in serum vitamin D levels reduced mortality from lung cancer.^{68–72}

Vitamin E

Vitamin E represents a group of lipid-soluble antioxidant components of the body's defense system that are exclusively obtained from the diet. The main role of vitamin E is prevention of oxidative stress normally produced by the body.⁷³ Data from the WCRF and ATBC demonstrated that there is limited evidence to suggest that dietary antioxidants have a role in reducing the risk of lung cancer.^{14,58} On the other hand, large pooled data analysis from 430,281

Table 2. Systematic reviews and meta-analyses on different vitamins and outcome measures.

Authors, year	Variable	Outcome measure, 95% CI	Conclusion
Gallicchio et al., 2008 ¹³	Dietary beta-carotene	RR: 1.10, 0.89–1.36	Decreased risk
	Dietary total carotene	RR: 0.79, 0.71–0.87	Decreased risk
Omenn et al., 1996 ⁵⁹	Dietary vitamin A	RR: 1.28, 1.04–1.57	No effect
Yu et al., 2015 ⁶⁰	Dietary vitamin A	RR: 0.85, 0.73–0.98	Decreased risk
	Dietary beta-carotene	RR: 0.76, 0.67–0.87	Decreased risk
Zhang et al., 2015 ⁶⁸	Dietary vitamin D	RR: 0.89, 0.74–1.06	No effect
Chen et al., 2015 ⁶⁹	Serum vitamin D	RR: 0.96, 0.94–0.99	Decreased risk
Liu et al., 2017 ⁷⁰	Dietary vitamin D	OR: 0.89, 0.83–0.97	Decreased risk
	Serum vitamin D	OR: 0.93, 0.87–1.00	Decreased risk
Feng et al., 2017 ⁷¹	Serum vitamin D	RR: 0.84, 0.74–0.95	Decreased risk
Wei et al., 2018 ⁷²	Serum vitamin D	RR: 1.04, 0.94–1.15	No effect
	Dietary vitamin D	RR: 0.85, 0.74–0.98	Decreased risk
Chen et al., 2015 ⁷⁴	Dietary vitamin E	RR: 0.85, 0.74–0.99	Decreased risk
Zhu et al., 2017 ⁷⁵	Dietary vitamin E	RR: 0.84, 0.76–0.93	Decreased risk
Luo et al., 2014 ⁷⁷	Dietary vitamin C	RR: 0.82, 0.73–0.93	Decreased risk

CI: confidence interval; OR: odds ratio; RR: relative risk.

Table 3. Systematic reviews and meta-analyses on minerals and outcome measures.

Authors, year	Variable	Outcome measure, 95% CI	Conclusion
Yang et al., 2016 ³⁴	Dietary calcium	RR: 0.85, 0.63–1.13	No effect
Song et al., 2018 ⁸⁷	Serum magnesium	SMD: 0.19, 1.50–1.89	No effect
Fonseca-Nunes et al., 2014 ⁹²	Dietary heme iron	RR: 1.12, 0.98–1.29	Increased risk
Zhang et al., 2018 ⁹³	Serum copper	SMD: 1.10, 1.04–1.16	Increased risk
Fritz et al., 2011 ⁹⁸	Dietary selenium	OR: 0.93, 0.61–1.43	No effect

CI: confidence interval; OR: odds ratio; RR: relative risk; SMD: standard mean difference.

participants demonstrated that higher vitamin E intake was inversely associated with lung cancer risk (RR 0.89, 95% CI 0.78–1.01).¹² This association was further ascertained by 2 meta-analyses that reported that a strong inverse relationship exists between vitamin E intake and lung cancer risk.^{74,75} Despite limited data in the literature, the 2 meta-analyses suggest a strong relationship between high vitamin E intake and reduced lung cancer risk (Table 2).

Vitamin C

Vitamin C is one of the most vital antioxidant vitamins present abundantly in fruits and vegetables capable of modulating immunity as it protects against DNA damage. To date, several epidemiologic studies have been published on the relationship of vitamin C and lung cancer risk and suggested a protective effect.^{76–78} One meta-analysis analyzed the results of prospective cohort studies and suggested a protective effect of dietary vitamin C on lung cancer risk (Table 2). In addition, a statistically significant dose–response association existed with each incremental increase of vitamin C intake.⁷⁷ With scarce data on the topic, the available literature is tending towards a beneficial effect of vitamin C intake on lung carcinogenesis.

Calcium

Dairy products are rich in calcium. While several studies have reported profound associations between calcium intake and colon and prostate cancers, studies in lung cancer have showed mixed results.^{79–81} In a large prospective study by Mahabir et al.,⁸² calcium intake was found to be protective against lung cancer for both smokers and non-smokers. Moreover, another large cohort study reported a higher mortality benefit in patients ingesting 800–1,000 mg/d of supplemental calcium.⁸³ One meta-analysis failed to report similar associations³⁴ (Table 3). The effects of calcium on lung carcinogenesis remain controversial due to the complexity of the process. The underlying mechanism is unclear, especially that calcium intake modifies the concentration of 1,25-OH₂ (D) serum levels.

Magnesium

Early studies have investigated the link between magnesium intake and lung cancer risk, yielding mixed results.^{82,84,85} A protective association was supported by evidence that minerals, especially magnesium, strengthen the body's response to DNA repair after damage.⁸⁶ A recent

large cohort study negated that idea and suggested a 21% increased risk for lung cancer in participants with the largest intake of magnesium.⁸² Along the same lines, 1 meta-analysis failed to find a protective association⁸⁷ (Table 3). To date, no meta-analyses exist on dietary magnesium intake and lung cancer. Other cohort studies with larger sample sizes are needed to properly assess the role of magnesium in lung carcinogenesis.

Zinc

Zinc is a necessary mineral with antioxidant effects essential to the human body as it is a cofactor for essential enzymes such as superoxide dismutase responsible for protecting against free radicals. Early studies have attributed an increased risk of lung cancer in patients with a low dietary intake of zinc.^{82,86,88} Mahabir et al.⁸⁸ reported that increased dietary intake of zinc was associated with a decreasing risk of lung cancer, with a 20%, 36%, and 43% significant reduction in risk with increasing quartile of intake (OR, 0.57 [95% CI, 0.42–0.75]). This has been confirmed by another large prospective study by Zhou et al.,⁸¹ where intake of dietary zinc was associated with a decreased risk of lung cancer (adjusted OR, 0.46 [0.31–0.68]). Similar associations were published in the Iowa Women's Health Initiative (IWHI) study. The authors reported that a diet high in zinc decreases the risk of lung cancer among postmenopausal women who consume high doses of vitamin C.⁷⁶ To date, no systematic review or meta-analysis has been performed to further clarify the role dietary or supplemental zinc plays in lung carcinogenesis. Nonetheless, the literature review suggests a clear protective role for zinc intake on lung parenchyma.

Iron

Iron is critical for several aspects of cellular and molecular function. On the other hand, it is capable of damaging biological molecules and generating reactive oxygen species and other forms of free radicals that can damage lipid membranes and DNA of pulmonary cellular nuclei.^{81,89} Iron can be categorized into 2 major subtypes: heme and nonheme iron. Heme iron is found mainly in animal products such as red meat. Nonheme iron is present in other dietary sources such as legumes and vegetables.⁹⁰ In lung cancer specifically, there is evidence that heme iron is present in sufficiently high amounts to support cancer cell progression.⁹¹ Zhou et al.⁸¹ reported a higher risk of lung cancer in participants with a higher total iron intake (OR, 2.06; 95% CI, 1.31–3.24). Data from IWHI supported this evidence, with an RR of 1.27 (95% CI, 0.67–2.40).⁷⁶ Moreover, data from the EPIC study reported a 16% increased risk for lung cancer in participants receiving larger amounts of heme iron (HR, 1.16; 95% CI, 1.02–1.32).⁹⁰ On the other hand, a protective trend was

suggested by Mahabir et al.,⁸² who reported an RR of 0.87 (95% CI, 0.73–1.03). Finally, one meta-analysis pointed more evidence towards the harmful effects of heme iron on lung tumorigenesis⁹² (Table 3). The current literature review suggests that heme iron specifically confers a harmful effect on lung cancer development.

Copper

Copper is an essential dietary trace element and a critical component of enzymes that are responsible for DNA integrity and protection from oxidative stress.⁸⁸ Case-control studies have suggested that copper plays an important role in protecting against lung cancer.^{82,86,88} Mahabir et al.⁸⁸ reported that with each increased quartile intake of dietary copper there was a 41%, 49%, and 66% lower risk of lung cancer, respectively (OR, 0.34 [95% CI, 0.26–0.45]). Zhang and Yang⁹³ published a meta-analysis on serum copper levels (Table 3), where they reported that patients with lung cancer had higher levels of serum copper. Overall, while earlier case-control studies suggested that copper has a protective role on lung parenchyma, pooled data from the meta-analysis proposed otherwise. One hypothesis to explain the result may be related to the fact that copper is associated with ceruloplasmin, which is found in higher in concentration in patients with malignant tumors.^{93,94}

Selenium

Selenium is an essential trace element and a key component of many enzymes such as glutathione peroxidase responsible for removing hydrogen peroxides generated by free radicals.⁹⁵ In 1996, the Nutritional Prevention of Cancer study showed that intake of 200 μ m of selenium daily decreases total cancer incidence by 47% and lung cancer incidence by 46% (RR, 0.54; 95% CI, 0.30–0.98).⁹⁶ A recent review of the epidemiologic evidence from serum, toenail, and dietary selenium found a significantly reduced risk of lung cancer with higher selenium exposure (RR, 0.74; 95% CI, 0.57–0.97).⁹⁷ In the large case-control study by Mahabir et al.,⁸⁸ no significant associations were present between dietary selenium intake and risk of lung cancer. One meta-analysis reported that there was a lack of a significant effect of selenium on lung cancer risk (Table 3).⁹⁸ More studies are needed to evaluate the effect of selenium on lung cancer risk properly and accurately. Nonetheless, earlier cohort studies have shown promising effects.

Discussion

Proper assessment of the potential effects different dietary components have on the risk of lung cancer is crucial. This assessment plays a role in future implementation of recommendations for healthy choices and lifestyle changes. Early on, the WCRF looked at data regarding

consumption of fruits and vegetables and its relation to decreasing the risk of lung cancer. The end result was that their effects were only probably protective.¹⁴ This was commensurate with the results from the EPIC study, which added that this protective effect was restricted to smokers only.¹⁵ Afterwards, 4 meta-analyses were published in regard to consumption of fruits and vegetables and the risk of lung cancer. Collectively, a significant decrease in lung cancer was noted upon high intake of fruits and vegetables in the diet.

As for red meat, the WCRF did not find conclusive evidence in 2007 to link red meat consumption to an increase in lung cancer risk. Prior to 2012, epidemiologic studies and small case-control studies failed to affirm the link between red meat and lung cancer.^{14,19,20} In 2012, the first meta-analysis reported that high intake of red meat was significantly associated with a 35% increase in the risk of lung cancer.²¹ A dose-response meta-analysis was published 3 years later reporting that consumption of 120 grams of red meat per day might increase the risk of lung cancer by 35% while intake of 50 grams of processed meat might increase the risk by 20%.²³ While the evidence points to the harmful effect red and processed meats have on lung parenchyma, white meat has not been studied as extensively. Yang et al.²¹ and Gnagnarella et al.²⁴ did not find evidence of white meat consumption effect on lung cancer risk.

Historically, fish and fish oil were considered a healthy addition to one's diet, with beneficial effects on the human body. Earlier epidemiologic studies reported a clear inverse relationship between fish intake and lung cancer risk in addition to a decrease in mortality rates.^{26,27} One meta-analysis by Song et al.¹¹ further confirmed the relationship while Yang et al.²¹ and Gnagnarella et al.²⁴ did not find a significant association. In general, there is solid evidence regarding the protective effect on the lungs of fish intake.

The cornerstone of most dairy products is milk. Some epidemiologic studies pointed to milk's ability to increase mortality in general and lung cancer risk.³⁰⁻³² However, this was later refuted by WCRF meta-analysis.¹⁴ Even after adjusting for age and smoking status, the meta-analysis by Yu et al.³³ did not find a significant association. Similar negative results were reported by Yang et al.³⁴ in the meta-analysis that followed. Subgroup analysis for cheese and yogurt did not reveal positive associations. Overall, earlier prospective studies and 2 meta-analyses found that the intake of dairy products, including total dairy, milk, cheese, or yogurt, was not significantly associated with lung cancer risk.

Limited data exist on legumes and their effect on lung cancer risk specifically. The available literature does not report a significant association between them. With absent meta-analyses or systematic reviews, it can be assumed that no protective effect is incurred by legume-rich diet on lung parenchyma.^{37,38}

The consumption of nuts was a subject for research on cancer for a long time. However, there are no meta-analyses or systematic reviews to date that further examine the association between nuts and lung cancer risk. Epidemiologic studies like the EAGLE and the AARP studies have reported solid evidence with a statistically significant reduction in lung cancer risks in individuals with high consumption of nuts.^{42,43}

As for fat in the diet, consumption was linked to an increase in all types of lung cancer with a dose-response pattern. In recent meta-analyses, fatty acids were further categorized into PUFA and saturated fats. Collectively, saturated fat was reported to increase the risk of lung cancer, while intake of PUFA had the opposite effect.⁴⁷⁻⁴⁹

Data on phytoestrogens and their effect on lung tissue remain limited. However, from the available literature, it can be suggested that they significantly reduce the risk of lung cancer, as is evident in 2 meta-analyses by Yang et al.^{53,55} in 2011 and 2012. In addition, earlier studies have reported a decrease in lung cancer risk in individuals with high intake of phytoestrogen-containing food.⁵²⁻⁵⁵ Substantial interest was present in the role vitamin A and its derivatives play in lung tumorigenesis. This is mostly because of its historic use as a treatment. Earlier studies did not find strong evidence of its protective effect on lung tissue. While Omenn et al.⁵⁹ confirmed this, Gallicchio et al.¹³ and Yu et al.⁶⁰ later reported that a diet rich in vitamin A or its derivatives is likely to reduce lung cancer risk. The evidence is strong regarding its protective effect on lung tissue. As for vitamin B, there were no meta-analyses to accurately assess its association with lung cancer risk. However, early studies such as the EPIC, ATBC, and LC3 studies have all reported a protective effect. In addition, individuals with higher serum vitamin B levels were less likely to develop lung cancer. The accumulated evidence suggests that B complex vitamins have a protective role on lung tissue.⁶³⁻⁶⁵

Early studies have supported the notion behind sun exposure leading to a decrease in cancer rates. Observational and case-control studies have further affirmed the association. The first meta-analysis was performed by Zhang et al. in 2015,⁶⁸ where the authors concluded that a high serum vitamin D level was associated with a statistically significant decrease in lung cancer risk, but high vitamin D supplementation was not. Chen et al.⁶⁹ later reported that there is a 5% statistically significant reduction in risk of lung cancer with each 10 nmol/L increment in 25(OH)D concentrations. Liu et al.⁷⁰ also studied this association and reported similar results where a serum high in vitamin D or a diet rich in vitamin D can reduce the risk of lung cancer. This has been further replicated and verified by Feng et al.,⁷¹ where with each 10 nmol/L incremental increase in serum 25(OH)D levels, there was a statistically significant 8% reduced risk in lung cancer. The meta-analysis by Wei et al.⁷² suggested that a 100 IU/day increase in supplemental vitamin D decreased risk of lung

cancer by 2.4%. The authors concluded that the risk of lung cancer was modestly decreased when higher doses of vitamin D were taken but not with high levels of circulating 25(OH)D. In general, strong and solid evidence exists on the protective effect of vitamin D on lung parenchyma.

For vitamin E, only 2 meta-analyses are present in the literature. An inverse relationship was reported by Chen et al.⁷⁴ in the first meta-analysis. Their results indicated that intake of vitamin E from the diet decreases the risk of lung cancer significantly. Two years later, another dose–response meta-analysis was published on updated studies. Zhu et al.⁷⁵ reported that for every daily 2 mg increase in dietary vitamin E consumption, lung cancer risk decreased statistically by 5%. Despite limited evidence in the literature, the published associations are strong. Scarce data exist on the relationship between vitamin C and lung cancer risk. Luo et al.⁷⁷ reported a statistically significant reduction in lung cancer risk in individuals with a diet rich in vitamin C (RR, 0.82; 0.73–0.93). Other earlier studies have also supported this association.^{76–78} Despite the presence of only 1 meta-analysis to date, evidence is strong regarding the protective effect of vitamin C on lung tissue.

While other dietary items seem to have a clear association with the risk of lung cancer, this is not the case for calcium. Earlier large prospective studies reported convincing data that supplemental calcium incurred mortality benefits for individuals. However, the latest meta-analysis revealed an inverse relationship that failed to achieve statistical significance. Future studies are needed to properly assess the role calcium plays in lung tumorigenesis, especially considering its complex interconnection to dairy products.³⁴ As for magnesium, early studies have reported a positive relationship with the risk of lung cancer with a borderline trend for increased risk. Pooled results from 1 meta-analysis by Song et al.⁸⁷ suggested that serum level of magnesium was not significantly lower in patients with lung cancer compared to healthy patients (summary standardized mean difference, 0.193). After subgroup analysis, the association remained unchanged. As such, more research is needed to evaluate this relationship, but the available current literature does not support a protective effect.

No meta-analyses have been published to examine the link between zinc and lung cancer risk. However, current literature reports a clearly protective association. Two large prospective studies have confirmed the protective role zinc plays in lung tissue development. A decreased risk for lung cancer has been reported in both studies where intake of dietary zinc alone was also associated with a decreased risk.^{81,88} Iron has had controversial reports regarding its potential for carcinogenesis. While it is important in human health, iron has been consistently shown in the literature to incur harmful effects by increasing the risk of lung cancer. This has been reported in early prospective studies and replicated by the meta-analysis done by Fonseca-Nunes et al.,⁹² which revealed a pooled RR of 1.12 (95% CI, 0.98–1.29) per 1 mg/day difference in

heme iron and concluded that intake of heme iron increased the risk of lung cancer in both men and women.

Data on copper and its role in lung tumorigenesis have been controversial. Early small studies have suggested a protective role. This was followed by a large study by Mahabir et al.,⁸⁸ who confirmed the results. On the other hand, only 1 meta-analysis was published and revealed that patients with lung cancer had higher serum levels of copper. No meta-analysis has been performed to examine the link between dietary copper and lung cancer but the current literature does not reveal a protective role.⁹³ Selenium has been long known for its antineoplastic properties. Mahabir et al.⁸⁸ failed to report a protective role of selenium in lung tumorigenesis. This was further reaffirmed by 1 meta-analysis that reported similar results. More research is needed to examine this association.^{88,98}

Foods that decrease the risk of lung cancer include cruciferous and noncruciferous vegetables, fruits, poultry, fish, cheese, PUFA-rich food, phytoestrogen-rich food, and soy. The food categories that were linked to higher risk of lung cancer were red meat, processed meat, and foods high in total or saturated fats.

Conclusion

Lung cancer remains a devastating disease with low survival rates despite advances in treatment options. There is a growing interest in the nutrition aspect of lung cancer prevention and treatment. Changing dietary habits to decrease the risk of lung cancer can be performed in parallel with other recommendations such as smoking cessation and lung cancer screening. Mixed results have emerged for the different aspects of diet and nutrition and their effect on lung cancer risk. Many reasons are present that can explain the inconsistent and mixed results, such as small sample sizes, different interventions for dietary supplements, study design, exposure assessment, selection of healthy controls or cases, overlap between different dietary aspects, and follow-up period duration. The dominant effect of smoking might have contributed to these discrepancies as it remains the main cause of lung cancer. To our knowledge, this is the first comprehensive and updated literature review on all systematic reviews and meta-analyses published in regard to the above-mentioned dietary components. Patients should continue to receive their standard of care treatment options, but physicians are encouraged to recommend nutritional changes that have been scientifically proven to decrease the risk of lung cancer.

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