Chapter

The Role of Lycopene in Chronic Lung Diseases

Emilio Balbuena, Junrui Cheng and Abdulkerim Eroglu

Abstract

Lycopene, a naturally occurring non-provitamin A carotenoid pigment, is responsible for the red to pink colors in tomato, watermelon, red bell peppers, and pink guava. There are many health benefits attributed to lycopene including but not limited to its antioxidant activity. According to the American Lung Association's State of Lung Cancer, lung cancer is still the leading cause of cancer death in the United States. Other chronic lung diseases such as asthma, emphysema, and chronic obstructive pulmonary disease are high prevalence. This chapter summarizes lycopene's protective role against lung diseases in both *in vitro* and *in vivo* studies. While it has been demonstrated that circulating lycopene can be used as a biomarker for several lung diseases, further studies are warranted to establish that. We aim to provide insights into how lycopene can remedy for lung diseases, including lung cancer.

Keywords: lycopene, lung diseases, oxidative stress, lung cancer, antioxidants, carotenoids

1. Introduction

1.1 Lycopene: chemical definition and metabolism

Lycopene, a major dietary carotenoid pigment responsible for the red color, is synthesized by plants and microorganisms [1]. It is mostly found in tomatoes and tomato products, albeit there is a small amount of lycopene in few other fruits, including watermelon, papaya, guava, and pink grapefruit [2]. Lycopene is one of the six most abundant carotenoids (others being α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin) in circulation in humans [3]. It has been shown that lycopene exerts cancer-preventive or chemopreventive properties against several cancer types, including prostate, lung, and colon cancers [4].

Lycopene has a chemical formula of $C_{40}H_{56}$, tetraterpene comprised of eight isoprene units that are purely containing carbon and hydrogen [5]. Lycopene can undergo isomerization from *trans* to *cis* by heat, light, and chemical reactions, although the all-*trans* isomeric form is the main isomer in nature [6].

Lycopene can be cleaved via two pathways (**Figure 1**). It can be metabolized by central cleavage, catalyzed by beta-carotene-15,15′-oxygenase (BCO1), yielding apo-15′-lycopenal [7]. It also can be metabolized by eccentric cleavage, catalyzed by beta-carotene-9′,10′-oxygenase (BCO2) yielding apo-10′-lycopenal, which can be either further oxidized into apo-10′-lycopenoic acid or reduced to apo-10′-lycopenol [8]. It has also been shown apo-lycopenals at various chain lengths can also be derived from the absorption of apo-lycopenals directly from food [9].

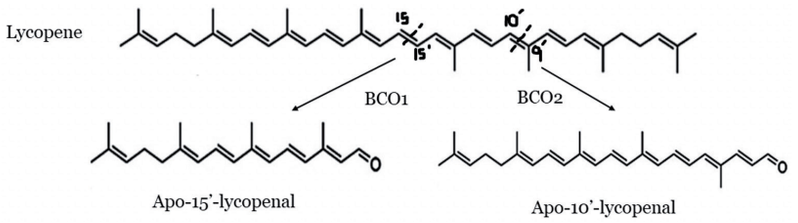

Figure 1.
Central and eccentric cleavage of lycopene. Oxidative cleavage of lycopene at the central 15, 15′ double bond is catalyzed by beta-carotene-15,15′-oxygenase 1 (BCO1) leading to the generation of two molecules of apo-15′-lycopenal [7]. Eccentric cleavage takes place at the 9′-10′ double bond and is catalyzed by beta-carotene-9, 10′-oxygenase 2 (BCO2) yielding apo-10′-lycopenal [8].

1.2 Lycopene: its antioxidant function

Lycopene is a linear, unsaturated hydrocarbon carotenoid with eleven and two unconjugated double bonds, making it highly reactive against oxygen and free radicals [10]. Lycopene displays the highest physical quenching rate constant of singlet oxygen (k_q = 31 × 10^9 M^{-1} s^{-1}) *in vitro*, while rate constants for α-carotene, β-carotene, and lutein were 19, 14, and 8, respectively [10]. Also, lycopene's antioxidant activity in liposomes was found to be greater than α-tocopherol [11]. It is worth highlighting its high quenching rate constant of singlet oxygen because lycopene's concentration in the circulation is 0.7 μM in humans. Lycopene can also scavenge hypochlorous acid, a precursor of free radicals in respiratory stress pathology [12]. It has been documented that tomato products with olive oil increased human plasma antioxidant activity [13]. The authors used the Ferric Reducing Antioxidant Power (FRAP) assay, a quantitative assay for measuring the antioxidant potential, to demonstrate the antioxidant activity of tomato products with olive oil, and it was increased from 930 to 1118 mmol/L [13]. Finally, lycopene could enhance the production of endogenous antioxidant enzymes, e.g., glutathione peroxidase (Gpx), glutathione reductase (GR), and superoxide dismutase (SOD) [14].

1.3 Lycopene: its dietary intake and bioavailability

Although lycopene can be consumed through various sources, processed tomato products (e.g., ketchup, tomato source, tomato juices, tomato extract) are the major dietary lycopene source in the United States [15]. Indeed, the mean lycopene content in these products is more than 90% [16]. The average lycopene intake in the U.S. is 6.6–10.5 mg/day in males and 5.7–10.4 mg/day in females [17].

Dietary lycopene intake amount is not always correlated with circulating lycopene levels because multiple factors can affect its bioavailability. Processed tomato products, for example, contain more lycopene than fresh fruits and vegetable [18]. While the lycopene content in ketchup is 9.9–13.44 mg lycopene/100 g [19], lycopene content in fresh tomatoes ranges from 1.82–11.9 mg/100 g wet weight [20]. Also, lycopene is more bioavailable in processed foods than in raw materials since the transformation of the all-*trans* isomer into the *cis*-isomer renders lycopene elevated solubility in bile acids [21, 22]. Since lycopene is a lipid-soluble compound, a diet with high levels of lipids may increase lycopene bioavailability. It has been shown that the addition of avocado to salad significantly increased lycopene absorption in humans, although the increase of lycopene bioavailability was not correlated with avocado co-consumption in a dose–response manner [23].

There has been growing research interest in genetic variant studies in recent years and the association between genetic variation and lycopene bioavailability.

In a study with 33 subjects, researchers revealed that 72% of the variance in the postprandial plasma lycopene response was explained by 28 single nucleotide polymorphisms (SNPs) in 16 genes [24]. Among these genes, ATP binding cassette subfamily a member 1 (ABCA1), lipoprotein lipase (LPL), insulin-induced gene 2 (INSIG2), solute carrier family 27 member 6 (SLC27A6), lipase C (LIPC), cluster of differentiation 36 molecule (CD36), and apolipoprotein B (APOB) play critical roles in cellular lipid intake and transportation, indicating that the bioavailability of lycopene is likely to depend on lipid metabolism. Another study found that although SNP genotypes were unrelated to usual dietary lycopene intake, two BCO1 SNPs predicted the plasma lycopene changes after subjects were given the same amount of tomato juice [25]. Such finding is intriguing because the activity of BCO1 is lower than BCO2 toward non-provitamin A carotenoids such as lycopene [26], so further studies are warranted to explore the underlying mechanism by which BCO1 SNPs led to different postprandial lycopene response.

Lycopene is widely distributed in various tissues in humans. However, the distribution is uneven, with liver, adipose tissue, testes, adrenal glands, and circulating blood being the major storage pools [27, 28] while lung and kidney have relatively low lycopene concentration [19]. It has been shown that familial resemblances were found in plasma lycopene, indicating that lycopene distribution variance is due to genetic and environmental factors [29]. Cigarette smoke, for example, decreased plasma carotenoid concentrations in humans [30, 31]. A lower serum lycopene concentration was reported in ever-smokers than in never-smokers [32], and lycopene concentration was even substantially lower in smokers who take more than three cigarettes per day [33]. Other factors, including aging, air pollution, and the initiation of diseases such as cardiovascular disease and diabetes, may also deplete lycopene levels due to increased oxidative stress and elevated reactive oxygen species (ROS) [34, 35]. While numerous studies reported the lycopene levels in patients with lung diseases, there is a gap in providing the overall picture. Therefore, our current work aims to shed light on the association between lung diseases and lycopene concentration and how lycopene supplementation affects lung disease initiation/development, offering further research directions.

2. Lycopene and lung diseases

2.1 *In vitro* and *in vivo* evidence

2.1.1 Asthma

Asthma is characterized as the narrowing or blockage of the airways, leading to breathing difficulties like shortness of breath, coughing, or wheezing. The onset of asthma is associated with elevated pulmonary inflammation, which characteristically involves airway infiltration of related inflammatory cells through the activation of Th2-type lymphocytes, eosinophils, and mast cells [36]. A combination of these immunological activities with genetic and environmental factors can lead to the progression of asthma.

To investigate strategies to potentially mitigate the effects of asthma, two *in vivo* studies utilized dietary lycopene supplementation within a murine model induced with this lung condition. These studies involved intraperitoneal (i.p.) injection of ovalbumin (OVA) to induce airway inflammation in BALB/c mice and demonstrated that subsequent lycopene supplementation of 8 and 16 mg/kg body weight (BW)/day alleviated such inflammatory cell infiltration into the bronchoalveolar lavage fluid (BALF) [37] as well as into the lung tissue and blood supply [38].

Lycopene treatment at both of these dosages decreased the expression of eosinophil peroxidase (EPO) and the gelatinolytic activity of matrix metalloproteinase-9 (MMP-9) caused by the i.p. injection of OVA [37]. Lycopene administration at both dosages also inhibited the OVA-specific release of Th2-associated cytokines interleukin-4 (IL-4) and interleukin-5 (IL-5) [37, 38]. The data presented in these studies revealed that dietary lycopene intervention could inhibit the infiltration of inflammatory immunocytes and alleviate asthma's pathogenesis and progression.

2.1.2 COPD and emphysema

Chronic obstructive pulmonary disease (COPD) is a coined term that governs a group of inflammatory lung conditions such as bronchiolitis and emphysema [39]. Bronchiolitis involves fibrosis-related obstruction of small air passages, while emphysema is characteristic of alveolar enlargement and alveolar wall damage. COPD symptoms commonly consist of a chronic cough, shortness of breath, excess phlegm or sputum, and chest tightness [40].

One of COPD's most prevalent risk factors is cigarette smoking, which can be usefully incorporated into *in vivo* studies to investigate potential remedies to alleviate proinflammatory symptoms and this chronic condition's progression. Due to its documented antioxidant capabilities, lycopene treatment can be utilized to reduce the oxidative stress induced by cigarette smoke. A study utilizing a ferret model investigated the efficacy of dietary lycopene stimulation upon both bronchiolitis and emphysema-related aspects of COPD [41]. Through i.p. injection of tobacco carcinogen nicotine-derived nitrosamine ketone (NNK) at 200 mg/kg BW/day and cigarette smoke exposure five days a week for four months, the COPD model was established in ferrets. Lycopene was administered via 10% w/w beadlets at a low dosage of 2.2 mg/kg BW/day and a high dosage of 6.6 mg/kg BW/day over 22 weeks. Following this exposure and treatment period, the findings illustrated that the high dose of lycopene decreased the incidence of NNK/cigarette smoke-induced bronchiolitis and emphysema in ferrets [41].

Tackling the issue of emphysema in particular, two *in vivo* studies investigated the antioxidant/anti-inflammatory efficacy of dietary lycopene supplementation on chronic cigarette smoke exposure alone in murine models. Lycopene administration at 25 and 50 mg/kg BW/day in C57BL/6 mice appeared to alleviate the detrimental effects of chronic cigarette smoke exposure (12 cigarettes/day) over 60 days [42]. Lycopene treatment at both dosages appeared to have improved redox balance and decreased lipid peroxidation and DNA damage; activities of SOD, catalase (CAT), and glutathione (GSH) were increased via lycopene treatment. Lycopene also decreased interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFNγ) levels at both dosages. On the other hand, the weight loss that occurred due to the smoke exposure was not recovered by lycopene treatment at either dosage. The same research team had previously conducted a short-term smoke exposure study [43] for just five days, not long enough to establish emphysema, that employed the same dosages of lycopene treatment (25 and 50 mg/kg BW/day). This earlier study described that lycopene administration decreased neutrophil initiation and macrophage influx into the BALF as well as similarly decreased levels of IL-10, TNF-α, and IFNγ at both dosages.

Another *in vivo* study investigated the association of age-related progression with emphysema development within a senescence-accelerated mouse (SAM) model [44]. Utilizing the SAM model that mimics the senile mouse lung, the study aimed to determine if the dietary lycopene supplementation could prevent the onset of emphysema through chronic cigarette smoke exposure (30 min/day, five days/week, for eight weeks). Tomato juice (containing 5 mg of lycopene)

administration in place of tap water was shown to have an inhibitory effect on the onset of cigarette smoke-induced emphysema.

Collectively, dietary lycopene supplementation appears to have alleviating effects upon chronic obstructive pulmonary disease, cigarette smoke-induced bronchiolitis, and emphysema due to its potent antioxidant and anti-inflammatory activities.

2.1.3 Acute lung injury

Acute lung injury (ALI) is an acute inflammatory pulmonary disorder that causes endothelial and epithelial barrier disruption, leading to compromised alveolar-capillary membrane integrity [45]. Factors such as lung infection, aspiration, sepsis, trauma, and shock can contribute to ALI's onset. Due to the loss of the alveolar-capillary membrane integrity, further complications characteristic of ALI can involve increased pulmonary edema permeability, increased infiltration of neutrophils, and increased release of pro-inflammatory cytotoxic mediators.

Several *in vivo* studies have been conducted utilizing dietary lycopene supplementation to determine potential treatment in alleviating the damage associated with acute lung injury. One method of generating ALI in these animals was through the administration of lipopolysaccharide (LPS). One study investigated the synergistic protective efficacy of lycopene and matrine, an alkaloid found in kinds of Sophora plants, against LPS-induced ALI compared to the corticosteroid dexamethasone (DEX) in BALB/c mice [46]. Mice were intraperitoneally injected with DEX (5 mg/kg BW), matrine (25 mg/kg BW), lycopene (100 mg/kg BW), or a combination of the matrine + lycopene treatments for seven days before a final dosage of LPS (5 mg/kg BW). Following 6 hours after LPS administration, the combined treatment of matrine and lycopene appeared to have similar beneficial effects. Furthermore, the combined treatment inhibited NF-κB p65 activity and reduced the expression of malondialdehyde (MDA), myeloperoxidase (MPO), interleukin-6 (IL-6), and TNF-α while simultaneously upregulating GSH.

Sarcandra glabra (SG), an herb native to Southeast Asia which is used for treating various oxidative stress diseases, was incorporated within another study in conjunction with lycopene to combat LPS-induced ALI in a rat model [47]. The rats were treated similarly as the other study with supplementation of SG (2.5 mg/kg BW) and lycopene (5 mg/kg BW) individually or in combination for two weeks before LPS (6 mg/kg BW) administration. Like the study involving matrine, the combination of SG and lycopene led to a significant decrease in LPS-induced histopathological injuries, as well as reduced levels of IL-6, TNF-α, NF-κB, and mitogen-activated protein kinase (MAPK). Furthermore, the combination treatment increased antioxidative activity and helped reverse the abnormal metabolism back towards normal status. Courtesy of the findings from these studies, lycopene treatment has the potential to alleviate LPS-induced acute lung injury. As lipopolysaccharide is not the only way to induce acute lung injury, other studies have incorporated alternative methods to study lycopene's effect. A study investigated the effects of Redivio® capsules (lycopene in 10% fluid suspension) against oleic acid (OA)-induced ALI in Wistar rats [48]. Over five weeks, the rats were treated with 100 mg/kg BW/day OA and 20 mg/kg BW/day lycopene. Lycopene supplementation decreased neutrophilic infiltration and decreased perivascular and alveolar edema. Lycopene treatment also decreased serum and tissue MDA, serum and tissue SOD, and increased tissue CAT levels; however, there was no effect on serum and tissue Gpx. ALI can additionally be brought on by hyperoxia, which was investigated in a study involving newborn rats that were housed in conditions of normoxia (ambient air) or hyperoxia and supplemented with 50 mg lycopene in olive oil/kg BW/day for 11 days [49]. Despite

the expected antioxidant effects of lycopene in these conditions, this treatment did not improve hyperoxia-induced injury as MDA, SOD, and IL-6 levels were not changed; interleukin-1β (IL-1β) and Gpx levels were not affected by hyperoxia or lycopene.

2.1.4 Pulmonary fibrosis

Lung fibrosis, or idiopathic pulmonary fibrosis (IPF), is considered an interstitial lung disease. It involves alveolar epithelial damage and scarring of the lungs due to excess deposition of extracellular matrix by myofibroblasts [50]. The alveolar epithelial degradation is considered an indicative initiating factor of IPF, and the associated damage can lead to interstitial pneumonia. Patients with IPF have a 20% higher risk of developing lung cancer, which can take approximately 2–4 years to reach end-stage respiratory insufficiency [51]. In this case, a treatment regime is quite crucial to shunt this detrimental progression.

Bleomycin (BLM), a polypeptide antitumor agent, can mimic lung fibrosis's pathological effects and can be incorporated within studies to study treatment efficacy. One *in vivo* study utilized this model via intratracheal instillation of BLM (4 mg/mL) in Sprague–Dawley rats to induce IPF [52]. Lycopene extracted from tomatoes was administered over 28 days at a dosage of 5 mg/kg BW/day appeared to alleviate the damage attributed to BLM-induced oxidative stress partially. Such lycopene treatment inhibited the extent of free radical injury, fibrosis, and alveolitis. Furthermore, supplemental lycopene decreased plasma and tissue levels of TNF-α and decreased plasma levels of MDA and nitric oxide (NO). Since lung fibroblasts can contribute to the onset of pulmonary fibrosis, this cell type can be studied within an *in vitro* context to identify methods of regulating their abnormal activity. Two *in vitro* studies capitalized on this cell line type by inducing DNA damage in Chinese lung fibroblasts, V79 cells, through peroxynitrite administration [53] and catechol estrogen [54]. The cells were pre-treated with β-carotene and lycopene at concentrations of 0–5 μM and 0–10 μM 24 hours before the damage. The treatment of these carotenoids decreased the DNA damage in these fibroblast cells by inhibiting single-strand breaks [53, 54] and decreasing the inflammation oxidative stress [53].

2.1.5 Lung cancer

Lung cancer is the leading cause of cancer mortality in the United States, constituting nearly one fourth of all cancer deaths [55]; thus bringing about the need to finding remedies in any way possible. In terms of carotenoid treatment, supplementation of lycopene and its metabolites may demonstrate some anti-cancer efficacy within both *in vitro* and *in vivo* settings by inhibiting carcinoma severity and progression; such a trend has been seen in multiple cell types including prostate, breast, hepatoma, stomach, colon and oral cancer cells [56–58]. In the studies regarding lung cancer, the models typically involve lung cancer cell lines, cigarette smoke exposure, and the administration of carcinogenic agents. As non-small cell lung cancer (NSCLC) accounts for the most lung cancer-related deaths, various *in vitro* studies have utilized cell lines that characterize this cell type. In these cases, lycopene and its metabolites appeared to be a potent inhibitor of cancer cell growth and proliferation [59–62], even more so than either α- carotene or β-carotene [59], by arresting the cell cycle at the G1 checkpoint [62]. In cigarette smoke-induced oxidative stress, the formation of reactive oxygen species (ROS) could lead to damage of cellular macromolecules, notably to genomic DNA that can cause mutations. Like in the case of the Chinese hamster fibroblasts [50], lycopene's antioxidant

potential was shown as its capability to quench ROS and upregulate enzymes related to base excision repair, such as DNA glycosylases [63].

Through the classic model of cancer-induction via cigarette smoke exposure *in vivo*, treatment of lycopene at both a low dose (1.1 mg/kg BW/day) and a high dose (4.3 mg/kg BW/day) for nine weeks reduced the extent of lung squamous metaplasia via apoptosis in a ferret model [64]. The apoptosis was attributed to the upregulation of plasma insulin-like growth factor binding protein-3 (IGFBP-3) levels and reduction of the IGF-1/IGFBP-3 ratio.

An alternate method of inducing tumorigenesis in animal models can be achieved through the administration of carcinogenic agents like benzo[a]pyrene (BaP), NNK, and dimethylhydrazine (DMH) [62–64]. An *in vivo* study utilized the DMH method of tumor-induction via subcutaneously injecting 20 mg/kg BW DMH into B6C3F1 mice, the F1 generation of a cross between C57BL/6 J females and C3H/HeJ males [65]. For 32 weeks, the mice were administered with DMH twice a week for five weeks and then lycopene (25 or 50 ppm in drinking water) starting at week 21. After this treatment period, anticancer effects were primarily seen in males as the high lycopene dose (50 ppm) decreased DMH-related tumor development and decreased multiplicities for lung adenomas and carcinomas [65]. Another two *in vivo* studies utilized the treatment of lycopene-enriched tomato oleserin (LTO) in models involving tumorigenesis induction via BaP only [66] or BaP and NNK [67]. In one of those particular studies, a proprietary MutaMouse model consisting of the F1 generation of a cross between BALB/c and DBA/2 mice was injected with 125 mg/kg BaP and treated with LTO (3.7% lycopene) at different doses in their diets (7 and 14 g LTO/kg diet, 0.5 and 1.0 mmol lycopene/kg diet). However, the BaP-induced lung mutagenesis was found to have increased with LTO supplementation, especially at the high dosage [66]. On the other hand, a study incorporating BaP and NNK-induced carcinogenesis into A/J mice investigated the effect of LTO (5.9% lycopene) at different doses in their diets (185 ppm, 1850 ppm, 9260 ppm). In this case, there was no overall effect on the weight gain or survivability of the mice; furthermore, none of the LTO-enriched treatments given before, during, or after BaP and NNK administration had any effect on tumor incidence or multiplicity [67]. The minimal or lack of effect that lycopene has on these carcinogenic agents may indicate that this carotenoid's anticancer efficacy is better suited against cigarette smoke exposure, possibly due to its antioxidant properties.

While lycopene is typically utilized within these carotenoid treatment studies, its metabolites have shown some anticancer efficacy, especially apo-10′-lycopenoic acid. In a joint *in vitro* and *in vivo* study, apo-10′-lycopenoic acid was shown to inhibit cell cycle progression in non-small cell lung cancer (NSCLC) and lung tumor multiplicity in A/J mice [62]. Approaching the *in vitro* aspect, normal human bronchial epithelial cells (NHBE), BEAS-2B-immortalized normal bronchial epithelial cells, and non-small cell lung cancer, A549 cells, were treated with 0–10 μM apo-10′-lycopenoic acid for five days; this treatment regime appeared to have decreased cyclin E and inhibited cell cycle progression from G1 to S phases as seen with lycopene previously [59]. Furthermore, cell cycle mediators (p21 and p27) were increased, indicating promoted mediation of checkpoint regulation.

Lycopene also appears to be involved in tumorigenesis suppression through several pathways, such as inhibiting NF-κB, activating sirtuin-1, or modulating reverse cholesterol transport mechanism by inhibiting 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase expression [1, 68, 69]. Furthermore, lycopene and its metabolites have been shown to upregulate retinoic acid receptor β (RARβ) activation [63], leading to reduced cell proliferation, increased apoptosis [70], and enhanced gap junction communication (GJC) by upregulating connexin-43 (Cx43) [63, 71].

3. Lycopene and lung diseases in human

To conclude the association between circulating lycopene and lung diseases, we performed a systematic review and meta-analysis by following the PRISMA guideline [72]. We conducted a comprehensive search of the following electronic databases: MEDLINE, Web of Science, EMBASE, and Google Scholar from inception up to November 8, 2020. We employed an integration of Medical Subject Heading (MeSH) terms and/or keywords to article-searching in these databases. The search terms are listed as follows:

("lung diseases"[MeSH Terms (MeSH), title or abstract (ti/ab)] OR (("lung"[MeSH] OR "lung"[All Fields]) AND "cancer*"[MeSH Terms]) OR "pulmonary disease, chronic obstructive"[MeSH, ti/ab] OR "pulmonary disease, chronic obstructive"[MeSH, ti/ab] OR "pulmonary disease, chronic obstructive"[MeSH, ti/ab] OR ("pulmonary emphysema"[MeSH, ti/ab] OR "emphysema"[MeSH, ti/ab]) OR "asthma"[MeSH, ti/ab] OR "acute lung injur*"[MeSH] OR "cystic fibrosis"[MeSH, ti/ab] OR "pulmonary fibrosis"[MeSH, ti/ab]) AND "lycopene"[MeSH, ti/ab].

3.1 Methods

3.1.1 Eligibility

We used these inclusion criteria while carrying out a meta-analysis and systematic review:

- patients with confirmed lung diseases including asthma, acute lung injuries, emphysema, COPD, lung fibrosis, and lung cancer;
- used one of the following study designs: randomized controlled trial (RCT), cohort study, case–control study, nested case–control study, and cross-sectional study;
- reported circulating lycopene level, dietary lycopene intake, dietary consumption of lycopene-enriched foods (e.g., tomato products);
- outcomes related to the incidence or development of lung diseases;
- provided statistical reports

When multiple studies included subjects from the same cohort, only the publication reported the most updated results were selected. *In vitro* studies and animal studies were excluded. Review articles were also excluded.

3.1.2 Data extraction

Data extraction was performed by two independent researchers (J. Cheng, A. Eroglu) by utilizing a structured form. A third investigator (E. Balbuena) would be involved if discrepancies occurred. The following information was collected from eligible studies: study characteristics (author, year of the study, study design, name of the cohort), subject characteristics (a type of lung disease, subject age), treatment information, and primary results, which included means, comparison of the groups, relative ratio (RR)/odds ratio (OR)/hazard ratio (HR), and the measure of variability (95% confidence interval and p-value). For studies that used both

univariate analysis and multivariate analysis, only the multivariate analysis results were extracted. A table was constructed (**Table 1**) to summarize the data.

3.1.3 Statistical analysis

We only included the studies that reported OR/RR/HR and 95% confidence interval to perform statistical analysis. Studies that failed to provide such information were excluded from meta-analysis but were still included in our systematic review with detailed information listed in **Table 1**. According to the rare disease assumption, the prevalence of lung diseases is low, and the relative risk approaches the odds ratio [73]. Therefore, we reported all risk estimates in our current meta-analysis as OR for simplicity. With the possibility that the variance between the studies was caused by heterogeneity, the pooled ORs of the risk of lung diseases were estimated using a random-effects model. Two-tailed p-values <0.05 were considered statistically significant. We performed statistical analyses by employing RevMan 5.4.1.

3.2 Results

The process of study selection was displayed in the flow chart (**Figure 2**). The search for the four databases yielded 105 articles, of which 101 were eventually screened (**Figure 2**). Forty-eight articles were included for final screening after we excluded 53 in vitro or animal studies. Among them, 11 articles were excluded with various rationales: the exposure is not lycopene-related (N = 1), outcomes are not related to lung diseases (N = 3), review articles (N = 3), full text unavailable (N = 1), or studies that used the same cohort (N = 4) which led to 37 papers included in this systematic review (**Figure 2**).

3.2.1 Asthma

A total of 13 articles reported the relation between asthma and lycopene concentration, or dietary lycopene intake [74–86]. Among them, 9 studies are observational studies: cross-sectional (N = 1), nested case–control (N = 1), or case–control studies (N = 7) [74–82], whereas other studies are randomized clinical trials (RCTs) [83–86].

In total, eight case–control (including nested case–control) studies included 1,280 current asthma patients and explored circulating lycopene levels in cases versus matched controls. Additionally, one cross-sectional study with 218 subjects reported the association between serum lycopene concentration and asthma severity [77]. In four studies, a significantly lower circulating lycopene concentration was observed in cases than in healthy controls [76–79]. Nevertheless, other case–control studies reported similar circulating lycopene levels in asthma patients than the matched control group, indicating that the risk of asthma was unrelated to circulating lycopene levels [74, 75, 81, 82]. Such discrepancy might be due to the heterogeneity of disease characteristics. Wood et al. showed a trend of higher plasma lycopene concentration in asthma patients with airway hyper-responsiveness [80]. It was also reported that plasma lycopene concentration was higher in atopic asthma subjects than in non-atopic asthma subjects [76]. Therefore, a high proportion of hyper-responsive asthma patients or atopic asthma patients may decrease the probability of observing a significant difference.

Two studies reported the correlation between circulating lycopene concentration and the severity of asthma. Forced expiratory volume in one second (FEV1) is defined as the volume of breath exhaled during a forced breath within one second.

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Rohan, 2002	Lung cancer	Nested case–control	196	40–59	NA	8	Lycopene intake was unrelated to lung cancer risk (RR = 1.04, 95% CI: 0.61–1.76, P trend = 0.233)
Sackesen, 2008	Asthma	Case–control	164	9.65 ± 1.55	NA	NA	• Plasma lycopene concentration was higher in children with atopic asthma vs. non-atopic asthma (0.46 ± 0.2 μmoL/L vs. 0.45 ± 0.2 μmoL/L, P = 0.027) • Plasma lycopene concentration was lower in cases vs. controls (P < 0.001)
Voorrips, 2000	Lung cancer	Nested case–control	939	55–69	NA	6.3 years	• Lycopene intake was lower in cases than in controls (983 ± 1517 μg/d vs. 1050 ± 1560 μg/d, P = NR) • A lower lycopene intake was correlated with higher lung cancer risk (RR = 1.12, 95% CI: 0.77–1.71, P trend = 0.04). However, after adjusted for folate intake, the correlation was not statistically significant (RR = 1.05, 95% CI: 0.75–1.46, P trend = 0.14)
Wood, 2005	Asthma	Case–control	15	48.4 ± 4.3	NA	NA	• Cases had a lower lycopene level vs. controls in whole blood (29 ug/L vs. 247 ug/L P 0.05) or whole sputum (31 ug/L vs. 9 ug/L, P > 0.05) • Daily lycopene intake was similar in cases vs. controls (3.90 mg/d vs. 2.51 mg/d, P > 0.05)
Kodama, 2015	Asthma-COPD overlap syndrome Bronchial asthma	Case–control	• 39 COPD patients • 21 patients with ACOS (asthma-COPD overlap syndrome) • 15 patients with BA (bronchial asthma)	• 72.7 ± 6.9 (COPD) • 66.8 ± 8.4 (ACOS) • 56.4 ± 13.7 (BA)	NA	NA	• Plasma lycopene concentration was lower in COPD subjects vs. controls (P 0.05) • Plasma was lycopene concentration similar in ACOS subjects vs. healthy controls (P > 0.05) • Plasma lycopene concentration was similar in BA subjects vs. healthy controls (P > 0.05)
Schock, 2003	Asthma	Case–control	78	7.2 ± 3.3	NA	NA	Lycopene concentration in the BAL was similar between cases vs. controls (0.146 μmoL/L vs. 0.156 μmoL/L, P = 0.33)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Ochs-Balcom, 2006	Asthma COPD	Cross-sectional	• 68 asthma patients • 121 COPD patients • 29 asthma and COPD patients	61.7 ± 10.3	NA	NA	• Serum lycopene was positively associated with %FVC (P 0.05) • Dietary lycopene intake was positively associated with %FEV1 and %FEV1/FVC (P 0.05)
Jun, 2020	Pulmonary function	Cross-sectional	15,792	54.1 ± NR	NA	NA	• Lycopene dietary intake was not correlated with FEV1/FVC ratio (P = 0.283) • The consumption of lycopene & lutein/zeaxanthin foods were not correlated with FEV1/FVC ratio (P = 0.518)
Ford, 2014	COPD	Prospective study	1,492	55.7 ± 0.7	NA	14 years	• Serum lycopene concentration was similar in cases vs. controls (0.41 ± 0.03 μmoL/L vs. 0.46 ± 0.01 μmoL/L, P = 0.120) • A higher serum lycopene concentration was correlated with a lower all-cause mortality among adults with obstructive lung function (HR = 0.80, 95% CI: 0.67–0.95, P = 0.013)
Ito, 2005	Lung cancer	Prospective study	3,182	39–79	NA	10.5 years	• Serum lycopene concentration was lower in lung cancer deaths vs. the survivors (0.229 ± NR μmoL/L vs. 0.328 ± NR μmoL/L, P = 0.007) • Serum lycopene concentration was unrelated to lung cancer mortality (HR = 0.93, 95% CI: 0.39–2.24, P trend = 0.76)
Stefani, 1993	Lung cancer	Case–control	541	30–89	NA	NA	• Lycopene intake was similar in cases vs. controls (1603.4 ± 1416 μg/d vs. 1666.6 ± 1439 μg/d, P = 0.47) • Dietary lycopene intake was unrelated to lung cancer risk (OR = 0.83, 95% CI: 0.56–1.21, P trend = 0.18) • A higher dietary tomato intake frequency was correlated with lower lung cancer risk (OR = 0.76, 95% CI: 0.55–1.07, P trend = 0.09)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Holick, 2002	Lung cancer	Prospective study	27,084	57.2	NA	14 years	• A higher dietary lycopene intake was correlated with lower lung cancer risk (Age-adjusted: RR = 0.63, CI 0.54–0.75, P trend <0.0001; Multivariate: RR = 0.72, 95% CI: 0.61–0.84, P trend <0.0001) • In subgroup analysis, a higher lycopene intake was correlated with lower lung cancer risk in subjects who took 5–19 cigarettes (RR = 0.65, 95% CI: 0.49–0.87, P for trend = 0.01), 20–29 cigarettes (RR = 0.81, 95% CI: 0.64–1.02, P for trend = 0.009), ≥30 cigarettes (RR = 0.63, 95% CI: 0.45–0.88, P for trend = 0.008)
Yuan, 2003	Lung cancer	Prospective study	63,257	63 ± NR	NA	8 years	Lycopene dietary intake was unrelated to lung cancer risk (RR = 0.89, 95% CI: NR, P trend: NR)
Asbaghi, 2015	Lung cancer	Case–control	55	NR	NA	NA	• Daily lycopene intake was lower in cases than in controls (P = 0.001) • Serum lycopene concentration was lower in cases than in controls (P = 0.004)
Talwar, 1997	Lung cancer	Case–control	22	66	NA	NA	Plasma lycopene concentration was lower in cases than in controls (<0.02 ± NR μmoL/L vs. 0.37 ± NR μmoL/L, P < 0.001)
Falk, 2005	Asthma	RCT	19	13.0 ± 2.15	Placebo Lycopene (30 mg/d)	1 week	Lycopene supplementation did not change FVC, predicted %FVC, FEV1, predicted %FEV1, PEF1, predicted %PEF1, FEF25–75, or predicted %FEF25–75 (P values were NR) among subjects who had exercise-induced asthma
Garcia-Closas, 1998	Lung cancer	Case–control	103	63	NA	NA	Dietary lycopene intake was unrelated to lung cancer risk (OR = 0.56, 95% CI: 0.26–1.24, P trend = 0.15)
Michaud, 2000	Lung cancer	Prospective study	46,924 men 77,283 women	NR	NA	10 years (men) 12 years (women)	• Lycopene intake was unrelated to lung cancer in males (RR = 0.86, 95% CI: 0.59–1.25, P = 0.51) or females (RR = 0.80, 95% CI: 0.64–0.99, P = 0.10) • In lag analysis, lycopene intake was not correlated with lung cancer risk (0–4-y lag: RR = 0.93, 95% CI: 0.76–1.15; 8–12-y lag: RR = 0.87, 95% CI: 0.61–1.24), except for in 4–8-y lag (RR = 0.68, 95% CI: 0.53–0.88)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Shareck, 2017	Lung cancer	Case–control	1,105	64.3 ± 7.8	NA	NA	Dietary lycopene intake was lower in cases vs. control (male: 15,888 ± 10,878 vs. 16,969 ± 9,285, P: NR; female: 11,911 ± 11,902 vs. 16,175 ± 10,985, P: NR) A higher lycopene intake was correlated with a lower lung cancer risk (OR = 0.75, 95% CI: 0.59–0.95, P = 0.03)
Satia, 2009	Lung cancer	Prospective study	521	67.0 ± 6.8	NA	3 years	• Lycopene supplementation frequency was similar between total lung cancer cases vs. controls (multivitamin use: HR = 1.06, CI 0.86–1.30; individual supplement use: HR = 0.98, 95% CI: 0.25–3.96, P trend = 0.61) • Lycopene supplementation frequency was similar between NSCLC cases vs. controls (multivitamin use: HR = 1.14, 95% CI: 0.90–1.44; individual supplement use: HR = 1.32, CI 0.33–5.30, P trend = 0.25) • Lycopene supplementation frequency was similar between SCLC cases vs. controls (multivitamin use: HR = 0.97, 95% CI: 0.55–1.71; individual supplement use data NR, P trend = 0.81) • Lycopene supplementation frequency was similar between other lung cancer cases vs. controls (multivitamin use: HR = 0.67, 95% CI: 0.33–1.37; individual supplement use data NR, P trend = 0.24)
Ito, 2005	Lung cancer	Nested case–control	211	40–79	NA	10 years	• In male, serum lycopene concentration was lower in cases vs. controls (0.06 μmoL/L vs. 0.07 μmoL/L, Univariate model: P = 0.025; Multivariate model: P = 0.032) • In female, serum lycopene concentration was similar in cases vs. controls (0.10 μmoL/L vs. 0.412 μmoL/L, Univariate model: P = 0.20; Multivariate model: P = 0.33) • In male, a higher serum lycopene concentration was correlated with a lower lung cancer risk (OR = 0.44, CI 0.19–1.05, P trend = 0.03) • In female, serum lycopene concentration was unrelated to lung cancer risk (OR = 0.82, CI 0.12–3.25, P trend = 0.5)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Wood, 2008	Asthma	Randomized, cross-over trial	32	52.1 ± 2.4	Low antioxidant diet then placebo, or tomato extract (45 mg lycopene/day), or tomato juice (45 mg lycopene/day)	• 10 days of low antioxidant diet • 7 days for each treatment • 10 days for each washout	• Low antioxidant diet: ↓ predicted %FEV1 (P = 0.004), %FVC (P = 0.0032), asthma control score (P = 0.0035), sputum %neutrophils (P = 0.038), %macrophages (P = 0.06); unchanged biomarkers including FEV1/FVC (P = 0.407), sputum PD15 (P = 0.838), total cell count (P = 0.401), %eosinophils (P = 0.894), exhaled nitric oxide (P = 0.975), and neutrophil elastase (P = 0.961) • Tomato juice supplementation ↓ sputum %neutrophils (P 0.05) • Tomato extract supplementation ↓ sputum %neutrophils (P < 0.05) and neutrophil elastase activity (P < 0.05)
Wood, 2012	Asthma	RCT	137	High-antioxidant diet (54 ± 14) Low-antioxidant diet (58 ± 14)	Low-antioxidant diet (<=2 servings of vegetables and 1 serving of fruit/day), then placebo or lycopene (45 mg/d)	14 weeks or until an exacerbation occurred	• Tomato extract supplementation ↓ plasma CRP (P = 0.010), IL-6 (P = 0.093), TNF-a (P = 0.070) • Tomato extract supplementation did not change %FEV1 (P = 0.948), %FVC (P = 0.534), %FEV1/%FVC (P = 0.918), DRS (P = 0.954), ACQ (P = 0.597), exhaled NO (P = 0.296), sputum %eosinophils (P = 0.299), eosinophil count (P = 0.384), IL-8 (P = 0.874), NE (P = 0.968), or 8-isoprostane (P = 0.720)
Larkin, 2015	Asthma	Nested case–control	150	52.5 ± 8.7	NA	8 years	• Plasma lycopene concentration was similar in cases vs. controls (6.8 mg/dl vs. 6.7 mg/dl, P = 0.79) • Plasma lycopene concentration was not correlated with asthma risk (OR = 0.9w6; 95% CI, 0.84–1.11)
Kentson, 2018	COPD	Case–control	66	70 ± NR	NA	NA	• Plasma lycopene concentration was similar between cases vs. controls (0.41 ± 0.20 μmoL/L vs. 0.48 ± 0.21 μmoL/L, P > 0.05) • Plasma lycopene concentration was positively correlated with blood oxygenation saturation in the COPD patients (P < 0.05)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Riccioni, 2007	Asthma	Case–control	40	37.1 ± 12.5	NA	NA	• Tomato intake was similar in the cases vs. controls (raw tomatoes: 18.1 g vs. 16.8 g, P > 0.05) • Serum lycopene was lower in cases vs. controls (0.10 ± 0.7 μmoL/L vs. 0.16 ± 0.8 μmoL/L, P < 0.001)
Riccioni, 2006	Asthma	Case–control	22	35.1 ± 11.7	NA	NA	Plasma lycopene concentration was lower in asthma patients vs. controls (8.12 ± 2.63 lg/dl vs. 18.13 ± 3.67 lg/dl, P < 0.001)
Yuan, 2001	Lung cancer	Nested case–control	209	64.8 ± NR	NA	12 years	• Serum lycopene concentration was lower in ever-smokers than in never-smokers (P = 0.0002) • A higher serum lycopene concentration was correlated with lower lung cancer risk in all subjects (OR = 0.46, 95% CI: 0.27–0.79, P trend = 0.003), but the adjusted OR was not statistically significant (OR = 0.15, 95% CI: 0.31–1.14, P = 0.15)
Wood, 2010	Asthma	Case–control	41	49 ± 3.4	NA	NA	• There was a trend of higher plasma lycopene concentration in hyper-responsive asthma patients vs. non-hyper-responsive asthma patients (0.115 ± 0.45 mg/L vs. 0.084 ± NR mg/L, P = 0.098) • Plasma lycopene concentration was similar in patients with asthma controlled or partly controlled vs. uncontrolled (0.10 mg/L vs. 0.08 mg/L, P = 0.581) • Plasma lycopene concentration was similar in patients with mild–moderate asthma vs. severe asthma (0.10 mg/L vs. 0.09 mg/L, P = 0.862)
Neuman, 2000	Asthma	RCT	20	23 ± 9	Placebo Lycopene (30 mg/d)	1 week	Lycopene supplementation increased forced expiratory volume in 1 s among patients who had exercise-induced asthma (P < 0.05)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Ford, 2004	Asthma	Case–control	• 771 current asthma • 352 former asthma	• 44.8 ± 0.7 (current asthma) • 44.2 ± 1.0 (former asthma)	NA	NA	• Plasma lycopene concentration was similar between current asthma patients vs. controls (0.44 ± 0.01 μmoL/L vs. 0.44 ± 0.00 μmoL/L) • Plasma lycopene concentration was similar between former asthma patients vs. controls (0.47 ± 0.04 μmoL/L vs. 0.44 ± 0.00 μmoL/L)
Klarod, 2011	Lung cancer	Case–control	49	58.8 ± NR	NA	NA	• Serum lycopene concentration was lower in total cases than in controls (P < 0.001) • Serum lycopene concentration was lower in both early stage patients (P = 0.09) and advanced stage patients (P = 0.001) than in controls. • Serum lycopene concentration was similar in early stage patients vs. advanced stage patients (P = 0.749)
Comstock, 2008	Lung cancer	Nested case–control	258	25–65	NA	15 years (CLUE I) 3 years (CLUE II)	• Serum lycopene concentration was similar in cases vs. controls (P = 0.76) • Serum lycopene concentration was unrelated to lung cancer risk (OR = 1.01, 95% CI: NR, P trend = 0.99) • In subgroup analysis, serum lycopene concentration was unrelated to lung cancer risk (Male: OR = 0.32, 95% CI: NR, P trend = 0.25; Female: OR = 0.83, CI NR, P trend = 0.83)
Marchand, 1989	Lung cancer	Case–control	332	NR	NA	NA	• A lower tomato (including tomato juice) intake was correlated with higher lung cancer risk in males (OR = 2.3, 95% CI: NR, P trend = 0.002) and females (OR = 3.7, 95% CI: NR, P trend <0.001)
Steinmetz, 1993	Lung cancer	Nested case–control	138	55–69	NA	4 years	• The consumption of the 'high-lycopene' foods was unrelated to lung cancer risk (OR = 1.21, 95% CI: 0.69–2.10, P trend = 0.53) • Tomato consumption was unrelated to lung cancer risk (OR = 1.00, 95% CI: 0.61–1.64. P trend = 0.99)

Author, Year	Lung disease	Study Design	Subject (N*)	Age (mean,yr)*	Treatment	Duration	Results
Schut, 1997	Lung cancer	Case–control	19	NR	NA	NA	Serum lycopene concentration was lower in lung cancer patients vs. controls (0.13 ± 0.10 μmoL/L vs. 0.42 ± 0.41 μmoL/L, P < 0.01)
Kawchak, 1999	Cystic fibrosis	Nested case–control	24	NR	Standard nutrition care and vitamin supplements that included 5,000 IU retinol	3 years	At the baseline, serum lycopene concentration was lower in cases vs. controls (0.05 ± 0.05 μmoL/L vs. NR, range 0.15–0.39 μmoL/L, P 0.05).

**Significance values presented individually in each study's result column.*

Table 1.
A table was constructed to summarize the data of clinical trials including study characteristics (author, year of the study, study design, name of the cohort), subject characteristics (a type of lung disease, subject age), treatment information, and primary results.

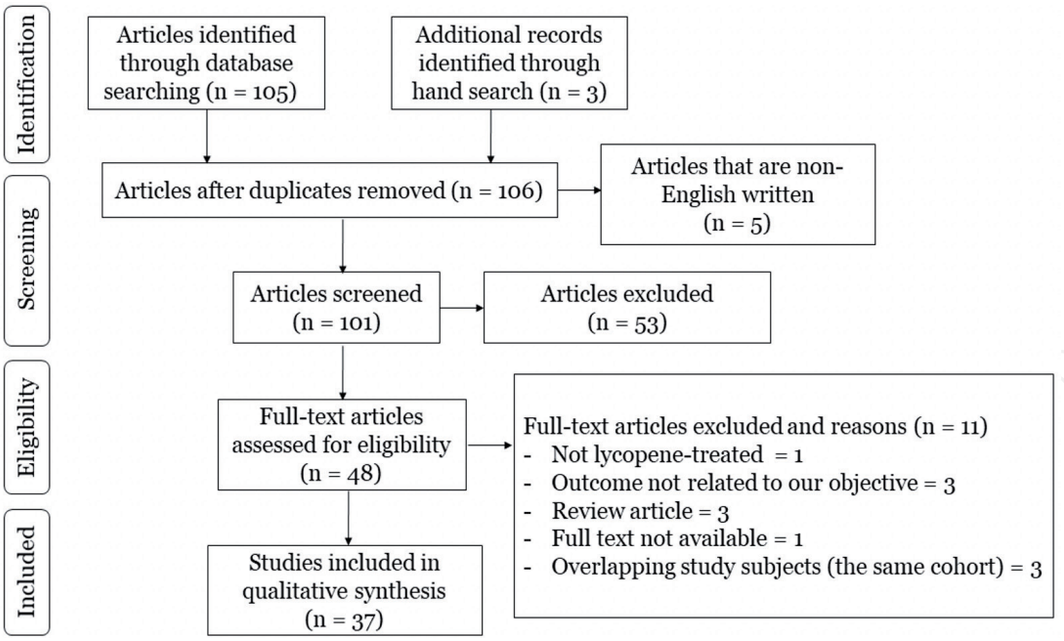

Figure 2.
Flow diagram of study selection according to the PRISMA guideline.

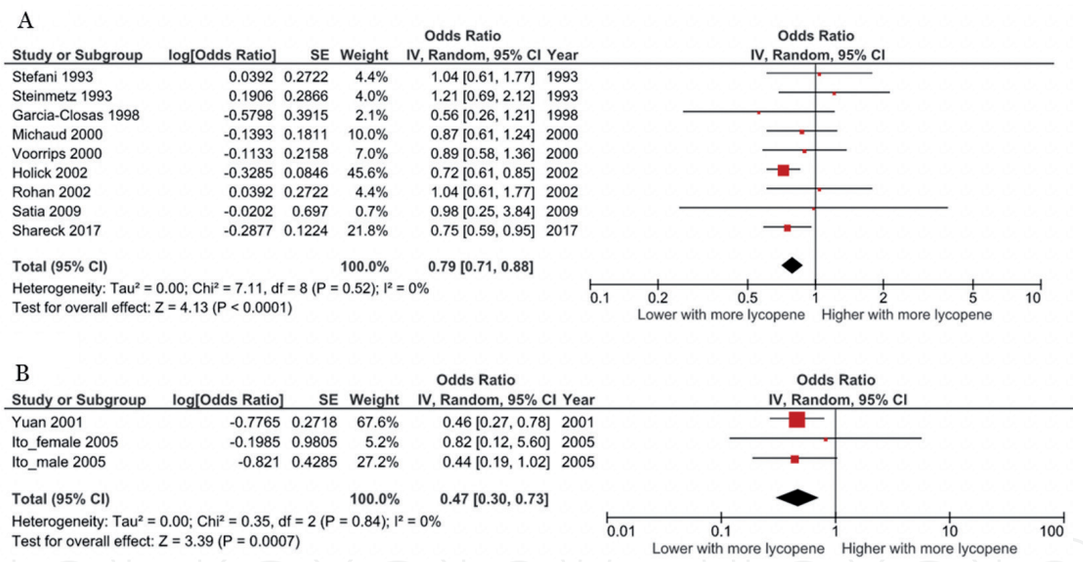

Figure 3.
Forest plots for lung cancer risk in (A) subjects with lower lycopene intake vs. subjects with higher lycopene intake, and (B) subjects with lower circulating lycopene levels vs. subjects with higher circulating lycopene levels.

Forced vital capacity (FVC) is the full air exhaled in the entire timeframe [87]. A low percentage predicted FEV1/FVC ratio is an indicator of reduced pulmonary function. Ochs-Balcom et al. reported a lack of association between serum lycopene concentration and %FEV1/FVC ratio in 22 asthma cases, indicating that circulating lycopene concentration is not correlated with pulmonary function [77]. Similarly, Wood et al. depicted that plasma lycopene concentration was similar in moderate asthma patients than patients with severe asthma [80]. Also, no difference was found in plasma lycopene levels between asthma controlled or partly controlled patients vs. uncontrolled patients [80], indicating that circulating lycopene levels are unrelated to asthma development.

Four RCTs supplemented asthma patients with lycopene or lycopene-enriched foods to investigate the effect of dietary lycopene on asthma [83–86]. They

examined their pulmonary function at the end of the study [83–86]. Two studies addressed exercise-induced asthma, where researchers gave asthma patients lycopene at a dosage of 30 mg/d for one week [80, 81]. Although one study found that lycopene supplementation increased %FEV1 [83], Falk et al. failed to observe any significant differences in pulmonary function indicators between patients with lycopene supplementation and the placebo group [84]. Such inconsistency may have resulted from the inadequate intensity of the exercise challenge in the study. In the study by Falk et al., the participants performed an eight-minute treadmill exercise at a load of 85% of the predicted maximal heart rate [84]. Such intensity may not be strenuous enough to induce exercise-induced bronchoconstriction, especially in physically active people [88]. Also, only 19 subjects were included in the trial, leading to a loss of power. Therefore, additional studies with larger samples size and higher exercise challenges are warranted to examine the effect of lycopene supplementation on exercise-induced asthma.

With a growing interest in investigating the synergistic effect of various antioxidants on lung diseases, Wood et al. provided the subjects with a 10-day low antioxidant diet, followed by either placebo or tomato extract (or tomato juice) supplementation that contains 45-mg lycopene for another ten days [85]. As a result, the low antioxidant diet significantly increased sputum neutrophils, decreased with tomato juice or tomato extract supplementation [85]. Furthermore, a reduced level of sputum neutrophil elastase activity was found in patients supplemented with tomato extract [85]. The neutrophil elastase released by neutrophils is a serine proteinase that may act as a biomarker of inflammation and pathogen invasion [89]. Since this enzyme is involved in lung tissue destruction, by inhibiting neutrophil elastase activity, tomato extract supplementation may hinder pulmonary inflammation, subsequently mitigate the swell of the airways and decrease mucus production [90], leading to alleviated asthma manifestations. Indeed, in a follow-up study with 137 subjects, Wood et al. portrayed decreased levels of plasma C-reactive protein (CRP), IL-6, and IL-1β in the asthma patients who consumed tomato extract that contains 45 mg/d lycopene [86]. Intriguingly, the repeated-measures analysis by time point showed a reduced risk of disease exacerbation in the patients with tomato extract supplementation compared to the placebo group. Additionally, the decrease of %FEV1 and %FVC from baseline was only observed in the placebo group, but not in the tomato extract-supplemented group [86].

Collectively, the results generated from these clinical trials did not show a consistent association between circulating lycopene and the initiation or development of asthma. Besides, there is a lack of evidence that dietary lycopene supplementation alleviating asthma progression. Whole foods that contain a high concentration of lycopene, such as tomato extract, showed beneficial efficacies against asthma. However, both RCTs subjects had a low-antioxidant diet at baseline to deplete their antioxidant levels, meaning that a similar alleviating effect may not be observed in people with normal circulating antioxidant concentrations. It is also important to note that tomato extract and tomato juice are high in lycopene and other antioxidants, such as ascorbic acid or β-carotene. Thus, lycopene itself may lack the capability of mitigating asthma. It should be noted that the combination of lycopene with other antioxidants produces a synergistic effect that can further inhibit pulmonary inflammation and lessen asthma manifestations.

3.2.2 COPD

Both asthma and COPD cause swelling in the airways and difficulties to breathe [91]. Several studies focused on tackling COPD and asthma-COPD overlap syndrome (ACOS) due to the similarities between the two diseases.

At the end of article screening, two case–control studies, one cross-sectional study, and one prospective study depicted the association between circulating lycopene concentration and COPD [75, 77, 81, 92]. Overall, 105 COPD patients and 21 ACOS patients were included in the case–control studies [77, 81], whereas the cross-sectional study included 218 subjects (68 asthma patients, 121 COPD patients, and 29 ACOS patients). The prospective study used the data from the Third National Health and Nutrition Examination Survey (NHANES III), recruiting 1,492 COPD patients [75].

In one case–control study, Kodama et al. reported a significantly lower plasma lycopene concentration in the COPD subjects than the healthy controls [81]. However, such an association was not observed in the ACOS subjects [81]. Interestingly, another case–control study did not find any differences in plasma lycopene levels between the COPD patients and the controls [92]. However, they demonstrated a positive correlation between plasma lycopene concentration and blood oxygenation saturation in COPD patients [92], indicating that circulating lycopene concentration may be related to COPD severity. Similarly, the cross-sectional study conducted by Ochs-Balcom et al. also reported that serum lycopene concentration was positively associated with %FVC, but not %FEV1 or %FEV1/FVC ratio [77]. In 2014, Ford et al. reported that although the COPD patients and the healthy controls appeared to have similar serum lycopene levels, they observed an inverse correlation between serum lycopene concentration and all-cause mortality among people with obstructive lung function [75]. With a large sample size and prospective study design, these findings highlighted the possibility that serum lycopene concentration could be a potential biomarker predicting COPD's development and prognosis.

3.2.3 Lung cancer

In total, 19 studies met our inclusion criteria and provided information on lycopene and lung cancer [32, 93–110]. Among them, there are 8 case–control studies that included 2,226 lung cancer patients [93, 95, 99, 100, 104, 105, 107, 110], 6 nested case–control studies that included 1,951 lung cancer cases [32, 94, 98, 102, 106, 108], and 5 prospective studies that included 218,251 subjects [96, 97, 101, 103, 109].

Among the studies that reported the association between lycopene intake and lung cancer risk, nine studies provided detailed study estimates [95, 96, 101–106, 108] (**Figure 3A**). Our meta-analysis results showed that the meta-OR of lung cancer with a higher dietary lycopene intake was 0.79 (95% CI: 0.71–0.88, overall $P < 0.0001$). The p-value of the Chi-squared (Chi^2) test is 0.52, and the between-study variance (I2) for lung cancer incidence is 0%, meaning that there was a minimum of heterogeneity in the studies. Two case–control studies found that lycopene or lycopene-enriched tomato juice's daily consumption was lower in lung cancer cases than in healthy controls [93]. In contrast, the Singapore Chinese Health Study failed to observe a significant correlation between lycopene dietary intake and lung cancer risk [109]. Multiple factors may contribute to the non-significant findings. In the case–control studies, studies that used the Food Frequency Questionnaire (FFQ) to collect lycopene intake frequencies may undergo recall bias, which led to a loss of power. It is also likely to observe a significant difference in lycopene consumption between cases and controls by including subjects who had a low baseline circulating lycopene level or dietary lycopene intake. Rohan et al. observed significantly different lycopene intake between the cases and the controls when the subjects' daily lycopene intake was between 983 μg to 1,050 μg [102]. However, by including the subjects who reported a baseline daily dietary lycopene

intake at 15.8 mg to 16.9 mg, which is about twice the amount of average daily lycopene intake in the U.S. [17], Shareck et al. found the dietary lycopene intake was comparable between the cases and the controls [104].

Three case–control studies [93, 99, 107] and three nested case–control studies [32, 94, 97] reported the association between circulating lycopene concentration and lung cancer risk. Two studies provided estimates [32, 98], thus were included in the meta-analysis. Since Ito et al. only reported the estimates in the male and female subgroups [98], we pooled the two subgroups and another study [32] to explore the relationship between circulating lycopene concentration and lung cancer risk by performing the meta-analysis. Our results showed that the meta-odds ratio of lung cancer with a higher circulating lycopene level was 0.47 (95% CI: 0.30–0.73, overall P = 0.0007), with the Chi^2 p-value at 0.84, and the I2 at 0% (**Figure 3B**). Such data indicates that a higher circulating level of lycopene is correlated with a lower risk of lung cancer. Intriguingly, the other three studies that were not included in the meta-analysis consistently showed that lung cancer cases had a significantly lower circulating lycopene concentration than the healthy controls [93, 99, 110]. Only one study reported a similar lycopene concentration in lung cancer subjects and the controls [94]. One possible explanation for this negative result is that Comstock et al. did not stratify the subjects according to the stage of lung cancer. Although serum lycopene concentration was comparable in the early stage patients and the advanced stage patients, serum lycopene concentration was more significant between the advanced lung cancer patients and the healthy controls [99]. If the majority of the patients included by Klarod et al. were cancer patients at an early stage, the difference of circulating lycopene level between the cases and the controls would be unapparent. One prospective study showed that serum lycopene concentration was lower in the lung cancer deaths than in the cancer survivors; however, such difference disappeared after the researchers adjusted the model for sex, age, smoking habit, and serum levels of total cholesterol and alanine aminotransferase (ALT) activity [97] suggesting that the association between lycopene and lung cancer mortality might be influenced by multiple factors, which warrants further investigation.

In conclusion, we found consistent reports showing that dietary lycopene intake, or the consumption of lycopene-enriched foods, was inversely related to lung cancer risk. Our systematic review and meta-analysis showed that the circulating lycopene level might be a potential biomarker predicting lung cancer risk.

4. Concluding remarks

We summarized the association between circulating lycopene and chronic lung diseases in a comprehensive manner. To accomplish this task, we first have screened both *in vitro* reports and *in vivo* animal models to delineate lycopene's role in chronic lung diseases including asthma, COPD, emphysema, acute lung injury, pulmonary fibrosis, and lung cancer. Dietary lycopene intervention could potentially decrease the infiltration of pro-inflammatory cytokines in ovalbumin-induced airway inflammation in a murine model of asthma [37, 38]. Lycopene was also found to inhibit smoke-induced bronchitis and emphysema through reverse cholesterol transport in the COPD model in ferrets [41]. In a murine model (C57BL/6 mice) for emphysema, lycopene administration lessened the detrimental effects of chronic cigarette smoke exposure [42]. Lycopene treatment was found to ease LPS-induced acute lung injury (ALI) in murine animal models [46], BALB/c mice, and LPS-induced ALI in a rat model [47]. Lycopene extracted from tomatoes could reduce the burden of lung fibrosis's pathological effects in a rodent study [52]. In terms of

lung cancer, lycopene could decrease the extent of squamous metaplasia in a ferret model using the conventional method of induction of lung cancer by cigarette smoke [64]. Alternative models using carcinogenic agents were not definitive in showing its chemoprevention capabilities [62–67].

Next, we conducted a systematic review and meta-analysis to reveal the link between lycopene concentration and lung diseases in clinical trials using multiple electronic databases. While several case–control studies reported markedly lower lycopene concentration in asthma patients [76–79], others found that asthma progression was not related to lycopene in the circulation [74, 75, 77, 80–82], suggesting that the association between asthma and lycopene concentrations in humans was not conclusive. We came across several epidemiological studies, including case–control, cross-sectional, and prospective studies, to demonstrate the association between lycopene concentration in the circulation and COPD in our meta-analysis. These trials reported similar lycopene concentrations in healthy subjects vs. COPD patients [75, 77, 81, 92]. Finally, we found that dietary lycopene is inversely associated with lung cancer risk, particularly in subjects with low lycopene in their circulation [93, 102, 104]. Furthermore, circulating lycopene displayed a significant association between advanced lung cancer patients and early-stage patients [99].

5. Future perspective

Overall, our comprehensive review in this chapter provides convincing evidence on the role of lycopene in chronic lung diseases including lung cancer. This chapter also contributes confirmatory data to the as yet unsettled proof on the hypothesized associations between lycopene in circulation and lung diseases. The health benefits of lycopene can be attributed to its antioxidant function as highlighted in this chapter. Lycopene can be used as a preventive and therapeutic compound by itself or in combination with other compounds to improve lung diseases. Further investigations and well-designed clinical trials are needed to confirm whether there is a casual relation between the disease and the circulating lycopene in humans.

Acknowledgements

The authors gratefully *acknowledge* the financial support of North Carolina State University. We also thank Baxter Miller for searching the research literature.

Abbreviations

FRAP	Ferric Reducing Antioxidant Power
Gpx	glutathione peroxidase
GR	glutathione reductase
SOD	superoxide dismutase
SNPs	single nucleotide polymorphisms
ABCA1	ATP binding cassette subfamily a member 1
LPL	lipoprotein lipase
INSIG2	insulin-induced gene 2
SLC27A6	solute carrier family 27 member 6
LIPC	lipase C
CD36	cluster of differentiation 36 molecule
APOB	apolipoprotein B

ROS	reactive oxygen species
i.p.	intraperitoneal
OVA	ovalbumin
BW	body weight
BALF	bronchoalveolar lavage fluid
EPO	eosinophil peroxidase
MMP-9	matrix metalloproteinase-9
IL-4	interleukin-4
IL-5	interleukin-5
COPD	Chronic obstructive pulmonary disease
NNK	nicotine-derived nitrosamine ketone
CAT	catalase
GSH	glutathione
IL-10	interleukin-10
TNF-α	tumor necrosis factor-alpha
IFNγ	interferon-gamma
SAM	senescence-accelerated mouse
ALI	Acute lung injury
LPS	lipopolysaccharide
MDA	malondialdehyde
MPO	myeloperoxidase
IL-6	interleukin-6
SG	Sarcandra glabra
MAPK	mitogen-activated protein kinase
OA	oleic acid
IL-1β	interleukin-1β
IPF	idiopathic pulmonary fibrosis
BLM	Bleomycin
NO	nitric oxide
NSCLC	non-small cell lung cancer
ROS	reactive oxygen species
BaP	insulin-like growth factor binding protein-3, benzo[a]pyrene
DMH	dimethylhydrazine
LTO	lycopene-enriched tomato oleserin
NHBE	normal human bronchial epithelial cells
HMG-CoA	3-hydroxy-3-methylglutaryl–coenzyme A
RARβ	retinoic acid receptor β
GJC	gap junction communication
Cx43	connexin-43
RCT	randomized controlled trial
RR	relative ratio
OR	odds ratio
HR	hazard ratio
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
ACOS	asthma-COPD overlap syndrome
NHANES III	National Health and Nutrition Examination Survey
ALT	alanine aminotransferase

Author details

Emilio Balbuena[1,2,†], Junrui Cheng[1,†] and Abdulkerim Eroglu[1,2*]

1 Plants for Human Health Institute, North Carolina State University, Kannapolis, NC, USA

2 Department of Molecular and Structural Biochemistry, College of Agriculture and Life Sciences, North Carolina State University, Raleigh, NC, USA

*Address all correspondence to: aeroglu@ncsu.edu

† Balbuena and Cheng contributed equally to this work.

IntechOpen

References

[1] Palozza, P., et al., *Tomato Lycopene and Inflammatory Cascade: Basic Interactions and Clinical Implications.* Curr Med Chem, 2010. **17**(23): p. 2547-2563.

[2] Rao, A.V. and A. Ali, *Biologically Active Phytochemicals in Human Health: Lycopene.* International Journal of Food Properties, 2007. **10**(2): p. 279-288.

[3] Eroglu, A. and E.H. Harrison, *Carotenoid metabolism in mammals, including man: formation, occurrence, and function of apocarotenoids.* J Lipid Res, 2013. **54**(7): p. 1719-1730.

[4] Rowles, J.L., 3rd and J.W. Erdman, Jr., *Carotenoids and their role in cancer prevention.* Biochim Biophys Acta Mol Cell Biol Lipids, 2020. **1865**(11): p. 158613.

[5] Olson, J.A. and N.I. Krinsky, *Introduction: the colorful, fascinating world of the carotenoids: important physiologic modulators.* Faseb j, 1995. **9**(15): p. 1547-1550.

[6] Palozza, P., et al., *Lycopene modulation of molecular targets affected by smoking exposure.* Curr Cancer Drug Targets, 2012. **12**(6): p. 640-657.

[7] Narayanasamy, S., et al., *Synthesis of apo-13- and apo-15-lycopenoids, cleavage products of lycopene that are retinoic acid antagonists.* J Lipid Res, 2017. **58**(5): p. 1021-1029.

[8] Hu, K.Q., et al., *The biochemical characterization of ferret carotene-9',10'-monooxygenase catalyzing cleavage of carotenoids in vitro and in vivo.* J Biol Chem, 2006. **281**(28): p. 19327-19338.

[9] Kopec, R.E., et al., *Identification and quantification of apo-lycopenals in fruits, vegetables, and human plasma.* J Agric Food Chem, 2010. **58**(6): p. 3290-6.

[10] Di Mascio, P., S. Kaiser, and H. Sies, *Lycopene as the most efficient biological carotenoid singlet oxygen quencher.* Arch Biochem Biophys, 1989. **274**(2): p. 532-538.

[11] Stahl, W., et al., *Carotenoid mixtures protect multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein.* FEBS Lett, 1998. **427**(2): p. 305-308.

[12] Pennathur, S., et al., *Potent antioxidative activity of lycopene: A potential role in scavenging hypochlorous acid.* Free Radic Biol Med, 2010. **49**(2): p. 205-213.

[13] Lee, A., D.I. Thurnham, and M. Chopra, *Consumption of tomato products with olive oil but not sunflower oil increases the antioxidant activity of plasma.* Free Radic Biol Med, 2000. **29**(10): p. 1051-1055.

[14] Subhash, K., C. Bose, and B.K. Agrawal, *Effect of short term supplementation of tomatoes on antioxidant enzymes and lipid peroxidation in type-II diabetes.* Indian J Clin Biochem, 2007. **22**(1): p. 95-98.

[15] Clinton, S.K., *Lycopene: chemistry, biology, and implications for human health and disease.* Nutr Rev, 1998. **56**(2 Pt 1): p. 35-51.

[16] Soares, N.d.C.P., et al., *Comparative Analysis of Lycopene Content from Different Tomato-Based Food Products on the Cellular Activity of Prostate Cancer Cell Lines.* Foods (Basel, Switzerland), 2019. **8**(6): p. 201.

[17] Porrini, M. and P. Riso, *What are typical lycopene intakes?* J Nutr, 2005. **135**(8): p. 2042s–5s.

[18] Kamiloglu, S., D. Boyacioglu, and E. Capanoglu, *The effect of food processing on bioavailability of tomato antioxidants.* Journal of Berry Research, 2013. **3**: p. 65-77.

[19] Başaran, N., M. Bacanlı, and A. Ahmet Başaran, *Chapter 28 - Lycopenes as Antioxidants in Gastrointestinal Diseases*, in *Gastrointestinal Tissue*, J. Gracia-Sancho and J. Salvadó, Editors. 2017, Academic Press. p. 355-362.

[20] Marković, K., M. Hruškar, and N. Vahčić, *Lycopene content of tomato products and their contribution to the lycopene intake of Croatians.* Nutrition Research, 2006. **26**(11): p. 556-560.

[21] Gärtner, C., W. Stahl, and H. Sies, *Lycopene is more bioavailable from tomato paste than from fresh tomatoes.* Am J Clin Nutr, 1997. **66**(1): p. 116-122.

[22] Danuta, G., et al., *Lycopene in tomatoes and tomato products.* Open Chemistry, 2020. **18**(1): p. 752-756.

[23] Unlu, N.Z., et al., *Carotenoid absorption from salad and salsa by humans is enhanced by the addition of avocado or avocado oil.* J Nutr, 2005. **135**(3): p. 431-436.

[24] Borel, P., et al., *Lycopene bioavailability is associated with a combination of genetic variants.* Free Radical Biology and Medicine, 2015. **83**: p. 238-244.

[25] Moran, N.E., et al., *Single Nucleotide Polymorphisms in β-Carotene Oxygenase 1 are Associated with Plasma Lycopene Responses to a Tomato-Soy Juice Intervention in Men with Prostate Cancer.* The Journal of Nutrition, 2019. **149**(3): p. 381-397.

[26] Wang, X.-D., *Lycopene metabolism and its biological significance.* The American journal of clinical nutrition, 2012. **96**(5): p. 1214S–1222S.

[27] Moran, N.E., J.W. Erdman, Jr., and S.K. Clinton, *Complex interactions between dietary and genetic factors impact lycopene metabolism and distribution.* Archives of biochemistry and biophysics, 2013. **539**(2): p. 171-180.

[28] Story, E.N., et al., *An update on the health effects of tomato lycopene.* Annual review of food science and technology, 2010. **1**: p. 189-210.

[29] Tremblay, B.L., et al., *Genetic and Common Environmental Contributions to Familial Resemblances in Plasma Carotenoid Concentrations in Healthy Families.* Nutrients, 2018. **10**(8): p. 1002.

[30] Rust, P., P. Lehner, and I. Elmadfa, *Relationship between dietary intake, antioxidant status and smoking habits in female Austrian smokers.* Eur J Nutr, 2001. **40**(2): p. 78-83.

[31] Lagiou, P., et al., *Plasma carotenoid levels in relation to tobacco smoking and demographic factors.* Int J Vitam Nutr Res, 2003. **73**(3): p. 226-231.

[32] Yuan, J.M., et al., *Prediagnostic levels of serum beta-cryptoxanthin and retinol predict smoking-related lung cancer risk in Shanghai, China.* Cancer Epidemiol Biomarkers Prev, 2001. **10**(7): p. 767-773.

[33] Rao, A.V. and S. Agarwal, *Effect of diet and smoking on serum lycopene and lipid peroxidation.* Nutrition Research, 1998. **18**(4): p. 713-721.

[34] Petyaev, I.M., *Lycopene Deficiency in Ageing and Cardiovascular Disease.* Oxidative medicine and cellular longevity, 2016. **2016**: p. 3218605-3218605.

[35] Steck-Scott, S., et al., *Plasma and lung macrophage responsiveness to carotenoid supplementation and ozone exposure in humans.* Eur J Clin Nutr, 2004. **58**(12): p. 1571-1579.

[36] Holgate, S.T., *The airway epithelium is central to the pathogenesis of asthma.* Allergol Int, 2008. **57**(1): p. 1-10.

[37] Lee, C.M., et al., *Lycopene suppresses ovalbumin-induced airway inflammation in a murine model of asthma.* Biochem

Biophys Res Commun, 2008. **374**(2): p. 248-252.

[38] Hazlewood, L.C., et al., *Dietary lycopene supplementation suppresses Th2 responses and lung eosinophilia in a mouse model of allergic asthma.* J Nutr Biochem, 2011. **22**(1): p. 95-100.

[39] Barnes, P.J., et al., *Chronic obstructive pulmonary disease.* Nat Rev Dis Primers, 2015. **1**: p. 15076.

[40] Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* Am J Respir Crit Care Med, 2013. **187**(4): p. 347-365.

[41] Mustra Rakic, J., et al., *Lycopene Inhibits Smoke-Induced Chronic Obstructive Pulmonary Disease and Lung Carcinogenesis by Modulating Reverse Cholesterol Transport in Ferrets.* Cancer Prev Res (Phila), 2019. **12**(7): p. 421-432.

[42] Campos, K.K.D., et al., *Lycopene mitigates pulmonary emphysema induced by cigarette smoke in a murine model.* J Nutr Biochem, 2019. **65**: p. 93-100.

[43] Campos, K.K.D., et al., *The antioxidant and anti-inflammatory properties of lycopene in mice lungs exposed to cigarette smoke.* J Nutr Biochem, 2017. **48**: p. 9-20.

[44] Kasagi, S., et al., *Tomato juice prevents senescence-accelerated mouse P1 strain from developing emphysema induced by chronic exposure to tobacco smoke.* Am J Physiol Lung Cell Mol Physiol, 2006. **290**(2): p. L396–L404.

[45] Johnson, E.R. and M.A. Matthay, *Acute lung injury: epidemiology, pathogenesis, and treatment.* J Aerosol Med Pulm Drug Deliv, 2010. **23**(4): p. 243-252.

[46] Li, W.W., et al., *Synergistic protection of matrine and lycopene against lipopolysaccharide-induced acute lung injury in mice.* Mol Med Rep, 2019. **20**(1): p. 455-462.

[47] Liu, T.Y. and S.B. Chen, *Sarcandra glabra combined with lycopene protect rats from lipopolysaccharide induced acute lung injury via reducing inflammatory response.* Biomed Pharmacother, 2016. **84**: p. 34-41.

[48] Türkoğlu, S., et al., *Effects of lycopene on the model of oleic acid-induced acute lung injury.* Tuberk Toraks, 2012. **60**(2): p. 101-107.

[49] Bastug, O., et al., *Effects of Lycopene in Hyperoxia-Induced Lung Injury in Newborn Rats.* Int J Vitam Nutr Res, 2018. **88**(5-6): p. 270-280.

[50] Ballester, B., J. Milara, and J. Cortijo, *Idiopathic Pulmonary Fibrosis and Lung Cancer: Mechanisms and Molecular Targets.* Int J Mol Sci, 2019. **20**(3).

[51] Ley, B., H.R. Collard, and T.E. King, Jr., *Clinical course and prediction of survival in idiopathic pulmonary fibrosis.* Am J Respir Crit Care Med, 2011. **183**(4): p. 431-440.

[52] Zhou, C., et al., *Lycopene from tomatoes partially alleviates the bleomycin-induced experimental pulmonary fibrosis in rats.* Nutr Res, 2008. **28**(2): p. 122-130.

[53] Muzandu, K., et al., *Effect of lycopene and beta-carotene on peroxynitrite-mediated cellular modifications.* Toxicol Appl Pharmacol, 2006. **215**(3): p. 330-340.

[54] Muzandu, K., et al., *Lycopene and beta-carotene ameliorate catechol estrogen-mediated DNA damage.* Jpn J Vet Res, 2005. **52**(4): p. 173-184.

[55] Jemal, A., et al., *Global cancer statistics.* CA Cancer J Clin, 2011. **61**(2): p. 69-90.

[56] Kim, L., A.V. Rao, and L.G. Rao, *Effect of lycopene on prostate LNCaP cancer cells in culture.* J Med Food, 2002. **5**(4): p. 181-187.

[57] Park, Y.O., E.S. Hwang, and T.W. Moon, *The effect of lycopene on cell growth and oxidative DNA damage of Hep3B human hepatoma cells.* Biofactors, 2005. **23**(3): p. 129-139.

[58] Fornelli, F., et al., *The influence of lycopene on the proliferation of human breast cell line (MCF-7).* Toxicol In Vitro, 2007. **21**(2): p. 217-223.

[59] Levy, J., et al., *Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene.* Nutr Cancer, 1995. **24**(3): p. 257-266.

[60] Choi, S.H., et al., *Changes in free amino acid, phenolic, chlorophyll, carotenoid, and glycoalkaloid contents in tomatoes during 11 stages of growth and inhibition of cervical and lung human cancer cells by green tomato extracts.* J Agric Food Chem, 2010. **58**(13): p. 7547-7556.

[61] Reddy, M.K., R.L. Alexander-Lindo, and M.G. Nair, *Relative inhibition of lipid peroxidation, cyclooxygenase enzymes, and human tumor cell proliferation by natural food colors.* J Agric Food Chem, 2005. **53**(23): p. 9268-9273.

[62] Lian, F., et al., *Apo-10'-lycopenoic acid inhibits lung cancer cell growth in vitro, and suppresses lung tumorigenesis in the A/J mouse model in vivo.* Carcinogenesis, 2007. **28**(7): p. 1567-1574.

[63] Cheng, J., et al., *Lycopene Protects against Smoking-Induced Lung Cancer by Inducing Base Excision Repair.* Antioxidants (Basel), 2020. **9**(7).

[64] Liu, C., et al., *Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets.* Cancer Res, 2003. **63**(12): p. 3138-3144.

[65] Kim, D.J., et al., *Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH.* Cancer Lett, 1997. **120**(1): p. 15-22.

[66] Hecht, S.S., et al., *Evaluation of butylated hydroxyanisole, myo-inositol, curcumin, esculetin, resveratrol and lycopene as inhibitors of benzo[a] pyrene plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice.* Cancer Lett, 1999. **137**(2): p. 123-130.

[67] Guttenplan, J.B., et al., *Effects of a lycopene-rich diet on spontaneous and benzo[a]pyrene-induced mutagenesis in prostate, colon and lungs of the lacZ mouse.* Cancer Lett, 2001. **164**(1): p. 1-6.

[68] Li, C.C., et al., *Tomato Powder Inhibits Hepatic Steatosis and Inflammation Potentially Through Restoring SIRT1 Activity and Adiponectin Function Independent of Carotenoid Cleavage Enzymes in Mice.* Mol Nutr Food Res, 2018. **62**(8): p. e1700738.

[69] Lim, J.Y. and X.D. Wang, *Mechanistic understanding of β-cryptoxanthin and lycopene in cancer prevention in animal models.* Biochim Biophys Acta Mol Cell Biol Lipids, 2020. **1865**(11): p. 158652.

[70] Palozza, P., et al., *Modulation of apoptotic signalling by carotenoids in cancer cells.* Arch Biochem Biophys, 2004. **430**(1): p. 104-109.

[71] Stahl, W., et al., *Stimulation of gap junctional communication: comparison of acyclo-retinoic acid and lycopene.* Arch Biochem Biophys, 2000. **373**(1): p. 271-274.

[72] Moher, D., et al., *Preferred reporting items for systematic reviews and*

meta-analyses: the PRISMA statement. BMJ, 2009. **339**: p. b2535.

[73] Greenland, S. and D.C. Thomas, *On the need for the rare disease assumption in case-control studies.* Am J Epidemiol, 1982. **116**(3): p. 547-553.

[74] Schock, B.C., et al., *Antioxidants and oxidative stress in BAL fluid of atopic asthmatic children.* Pediatr Res, 2003. **53**(3): p. 375-381.

[75] Ford, E.S., D.M. Mannino, and S.C. Redd, *Serum antioxidant concentrations among U.S. adults with self-reported asthma.* J Asthma, 2004. **41**(2): p. 179-187.

[76] Wood, L.G., et al., *Airway and circulating levels of carotenoids in asthma and healthy controls.* J Am Coll Nutr, 2005. **24**(6): p. 448-455.

[77] Ochs-Balcom, H.M., et al., *Antioxidants, oxidative stress, and pulmonary function in individuals diagnosed with asthma or COPD.* Eur J Clin Nutr, 2006. **60**(8): p. 991-999.

[78] Riccioni, G., et al., *Plasma lycopene and antioxidant vitamins in asthma: the PLAVA study.* J Asthma, 2007. **44**(6): p. 429-432.

[79] Sackesen, C., et al., *A comprehensive evaluation of the enzymatic and nonenzymatic antioxidant systems in childhood asthma.* J Allergy Clin Immunol, 2008. **122**(1): p. 78-85.

[80] Wood, L.G. and P.G. Gibson, *Reduced circulating antioxidant defences are associated with airway hyper-responsiveness, poor control and severe disease pattern in asthma.* Br J Nutr, 2010. **103**(5): p. 735-741.

[81] Kodama, Y., et al., *Antioxidant nutrients in plasma of Japanese patients with chronic obstructive pulmonary disease, asthma-COPD overlap syndrome and bronchial asthma.* Clin Respir J, 2017. **11**(6): p. 915-924.

[82] Larkin, E.K., et al., *New risk factors for adult-onset incident asthma. A nested case-control study of host antioxidant defense.* Am J Respir Crit Care Med, 2015. **191**(1): p. 45-53.

[83] Neuman, I., H. Nahum, and A. Ben-Amotz, *Reduction of exercise-induced asthma oxidative stress by lycopene, a natural antioxidant.* Allergy, 2000. **55**(12): p. 1184-1189.

[84] Falk, B., et al., *Effect of lycopene supplementation on lung function after exercise in young athletes who complain of exercise-induced bronchoconstriction symptoms.* Ann Allergy Asthma Immunol, 2005. **94**(4): p. 480-485.

[85] Wood, L.G., et al., *Lycopene-rich treatments modify noneosinophilic airway inflammation in asthma: proof of concept.* Free Radic Res, 2008. **42**(1): p. 94-102.

[86] Wood, L.G., et al., *Manipulating antioxidant intake in asthma: a randomized controlled trial.* Am J Clin Nutr, 2012. **96**(3): p. 534-543.

[87] Vaz Fragoso, C.A., et al., *The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease.* American journal of respiratory and critical care medicine, 2010. **181**(5): p. 446-451.

[88] Beck, K.C., M.J. Joyner, and P.D. Scanlon, *Exercise-Induced asthma: diagnosis, treatment, and regulatory issues.* Exerc Sport Sci Rev, 2002. **30**(1): p. 1-3.

[89] Thulborn, S.J., et al., *Neutrophil elastase as a biomarker for bacterial infection in COPD.* Respir Res, 2019. **20**(1): p. 170.

[90] Murdoch, J.R. and C.M. Lloyd, *Chronic inflammation and asthma.* Mutation research, 2010. **690**(1-2): p. 24-39.

[91] Cukic, V., et al., *Asthma and Chronic Obstructive Pulmonary Disease (COPD) - Differences and Similarities.* Materia socio-medica, 2012. **24**(2): p. 100-105.

[92] Kentson, M., et al., *Oxidant status, iron homeostasis, and carotenoid levels of COPD patients with advanced disease and LTOT.* Eur Clin Respir J, 2018. **5**(1): p. 1447221.

[93] Asbaghi, S., et al., *Dietary Intake and Serum Level of Carotenoids in Lung Cancer Patients: A Case-Control Study.* Nutr Cancer, 2015. **67**(6): p. 893-898.

[94] Comstock, G.W., et al., *The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acids, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity.* Am J Epidemiol, 2008. **168**(7): p. 831-840.

[95] Garcia-Closas, R., et al., *Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain.* Nutr Cancer, 1998. **32**(3): p. 154-158.

[96] Holick, C.N., et al., *Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study.* Am J Epidemiol, 2002. **156**(6): p. 536-547.

[97] Ito, Y., et al., *Cancer mortality and serum levels of carotenoids, retinol, and tocopherol: a population-based follow-up study of inhabitants of a rural area of Japan.* Asian Pac J Cancer Prev, 2005. **6**(1): p. 10-15.

[98] Ito, Y., et al., *Lung cancer mortality and serum levels of carotenoids, retinol, tocopherols, and folic acid in men and women: a case-control study nested in the JACC Study.* J Epidemiol, 2005. **15 Suppl 2**: p. S140–S149.

[99] Klarod, K., et al., *Serum antioxidant levels and nutritional status in early and advanced stage lung cancer patients.* Nutrition, 2011. **27**(11-12): p. 1156-1160.

[100] Le Marchand, L., et al., *Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii.* J Natl Cancer Inst, 1989. **81**(15): p. 1158-1164.

[101] Michaud, D.S., et al., *Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts.* Am J Clin Nutr, 2000. **72**(4): p. 990-997.

[102] Rohan, T.E., et al., *A cohort study of dietary carotenoids and lung cancer risk in women (Canada).* Cancer Causes Control, 2002. **13**(3): p. 231-237.

[103] Satia, J.A., et al., *Long-term use of beta-carotene, retinol, lycopene, and lutein supplements and lung cancer risk: results from the VITamins And Lifestyle (VITAL) study.* Am J Epidemiol, 2009. **169**(7): p. 815-828.

[104] Shareck, M., et al., *Inverse Association between Dietary Intake of Selected Carotenoids and Vitamin C and Risk of Lung Cancer.* Front Oncol, 2017. **7**: p. 23.

[105] Stefani, E.D., et al., *Dietary antioxidants and lung cancer risk: a case-control study in Uruguay.* Nutr Cancer, 1999. **34**(1): p. 100-110.

[106] Steinmetz, K.A., J.D. Potter, and A.R. Folsom, *Vegetables, fruit, and lung cancer in the Iowa Women's Health Study.* Cancer Res, 1993. **53**(3): p. 536-543.

[107] Talwar, D., et al., *Effect of inflammation on measures of antioxidant status in patients with non-small cell lung cancer.* Am J Clin Nutr, 1997. **66**(5): p. 1283-5.

[108] Voorrips, L.E., et al., *A prospective cohort study on antioxidant and folate intake and male lung cancer risk.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(4): p. 357-365.

[109] Yuan, J.M., et al., *Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study*. Cancer Epidemiol Biomarkers Prev, 2003. **12**(9): p. 890-898.

[110] Bakker Schut, T.C., et al., *Intracellular carotenoid levels measured by Raman microspectroscopy: comparison of lymphocytes from lung cancer patients and healthy individuals.* Int J Cancer, 1997. **74**(1): p. 20-25.