DHA May Have a Profoundly Protective Impact on the Lungs of Smokers

McCarty MF
Catalytic Longevity, 7831 Rush Rose Dr., Apt. 316, Carlsbad, CA 92009, USA

Corresponding author: McCarty MF, Catalytic Longevity, 7831 Rush Rose Dr., Apt. 316, Carlsbad, CA 92009, USA; Tel: 7602167272; Fax: 7607046379; E-mail: markfmcarty@gmail.com

Received date: Nov 26, 2015; Accepted date: Mar 28, 2016; Published date: Mar 31, 2016

Copyright: © 2016 McCarty MF. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Evidence has accumulated over the last twenty years that smokers who frequently ingest fish are at lower risk for both chronic obstructive pulmonary disease (COPD) and lung cancer. Plasma phospholipid levels of DHA, but not EPA, have been reported to correlate inversely with risk for COPD in smokers, suggesting that DHA may be primarily responsible for the apparent protection afforded to lungs of smokers by fish consumption. Meanwhile, evidence is emerging that certain metabolites of DHA - including 4 - hydroxy hexenal (4-HHE), 17 - oxo - DHA, and resolvin D1 - can activate Nrf2 - mediated transcription of heme oxygenase - 1 and other antioxidant / cytoprotective enzymes. Since the oxidant stress imposed by cigarette smoke exposure could be expected to promote peroxidation of membrane DHA and hence boost production of 4 - HHE, DHA in lung membranes may in effect up-regulate the protective feedback mechanism whereby oxidative stress provokes Nrf2 - mediated induction of cytoprotective enzymes. DHA can also give rise to the autacoid resolvin D1, which, via activation of a receptor, suppresses NF - kappaB activation and the consequent production of pro-inflammatory cytokines. Resolvin D1 can also inhibit macrophage NADPH oxidase and promote an anti-inflammatory M2 phenotype in lung macrophages. Not surprisingly, inhalation of resolvin D1 has a marked anti-inflammatory impact on the lungs of mice exposed to tobacco smoke. These considerations help to rationalize the epidemiology linking fish consumption to lung health, and suggest that smokers who can’t or won’t quit their habit would be well advised to consume fish or DHA supplements regularly. Higher intakes of fruits and vegetables - likely in part because many of these contain Nrf2 - activating phytochemicals - likewise are associated with lower risk for COPD, and can be recommended for smokers.

Keywords: COPD; Lung cancer; Fish; Docosahexaenoic acid (DHA); 4 - hydroxy hexenal; Nrf2; Resolvin D1

Fish Consumption May Protect Smokers from COPD

Limited but nonetheless compelling epidemiology has linked heavy dietary consumption of fresh fish to marked decreases in risk for lung cancer and chronic obstructive pulmonary disease (COPD) among smokers. The first key evidence in this regard emerged in 1994. Shahar et al. [1] studied subjects enrolled in the prospective Atherosclerosis Risk in Communities (ARIC) study, who had received a dietary assessment and a physical exam including lung spirometry, and had been questioned regarding lung symptoms [1]. COPD was defined by three separate criteria: self - reported symptoms of chronic bronchitis, physician diagnosis of emphysema, and via spirometry (FEV1 < 65% of predicted value). When risk for COPD was compared between the first and fourth quartiles of estimated daily intake of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), relative risk for COPD in the fourth quartile (mean omega-3 intake 480 mg) after appropriate multivariate adjustments was found to be 0.66 (95% CI 0.52 - 0.85), 0.31 (CI 0.18 - 0.52), and 0.50 (CI 0.32 - 0.79) for the three diagnostic criteria, respectively. Linear trends were statistically significant for each criterion. These findings suggested that even fairly modest intakes of long-chain omega-3s not uncommon in the U.S. might provide quite meaningful protection from COPD in smokers.

In the same year, a study appeared evaluating Japanese-American male smokers participating in the Honolulu Heart Program [2]. This study attempted to correlate forced expiratory volume in 1 sec (FEV1) with habitual fish consumption. Low fish consumption was defined as less than 2 fish meals weekly, high consumption as two or more fish meals weekly. After appropriate multivariate adjustments, the researchers found that, among men who smoked 30 or less cigarettes daily, high fish intake was associated with a FEV1 about 52 ml higher (95% CI 17 - 87) than in subjects with low fish intake. At higher intensities of smoking, the protective impact of increased fish consumption was attenuated and lost statistical significance. The authors concluded that regular fish consumption protected the lungs of moderate smokers, but that very heavy smoking seemed to overwhelm the protection afforded by fish. The title of this study was quite explicit: “Fish consumption may limit the damage of smoking on the lungs.”

A third study published in that year focused on a subsample of the First National Health and Nutritional Examination Study (NHANES I) who had received spirometry testing in addition to diet evaluation [3]. In a multiple regression analysis, fish consumption was found to correlate positively with FEV1, in agreement with the previous study.

A further pertinent analysis based in the ARIC study appeared in 1999 [4]. In this report, omega - 3 statuses was assessed by measuring EPA and DHA levels in plasma phospholipids, and COPD was defined by report of symptoms or spirometry. After multivariate adjustments, risk for bronchitis in the four quartiles of DHA was 1.0, 0.98, 0.88, and 0.69 (p for trend = 0.09). The corresponding risks for COPD defined by spirometry were 1.0, 0.65, 0.51, and 0.48 (p < 0.001). Intriguingly, levels of EPA showed no correlation with risk for COPD, suggesting that the apparent protection afforded by fish was likely to be mediated by DHA.
Although few subsequent studies have examined the impact of fish intake specifically on COPD risk, several studies have reported that a "prudent" dietary pattern characterized by ample intakes of fruits, vegetables, fatty fish, and whole grains is associated with a notably lower risk for COPD [5-8]. And a recent cross-sectional study in Singapore has confirmed that frequent fish intake (3 or more times weekly) as well as daily fish oil supplementation is associated with higher FEV1 values [9].

Despite the fact that numerous studies have pointed to fish consumption - likely because of its DHA content - as markedly protective for the lungs of smokers, there do not appear to have been any significant efforts on the part of public health authorities to alert smokers to these findings. This despite the fact that COPD is a leading cause of death - predicted by the World Health Organization to become the fourth leading cause of death worldwide by 2030 [10] for which smoking is the overwhelmingly predominant risk factor. Nonetheless, it is encouraging to report that Australian researchers are undertaking a 16 - week placebo - controlled study of fish oil ingestion (3.6 g omega-3 daily) in patients with COPD [11].

**Fish Consumption May Protect Smokers from Lung Cancer**

Of related interest are several studies that have evaluated the association of fish intake with lung cancer risk in smokers. A prospective Japanese study followed 5,885 subjects for 14 years, during which time 51 lung cancer cases developed [12]. Baseline fish intake was stratified as less than 1 time weekly, 1 or 2 times weekly and 3 or more times weekly. Multivariate-adjusted risks for lung cancer in these three categories were found to be 1.00, 0.37 (95% CI 0.16 - 0.83), and 0.19 (0.08 - 0.46); p for trend < 0.001. Although the size of this study was modest, the higher proportion of subjects with an ample fish intake enabled it to achieve a robust result.

An ecologic study attempted to correlate fish consumption and age-adjusted lung cancer mortality in 36 countries during 10 time periods between 1961-1994 [13]. After adjustment for smoking and other confounding variables, the log of fish consumption (as percent of total energy) was found to correlate inversely and significantly with lung cancer mortality in men in all ten time periods. An increase of fish intake corresponding to 1% of dietary energy was associated with a reduction in lung cancer mortality of 8.4%. This finding could not be reproduced in women, possibly because of the relatively low proportion of long-term female smokers during the times surveyed.

Additional case-control or cohort studies in Norway, Hong Kong, Australia, the United Kingdom, and Japan (the latter focused solely on adenocarcinomas) likewise have found that consumption of fish or fish liver oil correlates inversely with lung cancer risk or mortality [14-17]. A trend (p = 0.08) toward protection with fresh fish consumption was also reported in a study from New Caledonia [18]. A study in Hong Kong correlated fish consumption inversely with lung cancer risk in non-smoking women [19]. Several studies have failed to correlate fish intakes with lung cancer risk [20-24]; but the majority of these were conducted in countries with low average fish consumption. The only study to have reported a significant positive correlation between fish intake and lung cancer risk was a Chinese study in which controls consumed fish, on average, less than once per month, and this was often salt-preserved fish [24].

The impression that fish consumption may decrease lung cancer now finds support in a very recent meta-analysis [25]. This incorporated the findings of 20 case-control or cohort studies including a total of 8,799 cases of lung cancer. A relatively high consumption of fish, relative to lower consumption, was associated with a significantly lower risk for lung cancer: HR = 0.79, 95% CI 0.69 - 0.92.

Zhang et al. tellingly comment that, whereas men in Iceland and Hungary smoke at comparably high rates, the lung cancer mortality rate in Hungary is 3.4 times higher than in Iceland; it is probably not coincidental that Iceland is noted for high fish consumption, whereas Hungary is not [13]. Analogously, Japanese men smoke more intensely than US men do - but their lung cancer risk is notably lower.

Of related interest is a recent clinical study which measured serum levels of 8 - hydroxydeoxyguanosine (8 - OHdG) - a marker of oxidant-mediated DNA damage - and serum total antioxidant capacity (TAC) in 40 male cigarette smokers and 40 age-matched never-smokers [26]. 8 - OHdG was found to be higher, and TAC lower, in the smokers. The smokers were then randomized to receive 1 g of fish oil or a matching placebo for 3 months. Serum 8 - OHdG dropped significantly, and TAC rose significantly, in the smokers receiving fish oil, whereas these parameters did not change in the placebo-treated subjects. Also of interest is a study in which nitrosamine-induced lung cancer induction was markedly reduced in mice receiving a diet featuring fish oil, as opposed to mice receiving diets made with corn or soybean oil [27].

**DHA Provides Feedback Control of Oxidative Stress and Inflammation - Role of Nrf2**

When seeking the key mediator of dietary fish’s favorable impact on risk for COPD and lung cancer in smokers, suspicion naturally falls on DHA. Firstly, because the DHA content of plasma phospholipids has been reported to correlate inversely with COPD risk - whereas no such correlation emerged for EPA. Secondly, it is now known that DHA can give rise to at least three autocrines that exert antioxidant, anti-inflammatory, and inflammation-resolving effects: 4 - hydroxyhexenal, 17 - oxo - DHA, and resolvins D1.

It has long been known that peroxidative damage to linoleic acid in membrane phospholipids results in production of 4 - hydroxy nonenal (4 - HNE); this agent is an alpha-beta-unsaturated aldehyde that reacts avidly with free sulphydryl groups via a Michael addition reaction. The resulting covalent modification of proteins by 4 - HN is one of the notable ways in which oxidative stress exerts pathogenic effects. More recently, it has been appreciated that peroxidative damage to membrane DHA gives rise to the analogous product 4 - hydroxyhexenal (4 - HHE). Although, in excess, 4 - HHE can likewise be toxic to cells, it has the knack of efficiently boosting the transcriptional activity of the Nrf2 transcription factor [28]. (4-HNE can also achieve this, but at much higher concentrations.) Nrf2 activation leads to transcription of genes coding for a range of “phase 2” proteins that provide antioxidant and anti-mutagenic protection to the cell: heme oxygenase-1 (HO - 1), γ-glutamyl cysteine ligase (rate-limiting for glutathione synthesis), glutathione reductase, catalase, NAD(P)H quinone reductase, P63, and a range of glutathione S-transferases that mediate detoxification of electrophilic activated mutagens [29]. Nrf2 is usually retained in the cytoplasm and doomed to early proteasomal degradation by its interaction with the protein Keap1. However, Keap1 has a number cysteines which can interact covalently with hydrogen peroxide or certain electrophilic agents; the resulting alteration of Keap1’s structure can free nrf2 from its association with Keap1, enabling it to accumulate within the nucleus and promote...
transcription of its target genes. Hence, Nrf2 tends to be activated during oxidative stress or in the presence of electrophiles – some of which have mutagenic potential. Since 4 - HHE is electrophilic, the most straightforward and plausible explanation for 4-HH’s ability to boost nrf2 activity is that it binds to Keap1 with high efficiency.

Exposure of cultured endothelial cells to DHA - but not EPA - has been shown to give rise to 4 - HHE, promote nuclear translocation and DNA binding of Nrf2, and boost expression of the key cytoprotective enzyme HO – 1 [28]. Moreover, feeding a fish oil - rich diet to mice increases tissue levels of 4 - HHE and expression of HO – 1 in most organs examined – albeit HO - 1 was not induced in brain or spleen [28,30]. This fish oil-mediated induction of HO - 1 was not seen in Nrf2 - knockout mice - nor was the favorable impact of dietary fish oil on endothelium-dependent vasodilation observed in the aorta of normal mice [28].

These findings suggest the attractive hypothesis that the presence of DHA in the membranes of cells within the lung can markedly up-regulate the protective feedback mechanism whereby exposure to oxidant-rich cigarette smoke invokes increased expression of Nrf2 - dependent antioxidant and cytoprotective enzymes. Presumably, the oxidant stress imposed by cigarette smoke exposure should accelerate peroxidation of membrane DHA, boosting 4 - HHE generation and hence Nrf2 activation. This hypothesis should be readily testable, both in vitro and in vivo.

Another metabolic product of DHA shown to be capable of stimulating Nrf2 activity and HO - 1 expression - while doubling glutathione levels is 17 - oxo – DHA [31]. This, like 4 - HHE, is an alpha - beta - unsaturated electrophilic ketone, presumably capable of interacting with Keap1. However, the synthesis of 17 - oxo - DHA is catalyzed enzymatically in macrophages, by cyclooxygenase-2 (Cox-2) and a cellular dehydrogenase. Intriguingly, this synthesis is more robust when Cox - 2 has been acetylated by aspirin. Although 17 - oxo - DHA has an effect analogous to that of 4 - HHE on Nrf2 activation, it has an additional anti-inflammatory effect not mediated by Nrf2: in macrophages exposed to lipopolysaccharide, interleukin - 1 and / or cigarette smoke extract, 17 - oxo - DHA blocked induction of TNF-alpha; such an effect was still seen in macrophages pre-treated with siRNA targeting Nrf2. DHA per se did not have this effect, unless cigarette smoke extract was used as the trigger to TNF-alpha release; it is not clear whether 4 - HHE mediated the anti-inflammatory impact of DHA under these considerations, or whether increased production of 17 - oxo - DHA may have been stimulated by the extract.

DHA - Derived Autacoids Dampen Inflammation 

A third metabolic product of DHA with versatile anti-inflammatory activity is the autacoid resolvin D1, formed from DHA via the successive activities of lipoxygenase - 5 and lipoxygenase – 12 / 15. (A variant, more stable isofrom, 17-R-resolvin D1, can be produced via catalysis by aspirin-treated Cox-2 [32]) Although resolvin D1 has been shown to inhibit LPS induction-induced pulmonary edema in mice by inducing HO-1 in alveolar epithelial cells [33], this agent is not an electrophile and seems unlikely to interact with Keap1; rather, its effects are thought to be mediated primarily by stimulation of a membrane receptor [34]. As its name implies, resolvin D1 is now thought to play a key role in orchestrating the resolution of inflammation [35]. One of its effects is to promote the phagocytic engulfment of apoptotic immune cells in inflamed tissue (effecytosis); at the same time, it inhibits Nox2-dependent NADPH oxidase activity in macrophages, thereby protecting them from oxidant-driven apoptosis [36].

Several studies have examined the impact of resolvin D1 on inflammation triggered by cigarette smoke, both in vitro and in vivo. When primary human lung fibroblasts, small airway epithelial cells, and blood monocytes were exposed to either IL-1 or cigarette smoke extract in vitro, the resulting increased production of a range of pro-inflammatory cytokines was dose-dependently inhibited by concurrent exposure to resolvin D1 [37]. An analogous study showed that resolvin D1 could inhibit induction of interleukin-8 by cigarette smoke extract in a cell line derived from human bronchial epithelium; resolvin D1’s impact in this regard was traced to suppression of NF-kappaB activation [38]. When mice were exposed to mainstream cigarette smoke, prior inhalation of resolvin D1 was shown to block the recruitment of neutrophils to the lung and the production of pro-inflammatory cytokines evoked by smoke exposure; in addition, resolvin D1 enhanced lung levels of the anti-inflammatory cytokine interleukin-10, and promoted an inflammation-resolving, anti-inflammatory M2 phenotype in lung macrophages [37]. The authors of this latter study speculated that inhalable resolvin D1 - or some more stable analog thereof - might have potential as a drug for treating lung injury induced by inhalation of smoke or other toxic substances.

Clearly, the versatile effects of resolvin D1 - inhibiting NADPH oxidase, blocking NF-kappaB activation, suppressing production of pro-inflammatory cytokines, inhibiting neutrophil recruitment, inducing HO-1 and IL-10, and promoting inflammation-resolving behavior in macrophages, could be expected to alleviate the toxic impact of chronic or acute tobacco smoke exposure on the lungs as clearly is seen in smoke-exposed mice.

It seems likely that other DHA - derived autacoids with anti-inflammatory properties will be characterized - maresins being an example [39,40].

Finally, there is evidence that DHA per se - as well as EPA - can exert anti-inflammatory effects via direct activation of the GPR120 receptor, which is highly expressed in the lung [41,42]. The extent to which this receptor might mediate the lung protective effects of dietary omega-3 has not been assessed, but there is evidence that this receptor is a mediator of the favorable impact of omega-3 on metabolic syndrome in fat-fed mice [41].

Complementary Protection from Spirulina?

As noted, many DHA derivatives function to induce HO-1. The antioxidant properties of this enzyme are mediated largely via intracellular generation of free bilirubin, which functions physiologically to inhibit certain NADPH oxidase complexes [43-46]. Intriguingly, in a massive prospective study in the UK, serum levels of bilirubin at baseline were found to correlate inversely with risk for both COPD and lung cancer, after controlling for smoking habit [47]. Likewise, in a case - control study, serum free bilirubin was lower in patients with COPD than without [48]. And in COPD patients, serum bilirubin correlated directly with FEV1, and inversely with rate of FEV1 decline [49]. Another recent prospective study found that, in current smokers, lower bilirubin levels predicted a higher risk of developing and dying from lung cancer [50]. In a large Swiss cohort, serum bilirubin correlated positively with parameters of effective lung function [51]. And, in a rat model of smoking-induced emphysema, intraperitoneal administration of bilirubin suppressed pulmonary exacerbation of lung inflammation triggered by cigarette smoke, both in vitro and in vivo. When primary human lung fibroblasts, small airway epithelial cells, and blood monocytes were exposed to either IL-1 or cigarette smoke extract in vitro, the resulting increased production of a range of pro-inflammatory cytokines was dose-dependently inhibited by concurrent exposure to resolvin D1 [37]. An analogous study showed that resolvin D1 could inhibit induction of interleukin-8 by cigarette smoke extract in a cell line derived from human bronchial epithelium; resolvin D1’s impact in this regard was traced to suppression of NF-kappaB activation [38]. When mice were exposed to mainstream cigarette smoke, prior inhalation of resolvin D1 was shown to block the recruitment of neutrophils to the lung and the production of pro-inflammatory cytokines evoked by smoke exposure; in addition, resolvin D1 enhanced lung levels of the anti-inflammatory cytokine interleukin-10, and promoted an inflammation-resolving, anti-inflammatory M2 phenotype in lung macrophages [37]. The authors of this latter study speculated that inhalable resolvin D1 - or some more stable analog thereof - might have potential as a drug for treating lung injury induced by inhalation of smoke or other toxic substances.

Clearly, the versatile effects of resolvin D1 - inhibiting NADPH oxidase, blocking NF-kappaB activation, suppressing production of pro-inflammatory cytokines, inhibiting neutrophil recruitment, inducing HO-1 and IL-10, and promoting inflammation-resolving behavior in macrophages, could be expected to alleviate the toxic impact of chronic or acute tobacco smoke exposure on the lungs as clearly is seen in smoke-exposed mice.

It seems likely that other DHA - derived autacoids with anti-inflammatory properties will be characterized - maresins being an example [39,40].

Finally, there is evidence that DHA per se - as well as EPA - can exert anti-inflammatory effects via direct activation of the GPR120 receptor, which is highly expressed in the lung [41,42]. The extent to which this receptor might mediate the lung protective effects of dietary omega-3 has not been assessed, but there is evidence that this receptor is a mediator of the favorable impact of omega-3 on metabolic syndrome in fat-fed mice [41].

Complementary Protection from Spirulina?

As noted, many DHA derivatives function to induce HO-1. The antioxidant properties of this enzyme are mediated largely via intracellular generation of free bilirubin, which functions physiologically to inhibit certain NADPH oxidase complexes [43-46]. Intriguingly, in a massive prospective study in the UK, serum levels of bilirubin at baseline were found to correlate inversely with risk for both COPD and lung cancer, after controlling for smoking habit [47]. Likewise, in a case - control study, serum free bilirubin was lower in patients with COPD than without [48]. And in COPD patients, serum bilirubin correlated directly with FEV1, and inversely with rate of FEV1 decline [49]. Another recent prospective study found that, in current smokers, lower bilirubin levels predicted a higher risk of developing and dying from lung cancer [50]. In a large Swiss cohort, serum bilirubin correlated positively with parameters of effective lung function [51]. And, in a rat model of smoking-induced emphysema, intraperitoneal administration of bilirubin suppressed pulmonary...
injury, decreasing influx of inflammatory cells and lessening pro-inflammatory cytokines in bronchoalveolar lavage fluid [48].

These findings may be of some practical importance, in light of the discovery that the bilirubin homolog phycocyanobilin, a major component of cyanobacteria such as spirulina employed as foods, can mimic bilirubin’s inhibitory impact on NADPH oxidase - likely accounting for many of the versatile antioxidant and anti-inflammatory effects of dietary spirulina documented in rodents [52-54]. This raises the prospect that ingestion of spirulina, or of phycocyanobilin-enriched spirulina extracts, might complement the utility of DHA in protecting the lungs of smokers. Unfortunately, no studies to date have examined the impact of spirulina on smoke-induced lung pathology - although oral administration of phycocyanin (the spirulina protein containing phycocyanobilin as a chromophore) was reported to provide protection in rodent models of lipopolysaccharide or paraquat-induced lung injury [55,56].

### Adjuvant Strategies Targeting Nrf2

Clearly, there is ample reason to suspect that activation of the transcriptional activity of Nrf2 is a key mediator of the apparent protection afforded by DHA to the lungs of smokers. A number of researchers have proposed that Nrf2 activation should be a central goal in the prevention and management of COPD, and have presented evidence that Nrf2 can protect oxidant-stressed lungs in a range of complementary ways [57,58]. Nrf2 supports efficient proteasomal activity by inducing certain proteasomal subunits; this in turn can mitigate cigarette smoke-induced endoplasmic reticulum stress and subsequent apoptosis [59]. Autophagic death of smoke-exposed airway epithelial cells is suspected to play a pathogenic role in COPD; Nrf2 opposes this, at least in part by inducing p62, which in turn blocks overexpression of the autophagy mediator LC3B [60]. By inducing the scavenger receptor MARCO, Nrf2 enables the capacity of alveolar macrophages to phagocytize bacterial pathogens that episodically exacerbate the clinical course of COPD patients [61]. Via its antioxidant effects, Nrf2 helps to preserve the expression and activity of the deacetylase HDAC2; [62,63]. This enzyme, whose activity is characteristically low in smokers most notably in those with COPD [64,65] is essential to the trans-repression activity of the activated glucocorticoid receptor, whereby this receptor binds to NF-kappaB transcriptional complexes and inhibits expression of pro-inflammatory cytokines and metalloproteinases [66]. Hence, Nrf2 activity tends to restore the impaired glucocorticoid responsiveness of COPD patients [63]. The multiple antioxidant effects of Nrf2 can be expected to act upstream of NF- kappaB to down-regulate its activation. Not surprisingly, Nrf2 knockout mice are unusually susceptible to induction of emphysema with cigarette smoke or elastase inhalation [67,68]. Conversely, various natural and synthetic chemical agents that activate the phase II response have been reported to suppress induction of emphysema, lung cancer, and pulmonary hypertension in cigarette smoke-exposed mice [69-71].

Although oxidative stress can promote activation of Nrf2 by covalent modification of its antagonist Keap1, a mechanism likely up-regulated by DHA - Nrf2 activity unfortunately is down-regulated in COPD by several factors. By deacetylating Nrf2, HDAC2 prolongs Nrf2's half-life; hence, the oxidant-mediated suppression of HDAC2 activity seen in COPD tends to destabilize Nrf2 [72]. The resultant increase in oxidative stress could then be expected to further degrade HDAC2 activity a vicious cycle which may contribute to the intransigence of inflammation in COPD. Oxidant-mediated impairment of a positive regulator for Nrf2, DJ-1, may diminish Nrf2's transcriptional activity in COPD [73]. And expression of Nrf2 mRNA in the lavaged macrophages of older smokers and COPD patients has been found to be decreased [74]. For these reasons, effective countermeasures for amplifying lung Nrf2 activity may be crucial for prevention and control of COPD.

As is well known, various foods - notably cruciferous vegetables, allium vegetables (garlic, onions), and green tea contain phytochemicals capable of activating a phase II response [75]. Supraphysiological levels of the cofactor lipoic acid also have this potential [76-78]. Potentially, regular high intakes of these foods or effective extracts thereof as well as supplemental lipoic acid, could provide protection to the lungs of smokers by boosting Nrf2 activity. Unfortunately, rodent or human trials evaluating this possibility appear to be lacking, as does epidemiology focusing specifically on phase II-inducer foods. Nonetheless, a number of epidemiological studies have concluded that lung function is superior, and risk for COPD lower, in people who consume relatively large amounts of fruits and / or vegetables [5-7,89-82]. Hence, it is prudent to advise smokers to consume fruits and vegetables regularly and copiously, with emphasis on cruciferous and allium vegetables. Unfortunately, a 12 week randomized trial of advice to increase fruit and vegetable consumption failed to improve markers of lung inflammation in patient with COPD [83]. A meta-analysis of epidemiological studies focusing on green tea and lung cancer risk found a borderline-significant favorable impact of heavy green tea consumption on lung cancer risk (RR = 0.78, 95% CI 0.61 - 1.00) albeit this effect may be more substantial in non-smokers than in smokers [84,85]. The impacts of lipoic acid, aged garlic extract, sulforaphane-rich broccoli sprout extract, and green tea polyphenols on rodent models of smoke-induced lung damage merit investigation.

In COPD, peroxynitrite-mediated tyrosine nitration of key residues in HDAC2 plays a key role in suppressing the expression and activity of this enzyme [86]. Nitrooxidative stress is indeed increased in COPD, and inhibition of inducible nitric oxide synthase protects mice from smoke-induced emphysema and pulmonary hypertension [87-90]. When folic acid is administered in supraphysiologic doses, high intracellular concentrations of tetrahydrofolates accumulate in most cells, and can exert potent oxidant scavenging effects most notably, scavenging of peroxynitrite - derived radicals [91,92]. This may explain high dose folate's ability to recouple endothelial nitric oxide synthase in patients with endothelial dysfunction, and to provide marked protection from cardiac ischemia reperfusion damage [93-99]. Studying the antioxidant impact of high-dose folate on cell cultures stressed with cigarette smoke extract, or in rodent models of smoke exposure, could prove fruitful. Activation of PI3K-delta by oxidative stress somehow sensitizes HDAC2 to inhibition by nitrooxidative stress; low concentrations of theophylline can inhibit PI3K-delta, likely explaining why low-dose theophylline can promote glucocorticoid responsiveness in chronic lung inflammation [100,101]. Hence, low, relatively well tolerated doses of theophylline may aid control of COPD both by restoring glucocorticoid sensitivity, and by promoting effective Nrf2 function [102,103].

### Conclusion

In summary, there is limited but reasonably consistent epidemiological evidence that frequent fish ingestion may provide smokers with a measure of protection from COPD and lung cancer. Moreover, epidemiology points to DHA as the likely key mediator of this benefit. This model accords nicely with growing evidence that...
various endogenous metabolites of DHA including 4-HHE, 17-oxo-DHA, and resolvins D1 can exert a range of anti-inflammatory and cytoprotective effects, including activation of Nrf2 (leading to induction of a range of protective enzymes, including HO-1), suppression of NF-kappaB activation (blocking production of many pro-inflammatory cytokines), inhibition of neutrophil influx, and a skewing of macrophage behavior to an inflammation-resolving M2 phenotype.

To firm up these conclusions, further epidemiology correlating habitual fish consumption or plasma DHA levels with lung health in long-term smokers would be helpful. However, there isn't any reason why smokers shouldn't be acquainted with the rather compelling evidence that currently exists suggesting that fish consumption or DHA supplementation could protect them provided that it is concurrently made clear that smoking cessation will be far more protective than any counter measure that might be contemplated. In the impressive Takezaki study [12] the most substantial reduction in lung cancer risk roughly an 80% reduction relative to that of subjects eating fish rarely was noted in subjects consuming 3 or more fish meals weekly. I calculate that 4.5 ounce servings of Bluefin tuna weekly would provide an intake of long-chain omega-3 averaging out to about 1.3 g daily the majority of which would be DHA. Hence, targeting a daily intake of about 1 g DHA daily, from fish or supplements, would seem to be a prudent and feasible goal though lower intakes would seem likely to provide some useful protection as well. Recall that, in the analysis of the ARIC cohort, a marked reduction in risk for COPD was observed in subjects consuming 480 mg of total omega-3 daily [1].

Epidemiology also points to frequent consumption of fruits, vegetables, and whole grains as likely to provide some protection from COPD. This may reflect, in part, the phase II inductive capacity of many phytochemicals in these foods and effect with would be expected to complement the impact of DHA metabolites on lung health. Supplementation with lipoic acid and with concentrated sources of phase II-inductive phytochemicals merits study in rodent models of COPD. High-dose folate and low-dose theophylline may have potential for preserving the activity of HDAC2, whose subnormal activity in COPD promotes glucocorticoid resistance and destabilizes Nrf2.

Conflicts of Interest

The author is co-inventor and co-owner of a US patent on nutraceutical uses of spirulina extracts enriched in phycocyanobilin oligopeptides.

References


