Journal of Nutrition & Food Sciences

McCarty, J Nutr Food Sci 2016, 6:2
http://dx.doi.org/10.4172/2155-9600.1000480

Review Article Open Access

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: markfmccarty@gmail.com

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

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 autocoids that exert antioxidant, anti-inflammatory, and inflammation-resolving effects: 4 - hydroxy hexenal, 17 - oxo - DHA, and resolvin 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 sulfhydryl 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 - hydroxy hexenal (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 isoform, 17-R-resolvin D1, can be produced via catalysis by aspirin-treated Cox-2 [32]) Although resolvin D1 has been shown to inhibit LPS inhalation-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 (efferocytosis); 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

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 enhances 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 Nfr2 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 which 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 [5-8,79-82]. 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]. Nitroxidative 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 nitroxidative 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 glucorticoid 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 resolvin 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

1. Shahar E, Folsom AR, Melnick SL, Tockman MS, Comstock GW, et al. (1994) Dietary n-3 polyunsaturated fatty acids and smoking-related chronic obstructive pulmonary disease. Atherosclerosis Risk in Communities Study Investigators. N Engl J Med 331: 228-233.
2. Sharp DS, Rodriguez BL, Shahar E, Hwang LJ, Burchfiel CM (1994) Fish consumption may limit the damage of smoking on the lung. Am J Respir Crit Care Med 150: 983-987.
3. Schwartz J, Weiss ST (1994) The relationship of dietary fish intake to level of pulmonary function in the first National Health and Nutrition Survey (NHANES I) Eur Respir J 7: 1821-1824.
4. Shahar E, Boland LL, Folsom AR, Tockman MS, McGovern PG, et al. (1999) Docosahexaenoic acid and smoking-related chronic obstructive pulmonary disease. The Atherosclerosis Risk in Communities Study Investigators. Am J Respir Crit Care Med 159: 1780-1785.
5. Tabak C, Feskens EJ, Heederik D, Kromhout D, Menotti A, et al. (1998) Fruit and fish consumption: a possible explanation for population differences in COPD mortality (The Seven Countries Study). Eur J Clin Nutr 52: 819-825.
6. Varraso R, Fung TT, Hu FB, Willett W, Camargo CA (2007) Prospective study of dietary patterns and chronic obstructive pulmonary disease among US men. Thorax 62: 786-791.
7. Shaheen SO, Jameson KA, Syddall HE, Aihie Sayer A, Dennison EM, et al. (2010) The relationship of dietary patterns with adult lung function and COPD. Eur Respir J 36: 277-284.
8. Varraso R, Fung TT, Barr RG, Hu FB, Willett W, et al. (2007) Prospective study of dietary patterns and chronic obstructive pulmonary disease among US women. Am J Clin Nutr 86: 488-495.
9. Ng TP, Niti M, Yap KB, Tan WC (2014) Dietary and supplemental antioxidant and anti-inflammatory nutrient intakes and pulmonary function. Public Health Nutr 17: 2081-2086.
10. Barnes PJ (2007) Chronic obstructive pulmonary disease: a growing but neglected global epidemic. PLoS Med 4: e112.
11. Fulton AS, Hill AM, Williams MT, Howe PR, Frith PA, et al. (2013) Feasibility of omega-3 fatty acid supplementation as an adjunct therapy for people with chronic obstructive pulmonary disease: study protocol for a randomized controlled trial. Trials 14: 107.
12. Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, et al. (2003) Diet and lung cancer risk from a 14 year population-based prospective study in Japan: with special reference to fish consumption. Nutr Cancer 45: 160-167.
13. Zhang J, Temme EH, Kesteloot H (2000) Fish consumption is inversely associated with male lung cancer mortality in countries with high levels of cigarette smoking or animal fat consumption. Int J Epidemiol 29: 615-621.
14. Veierød MB, Laake P, Thelle DS (1997) Dietary fat intake and risk of lung cancer: a prospective study of 51,452 Norwegian men and women. Eur J Cancer Prev 6: 540-549.
15. Pierce RJ, Kune GA, Kune S, Watson LF, Field B, et al. (1989) Dietary and alcohol intake, smoking pattern, occupational risk, and family history in lung cancer patients: results of a case-control study in males. Nutr Cancer 12: 237-248.
16. Darby S, Whitley E, Doll R, Key T, Silcocks P (2001) Diet, smoking and lung cancer: a case-control study of 1000 cases and 1500 controls in South-West England. Br J Cancer 84: 728-735.
17. Takezaki T, Hirose K, Inoue M, Hamajima N, Yatabe Y, et al. (2001) Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. Br J Cancer 84: 1199-1206.
18. Marchand JL, Luce D, Goldberg P, Bugel I, Salomon C, et al. (2002) Dietary factors and the risk of lung cancer in New Caledonia (South Pacific). Nutr Cancer 42: 18-24.
19. Koo LC (1988) Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr Cancer 11: 155-172.
20. Goodman MT, Hankin JH, Wilkens LR, Kolonel LN (1992) High-fat foods and the risk of lung cancer. Epidemiology 3: 288-299.
21. Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, et al. (2001) Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. Jpn J Cancer Res 92: 1259-1269.
22. Kvale G, Bjelke E, Gart JJ (1983) Dietary habits and lung cancer risk. Int J Cancer 31: 397-405.
23. Sankaranarayanan R, Varghese C, Duffy SW, Padmakumary G, Day NE, et al. (1994) A case-control study of diet and lung cancer in Kerala, south India. Int J Cancer 58: 644-649.
24. Swanson CA, Mao BL, Li JY, Lubin JH, Yao SX, et al. (1992) Dietary determinants of lung-cancer risk: results from a case-control study in Yunnan Province, China. Int J Cancer 50: 876-880.
25. Song J, Su H, Wang BL, Zhou YY, Guo LL (2014) Fish consumption and lung cancer risk: systematic review and meta-analysis. Nutr Cancer 66: 539-549.

26. Ghorbanihaghjo A, Safa J, Alizadeh S, Argani H, Rashtchizadeh N, et al. (2013) Protective effect of fish oil supplementation on DNA damage induced by cigarette smoking. J Health Popul Nutr 31: 343-349.
27. Mernitz H, Lian F, Smith DE, Meydani SN, Wang XD (2009) Fish oil supplementation inhibits NNK-induced lung carcinogenesis in the A / J mouse. Nutr Cancer 61: 663-669.
28. Ishikado A, Morino K, Nishio Y, Nakagawa F, Mukose A, et al. (2013) 4-Hydroxy hexenal derived from docosahexaenoic acid protects endothelial cells via Nrf2 activation. PLoS One 8: e69415.
29. Kobayashi M, Yamamoto M (2005) Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. Antioxid Redox Signal 7: 385-394.
30. Nakagawa F, Morino K, Ugi S, Ishikado A, Kondo K, et al. (2014) 4-Hydroxy hexenal derived from dietary n-3 polyunsaturated fatty acids induces anti-oxidative enzyme heme oxygenase-1 in multiple organs. Biochem Biophys Res Commun 443: 991-996.
31. Cipollina C, Di VS, Gerbino S, Siena L, Gjomarkaj M, et al. (2014) Dual anti-oxidant and anti-inflammatory actions of the electrophilic cyclooxygenase-2-derived 17-oxo-DHA in lipopolysaccharide- and cigarette smoke-induced inflammation. Biochim Biophys Acta 1840: 2299-2309.
32. Serhan CN, Gotlinger K, Hong S, Arita M (2004) Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their aspirin-triggered endogenous epimers: an overview of their protective roles in catabasis. Prostaglandins Other Lipid Mediat 73: 155-172.
33. Xie W, Wang H, Wang L, Yao C, Yuan R, et al. (2013) Resolvin D1 reduces deterioration of tight junction proteins by upregulating HO-1 in LPS-induced mice. Lab Invest 93: 991-1000.
34. Wang L, Cano M, Handa JT (2014) p62 provides dual cytoprotection against oxidative stress in the retinal pigment epithelium. Biochim Biophys Acta 1843: 1248-1258.
35. Ariel A, Serhan CN (2007) Resolvins and protectins in the termination program of acute inflammation. Trends Immunol 28: 176-183.
36. Lee HN, Surh YJ (2013) Resolvin D1-mediated NOX2 inactivation rescues macrophages undertaking efferocytosis from oxidative stress-induced apoptosis. Biochem Pharmacol 86: 759-769.
37. Hsiao HM, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, et al. (2013) A novel anti-inflammatory and pro-resolving role for resolvin D1 in acute cigarette smoke-induced lung inflammation. PLoS One 8: e58258.
38. Dong J, Zhang M, Liao Z, Wu W, Wang T, et al. (2014) Resolvin-D1 inhibits interleukin-8 and hydrogen peroxide production induced by cigarette smoke extract in 16HBE cells via attenuating NF-kappaB activation. Chin Med J (Engl) 127: 511-517.
39. Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, et al. (2009) Maresins: novel macrophage mediators with potent anti-inflammatory and proresolving actions. J Exp Med 206: 15-23.
40. Giudetti AM, Cagnazzo R (2012) Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. Prostaglandins Other Lipid Mediat 99: 57-67.
41. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, et al. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell 142: 687-698.
42. Moore K, Zhang Q, Murgolo N, Hosted T, Duffy R (2009) Cloning, expression, and pharmacological characterization of the GPR120 free fatty acid receptor from cynomolgus monkey: comparison with human GPR120 splice variants. Comp Biochem Physiol B Biochem Mol Biol 154: 419-426.
43. Lanone S, Bloc S, Foresti R, Almolki A, Taille C, et al. (2005) Bilirubin decreases nos2 expression via inhibition of NAD(P)H oxidase: implications for protection against endotoxic shock in rats. FASEB J 9: 1890-1892.
44. Matsumoto H, Ishikawa K, Itabe H, Maruyama Y (2006) Carbon monoxide and bilirubin from heme oxygenase-1 suppresses reactive oxygen species generation and plasminogen activator inhibitor-1 induction. Mol Cell Biochem 291: 21-28.
45. Jiang F, Roberts SJ, Datla Sr, Dusting GJ (2006) NO modulates NADPH oxidase function via heme oxygenase-1 in human endothelial cells. Hypertension 48: 950-957.
46. Datla SR, Dusting GJ, Mori TA, Taylor CJ, Croft KD, et al. (2007) Induction of heme oxygenase-1 *in vivo* suppresses NADPH oxidase derived oxidative stress. Hypertension 50: 636-642.
47. Horsfall LJ, Rait G, Walters K, Swallow DM, Pereira SP, et al. (2011) Serum bilirubin and risk of respiratory disease and death. JAMA 305: 691-697.
48. Wei J, Zhao H, Fan G, Li J (2015) Bilirubin treatment suppresses pulmonary inflammation in a rat model of smoke-induced emphysema. Biochem Biophys Res Commun 465: 180-187.
49. Apperley S, Park HY, Holmes DT, Man SF, Tashkin D, et al. (2015) Serum Bilirubin and Disease Progression in Mild COPD. Chest 148: 169-175.
50. Wen CP, Zhang F, Liang D, Wen C, Gu J, et al. (2015) The ability of bilirubin in identifying smokers with higher risk of lung cancer: a large cohort study in conjunction with global metabolomic profiling. Clin Cancer Res 21: 193-200.
51. Curjuric I, Imboden M, Adam M, Bettschart RW, Gerbase MW, et al. (2014) Serum bilirubin is associated with lung function in a Swiss general population sample. Eur Respir J 43: 1278-1288.
52. McCarty MF (2007) Clinical potential of Spirulina as a source of phycocyanobilin. J Med Food 10: 566-570.
53. Zheng J, Inoguchi T, Sasaki S, Maeda Y, McCarty M, et al. (2012) Phycocyanin and Phycocyanobilin from Spirulina Platensis Protect against Diabetic Nephropathy by Inhibiting Oxidative Stress. Am J Physiol Regul Integr Comp Physiol 304: R110-R120.
54. Romay Ch, González R, Ledón N, Remirez D, Rimbau V (2003) C-phycocyanin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. Curr Protein Pept Sci 4: 207-216.
55. Leung PO, Lee HH, Kung YC, Tsai MF, Chou TC (2013) Therapeutic effect of C-phycocyanin extracted from blue green algae in a rat model of acute lung injury induced by lipopolysaccharide. Evid Based Complement Alternat Med 2013: 916590.
56. Sun Y, Zhang J, Yan Y, Chi M, Chen W, et al. (2011) The protective effect of C-phycocyanin on paraquat-induced acute lung injury in rats. Environ Toxicol Pharmacol 32: 168-174.
57. Biswal S, Thimmulappa RK, Harvey CJ (2012) Experimental therapeutics of Nrf2 as a target for prevention of bacterial exacerbations in COPD. Proc Am Thorac Soc 9: 47-51.
58. Boutten A, Goven D, Artaud-Macari E, Boczkowski J, Bonay M (2011) NRF2 targeting: a promising therapeutic strategy in chronic obstructive pulmonary disease. Trends Mol Med 17: 363-371.
59. Malhotra D, Thimmulappa R, Vij N, Navas-Acien A, Sussan T, et al. (2009) Heightened endoplasmic reticulum stress in the lungs of patients with chronic obstructive pulmonary disease: the role of Nrf2-regulated proteasomal activity. Am J Respir Crit Care Med 180: 1196-1207.
60. Zhu L, Barrett EC, Xu Y, Liu Z, Manoharan A, et al. (2013) Regulation of Cigarette Smoke (CS)-Induced Autophagy by Nrf2. PLoS One 8: e55695.
61. Harvey CJ, Thimmulappa RK, Sethi S, Kong X, Yarmus L, et al. (2011) Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. Sci Transl Med 3: 78ra32.
62. Adenuga D, Caito S, Yao H, Sundar IK, Hwang JW, et al. (2010) Nrf2 deficiency influences susceptibility to steroid resistance via HDAC2 reduction. Biochem Biophys Res Commun 403: 452-456.
63. Malhotra D, Thimmulappa RK, Mercado N, Ito K, Kombairaju P, et al. (2011) Denitrosylation of HDAC2 by targeting Nrf2 restores glucocorticosteroid sensitivity in macrophages from COPD patients. J Clin Invest 121: 4289-4302.
64. Ito K, Ito M, Elliott WM, Cosio B, Caramori G, et al. (2005) Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 352: 1967-1976.
65. Barnes PJ (2009) Role of HDAC2 in the pathophysiology of COPD. Annu Rev Physiol 71: 451-464.

66. Ito K, Yamamura S, Essilfie-Quaye S, Cosio B, Ito M, et al. (2006) Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-kappaB suppression. J Exp Med 203: 7-13.
67. Iizuka T, Ishii Y, Itoh K, Kiwamoto T, Kimura T, et al. (2005) Nrf2-deficient mice are highly susceptible to cigarette smoke-induced emphysema. Genes Cells 10: 1113-1125.
68. Ishii Y, Itoh K, Morishima Y, Kimura T, Kiwamoto T, et al. (2005) Transcription factor Nrf2 plays a pivotal role in protection against elastase-induced pulmonary inflammation and emphysema. J Immunol 175: 6968-6975.
69. Sussan TE, Rangasamy T, Blake DJ, Malhotra D, El-Haddad H, et al. (2009) Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. Proc Natl Acad Sci U S A 106: 250-255.
70. Guan SP, Tee W, Ng DS, Chan TK, Peh HY, et al. (2013) Andrographolide protects against cigarette smoke-induced oxidative lung injury via augmentation of Nrf2 activity. Br J Pharmacol 168: 1707-1718.
71. Liu W, Tan X, Shu L, Sun H, Song J, et al. (2012) Ursolic acid inhibits cigarette smoke extract-induced human bronchial epithelial cell injury and prevents development of lung cancer. Molecules 17: 9104-9115.
72. Mercado N, Thimmulappa R, Thomas CM, Fenwick PS, Chana KK, et al. (2011) Decreased histone deacetylase 2 impairs Nrf2 activation by oxidative stress. Biochem Biophys Res Commun 406: 292-298.
73. Malhotra D, Thimmulappa R, Navas-Acien A, Sandford A, Elliott M, et al. (2008) Decline in NRF2-regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1. Am J Respir Crit Care Med 178: 592-604.
74. Suzuki M, Betsuyaku T, Ito Y, Nagai K, Nasuhara Y, et al. (2008) Down-regulated NF-E2-related factor 2 in pulmonary macrophages of aged smokers and patients with chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 39: 673-682.
75. Surh YJ, Kundu JK, Na HK (2008) Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. Planta Med 74: 1526-1539.
76. Flier J, Van Muiswinkel FL, Jongenelen CA, Drukarch B (2002) The neuroprotective antioxidant alpha-lipoic acid induces detoxication enzymes in cultured astroglial cells. Free Radic Res 36: 695-699.
77. Cao Z, Tsang M, Zhao H, Li Y (2003) Induction of endogenous antioxidants and phase 2 enzymes by alpha-lipoic acid in rat cardiac H9C2 cells: protection against oxidative injury. Biochem Biophys Res Commun 310: 979-985.
78. Jia Z, Hallur S, Zhu H, Li Y, Misra HP (2008) Potent upregulation of glutathione and NAD(P)H:quinone oxidoreductase 1 by alpha-lipoic acid in human neuroblastoma SH-SY5Y cells: protection against neurotoxicant-elicited cytotoxicity. Neurochem Res 33: 790-800.
79. Tabak C, Smit HA, Heederik D, Ocke MC, Kromhout D (2001) Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study). Clin Exp Allergy 31: 747-755.
80. Walda IC, Tabak C, Smit HA, Räsänen L, Fidanza F, et al. (2002) Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. Eur J Clin Nutr 56: 638-643.
81. Varraso R, Willett WC, Camargo CA Jr (2010) Prospective study of dietary fiber and risk of chronic obstructive pulmonary disease among US women and men. Am J Epidemiol 171: 776-784.
82. Hirayama F, Lee AH, Binns CW, Zhao Y, Hiramatsu T, et al. (2009) Do vegetables and fruits reduce the risk of chronic obstructive pulmonary disease? A case-control study in Japan. Prev Med 49: 184-189.
83. Baldrick FR, Elborn JS, Woodside JV, Treacy K, Bradley JM, et al. (2012) Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD: a randomised controlled trial. Eur Respir J 39: 1377-1384.
84. Tang N, Wu Y, Zhou B, Wang B, Yu R (2009) Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer 65: 274-283.
85. Yuan JM (2013) Cancer prevention by green tea: evidence from epidemiologic studies. Am J Clin Nutr 98: 1676S-1681S.
86. Osoata GO, Yamamura S, Ito M, Vuppusetty C, Adcock IM, et al. (2009) Nitration of distinct tyrosine residues causes inactivation of histone deacetylase 2. Biochem Biophys Res Commun 384: 366-371.
87. Ichinose M, Sugiura H, Yamagata S, Koarai A, Shirato K (2000) Increase in reactive nitrogen species production in chronic obstructive pulmonary disease airways. Am J Respir Crit Care Med 162: 701-706.
88. Kanazawa H, Shiraishi S, Hirata K, Yoshikawa J (2003) Imbalance between levels of nitrogen oxides and peroxynitrite inhibitory activity in chronic obstructive pulmonary disease. Thorax 58: 106-109.
89. Osoata GO, Hanazawa T, Brindicci C, Ito M, Barnes PJ, et al. (2009) Peroxynitrite elevation in exhaled breath condensate of COPD and its inhibition by fudosteine. Chest 135: 1513-1520.
90. Seimetz M, Parajuli N, Pichl A, Veit F, Kwapiszewska G, et al. (2011) Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. Cell 147: 293-305.
91. Rezk BM, Haenen GR, van der Vijgh WJ, Bast A (2003) Tetrahydrofolate and 5-methyltetrahydrofolate are folates with high antioxidant activity. Identification of the antioxidant pharmacophore. FEBS Lett 555: 601-605.
92. Antoniades C, Shirodaria C, Warrick N, Cai S, de BJ, et al. (2006) 5-methyltetrahydrofolate rapidly improves endothelial function and decreases superoxide production in human vessels: effects on vascular tetrahydrobiopterin availability and endothelial nitric oxide synthase coupling. Circulation 114: 1193-1201.
93. Verhaar MC, Wever RM, Kastelein JJ, van DT, Koomans HA, et al. (1998) 5-methyltetrahydrofolate, the active form of folic acid, restores endothelial function in familial hypercholesterolemia. Circulation 97: 237-241.
94. Stroes ES, van Faassen EE, Yo M, Martasek P, Boer P, et al. (2000) Folic acid reverts dysfunction of endothelial nitric oxide synthase. Circ Res 86: 1129-1134.
95. Milstien S, Katusic Z (1999) Oxidation of tetrahydrobiopterin by peroxynitrite: implications for vascular endothelial function. Biochem Biophys Res Commun 263: 681-684.
96. Tawakol A, Migrino RQ, Aziz KS, Waitkowska J, Holmvang G, et al. (2005) High-dose folic acid acutely improves coronary vasodilator function in patients with coronary artery disease. J Am Coll Cardiol 45: 1580-1584.
97. Moens AL, Claeys MJ, Wuyts FL, Goovaerts I, Van Hertbruggen E, et al. (2007) Effect of folic acid on endothelial function following acute myocardial infarction. Am J Cardiol 99: 476-481.
98. Moens AL, Champion HC, Claeys MJ, Tavazzi B, Kaminski PM, et al. (2008) High-Dose Folic Acid Pretreatment Blunts Cardiac Dysfunction During Ischemia Coupled to Maintenance of High-Energy Phosphates and Reduces Post-reperfusion Injury. Circulation 117: 1810-1819.
99. McCarty MF (2007) Oster rediscovered--mega-dose folate for symptomatic atherosclerosis. Med Hypotheses 69: 325-332.
100. To Y, Ito K, Kizawa Y, Failla M, Ito M, et al. (2010) Targeting phosphoinositide-3-kinase-delta with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 182: 897-904.
101. Marwick JA, Caramori G, Stevenson CS, Casolari P, Jazrawi E, et al. (2009) Inhibition of PI3Kdelta restores glucocorticoid function in smoking-induced airway inflammation in mice. Am J Respir Crit Care Med 179: 542-548.
102. Barnes PJ (2013) Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 131: 636-645.
103. Sun X, Li Q, Gong Y, Ren L, Wan H, et al. (2012) Low-dose theophylline restores corticosteroid responsiveness in rats with smoke-induced airway inflammation. Can J Physiol Pharmacol 90: 895-902.