



Chronic cellular hypoxia as the prime cause of cancer: What is the de-oxygenating role of adulterated and improper ratios of polyunsaturated fatty acids when incorporated into cell membranes?

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Received 14 May 2007; accepted 22 May 2007

Summary With the exception of melanoma and non-Hodgkin's lymphoma, the incidence of cancer has peaked in the last several years, but rates and mortality are still high. Moreover, despite 50 years of intensive cancer research increasingly focused on genetic causes, no single unifying cause for cancer has been established. Although it is well-known that tumors are hypoxic, and that there is a correlation between the level of hypoxia and prognosis, with the exception of Warburg's studies, little work has been done to investigate the relationship between hypoxia and cancer. Over 70 years ago, Warburg showed that cells could always be made cancerous by subjecting them to periods of hypoxia. Moreover, he demonstrated that once cells had converted to a cancerous state, reversion could not occur. Modern biochemistry acknowledges that there is a switch from oxidative phosphorylation to glycolysis in tumors that might be concurrent with hypoxia, but does not address the cancer causation. It is our hypothesis that long-term hypoxia of cells in the body, measured in years, is the primary trigger for cancer. We believe that the hypoxia, which has to meet Warburg's findings of a critical 35% reduction in intracellular oxygen levels to initiate cancer, is linked to the incorporation of adulterated, non-oxygenating, or inappropriate polyunsaturated fatty acids (PUFAs) into the phospholipids of cell and mitochondrial membranes. Such incorporation causes changes in membrane properties that impair oxygen transmission into the cell. Trans fats, partially oxidized PUFA entities, and inappropriate omega-6:omega-3 ratios are all potential sources of unsaturated fatty acids that can disrupt the normal membrane structure. In this paper, we explore this hypothesis by examining the evidence, and additionally propose an appropriate PUFA dosage for humans by analyzing requirements and taking into account current PUFA consumption patterns.
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Introduction

Since the 1950s, cancer rates have generally increased with few exceptions. For example, the

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incidence rates for non-Hodgkin's lymphoma (NHL) nearly tripled between 1950 and 1995, and death rates more than doubled [1]. A similar picture has emerged for other cancers, such as lung cancer and testicular cancer [2,3]. Although accurate cancer statistics are not available prior to the 1950s, it has been established that cancer rates were significantly lower at the beginning of the twentieth century. Thus in the 1900s, lung cancer was relatively rare, causing fewer than 10 deaths per 100 000 men, whereas by the 1980s it had exceeded 100 deaths per 100 000 men [4]. What is most interesting is that in more isolated geographic groups, high cancer rates are a relatively recent phenomenon, which suggests that adoption of a Western culture is partially responsible for the increase in the disease [5].

Although with the exception of melanoma and NHL, cancer rates have plateaued or slightly declined in the last 5–10 years, there has been no overall dramatic decline despite the plethora of lifestyle and nutritional changes that have been advocated. Part of the explanation for this failure is the embodied concept in the cancer literature that many cancers are caused by the activation of oncogenes – genes that predispose the individual toward cancer. However, not all researchers agree with this idea. For example, Weinberg, the discoverer of oncogenes, recently reversed his position, stating “The notion that a cancer developed through the successive activation of a series of oncogenes had lost its link to reality” [6]. Other cancer studies have implicated hundreds of different causes – termed secondary causes – which have included environmental, chemical, and radiation factors, as well as viruses. Yet there appears to be no common cell mechanism described that links these causes. Further, 35 years ago, Harris et al. showed through cell fusion experiments that cancerous cells cannot easily force other cells to become cancerous, thereby demonstrating that metastasis is not the result of cancer cells in one organ of the body secreting a factor to cause cells in another organ to become cancerous [7].

What then causes cancer and how can it be prevented?

In this article it is proposed that cell hypoxia is the fundamental predisposing step to cancer, and that this condition is arrived through consumption of inappropriate polyunsaturated fatty acids (PUFAs), which are incorporated into cell membranes and interfere with oxygen transmission into cells. Several lines of evidence will be cited to support this hypothesis. In addition, an analysis will be performed to demonstrate the ideal PUFA consumption in terms of absolute amounts, and correct

supplemental omega-6:omega-3 ratios to prevent cancer formation.

Cellular oxygen levels and the trigger for cancer

A majority of oncologists now believe that relatively low levels of oxygen exist within a tumor and that the lower the oxygen level, the poorer the prognosis of the patient, the greater the probability of metastases, and the more resistant the tumor will be in terms of treatment, such as radiation therapy [8–13]. Oxygen levels do vary considerably in the tumor interstitium, due to temporal variation in the red cell flux of the surrounding microvessels [14], but oxygen is necessary to provide the necessary free radical development in radiation therapy. By using hyperbaric oxygen therapy in conjunction with radiation, the response to the radiation therapy of tumors can be improved by increasing the oxygen levels supplied to tumors [15], although this approach is not always successful [16].

Although there might be other origins, Warburg showed that cancer could always be initiated with a decrease in cellular oxygen [17,18]. Specifically, he determined that 35% inhibition of oxygen respiration was sufficient to bring about transformation of a normal cell to a cancerous cell [19]. These general results were validated by Goldblatt and Cameron in 1953 [20] and Malmgren and Flanigan in 1955 [21]. In the decades since the 1950s, however, research has focused on what happens in the hypoxic cellular environment in terms of gene expression, which includes the effects of the hypoxia-inducible factors and activating transcription factors [22,23]. While there is no doubt that once a tumor is established there are likely to be several control mechanisms in play that keep the cancerous cell growing, this research does not address the initiation events.

When cellular oxygen deficiency occurs, there is a fundamental change in the way in which energy in the cell is created. As Warburg and coworkers reported over 80 years ago, cancer cells use a greater ratio of glycolysis/respiration compared to normal cells [24], and cannot regain normal respiration because the injury to respiration is irreversible. Furthermore, the transition from normal cell to cancer takes place gradually [18]. This long time-frame is the key to prevent “sleeping cancer” (benign) cells from differentiating into carcinogenic cells and metastasizing by eliminating the hypoxia.

Although many modern biochemists acknowledge Warburg's discovery, they postulate that

mutations in signaling pathways cause changes in glucose uptake, which leads to a switch to glycolysis and the conversion to a cancer cell [25]. Chance [26] has also suggested that Warburg's concept of a defective respiratory chain was in error, implying that had he known of the affinity of ADP for mitochondria versus glycolysis (30 μM versus 300 μM), his work in cancer might have gone in a different direction. In essence, what Chance and coworkers found [27] was that ascites tumor cells had respiratory activities greater than cardiac or yeast mitochondria and a very high content of cytochrome c. Chance later proposed that there is a delicate balance between the control of oxidative phosphorylation and glycolysis that is upset by hypoxia [26]. Interesting though this work is, it still does not address the fundamental problem of how cell hypoxia can be caused, nor does Chance's "ADP theory" explain why cancerous cells cannot revert back to a precancerous state if given enough oxygen.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) constitute a group of nutrients essential to normal physiological functioning in mammals, and are also known as essential fatty acids (EFAs) because the body cannot synthesize them. The parent entities, linoleic acid (LA, 18:2 n -6) and alpha-linolenic acid (ALA, 18:3 n -3), are found largely in the seeds of vegetable oils, nuts, and the leaves of plants [28]. Both PUFAs can be converted to several active metabolites, including LA to arachidonic acid (AA, 20:4 n -6), a precursor of many prostanoids, and ALA to eicosapentaenoic acid (EPA, 20:5 n -3) and docosahexaenoic acid (DHA, 22:6 n -3) [29]. In humans, Western diets typically provide high LA:ALA ratios of 10–12:1, with LA and ALA originating from vegetable oils and animal products respectively, and EPA/DHA largely sourced from fish and seafood [30].

Correct omega-6:omega-3 ratios and adulterated PUFAs

High ratios of omega-6:omega-3 PUFAs in Western diets have been of concern and implicated in a wide range of diseases. As a result, experiments in animals and humans have investigated the supplementation of diets with fish oils, which are rich in omega-3 series fats, to determine if such supplements are beneficial in preventing cardiovascular problems or cancer. The rationale was such supple-

ments would balance the detrimental effects of too much omega-6 PUFA. However, a recent meta-analysis of these studies has concluded that the addition of such supplements does little to change the risk of acquiring cancer or cardiovascular disease [31]. This was puzzling, given that many publications seemed to indicate positive results in cancer studies [32–35], but investigators often overlook several factors.

First, an important aspect in understanding the role of PUFAs with respect to cancer is the metabolic fate of the parent compounds. Many researchers do not differentiate between the parent and derivative (biochemically derived from the parent) structure of the omega-6 and omega-3 PUFA series. For example, fish oil consists of significantly more omega-3 derivatives than parent omega-3, whereas in flax oil the reverse situation predominates. Substituting a derivative for a parent structure is problematic if it is performed without rationale. In addition, LA significantly accumulates in the tissues, whereas ALA does to a much lesser extent. Furthermore, only a small percentage of ALA is converted to such derivatives as EPA and DHA, regardless of quantity ingested. The majority, but not all of the remainder is eventually utilized for ATP production via beta-oxidation [36–38]. Thus some of the excess is incorporated into cell membranes, which can be detrimental (see Appropriate PUFA Consumption to Prevent Cancer section).

Second, while mice are good PUFA models since Lands et al. showed that PUFA metabolism is similar to that in humans [29], many experiments typically use diets that contain excessive amounts of PUFAs in an attempt to "mimic" the Western diet. Taking an example from the literature, Kelavkar et al. [33] used a 10.5 wt% LA diet for their "high omega-6 diet" in mice, which is the equivalent of approximately 250 mg LA daily, or two orders of magnitude larger than the estimated mouse requirement, using the human requirement as reference. Selecting two more studies at random, similar problems can be found in the experiments conducted by Hardman et al. [39] and Hansen Petrick et al. [40] noting that very high levels of omega-3 were used in many of the animal studies, often 20–24% by weight of the diet. In addition, Berry cites dosage and compliance problems, as well as the issue of high background linoleate consumption [41]. Moreover, Berry points out that n -3 and n -6 polyunsaturated functions cannot be assessed in isolation but must be considered together [41].

Trans fats and related compounds constitute the third issue. These entities are formed by the partial hydrogenation of PUFAs during manufacture of

margarines, processing of foods to prevent spoilage, excessive and repetitive heating of cooking oils for deep frying foods, as well as feeding unnatural diets to ruminants, poultry, and other non-ruminants [42]. The results are impaired membrane function, similar to that arising from PUFA deficiency [28], which, in the case of mitochondria, leads to the uncoupling of oxidation and phosphorylation. Such entities might be able to initiate carcinogenesis, although the evidence to date is not conclusive [43–46]. The presence of such trans fats is overlooked in most experiments. Estimates of dietary consumption in Western countries vary from 0.5% to 2.5% of energy intake, which is a substantial amount of adulterated monounsaturated or polyunsaturated fatty acid [47–49].

Finally, the question of PUFA stability remains. Since PUFAs are easily oxidized, not only must provision be made to ensure the use of pure, unadulterated materials, but also that partially oxidized entities are not inadvertently employed in studies. Udilova et al. [50] investigated the effects of LA hydroperoxide generated by heating and found a substantial decrease in membrane fluidity. Further, it was determined that the hydroperoxide caused cell death via both apoptosis and necrosis in cultured IEC18 intestinal epithelial, SW480, and HT29/HI1 colon carcinoma cells. That commonly used rodent feed is contaminated by oxidized entities has been confirmed by our own experiments. For example, irradiated Prolab RMH 2500 mouse chow analyzed by Eurofins Scientific, Inc. (Des Moines, IA) to determine the peroxide value (AOCS official method Cd8-53) showed a peroxide value of 61 meq/kg fat, indicating significant oxidation of the PUFAs.

Purification of PUFAs by temperatures in excess of boiling point, in processes such as distillation, and the presence of chemicals, such as bleach, can cause alterations in chemical structure. If researchers can comprehend the purification problem, they will also understand why their results are often contradictory, because a defective substance is unknowingly being utilized in experimentation.

PUFAs and cell membranes

For many years, PUFAs, as well as their metabolites, have been known to incorporate in both cell and the inner mitochondrial membranes responsible for cellular respiration. Changes in the relative levels of PUFAs, effected by dietary modifications, are reflected in the fatty acid composition of membrane phospholipids, and changes in nuclear membranes and microsomes can also be effected [51–

54,37]. This is important, because trans fats and the oxidized PUFA compounds discussed in the previous section can also be incorporated into biomembranes. The results are impaired membrane function, similar to that arising from PUFA deficiency [28], which, in the case of mitochondria, leads to the uncoupling of oxidation and phosphorylation. Interestingly, the reverse process of changing the fatty acid composition of cancer cell biomembranes has been proposed as a therapeutic treatment [55–57].

While changes in tissue PUFAs will alter the composition of membrane-bound phospholipids, evidence also exists that such changes can increase the intracellular oxygen levels. For example, Campbell et al. found that LA can associate with oxygen and dissociate the oxygen at relatively high oxygen pressure in erythrocyte membranes [58]. These researchers also found that fatty acids affect the permeability of cell membranes to molecular oxygen, and given PUFA deficiency, interference with the movement of oxygen could occur at any cell membrane in any tissue. Thus there would be a general reduction in the supply of cellular oxygen throughout the body. Moreover, PUFA deficiency causes substitution with inferior fats, and results in the systemic deficiency of the cholesterol structure, and incapability of sufficient oxygen transport.

Physico-chemical experiments show that LA can bind twice as much oxygen, which disassociates at a much higher pressure, much closer to the binding dynamics of hemoglobin, than does oleic acid [58]. Given that the oxygen disassociation curves for oleic acid compared with LA, show a 50% reduction in oxygen transfer, the cancer-causing 35% reduction threshold could easily be reached during PUFA deficiency.

Appropriate PUFA consumption to prevent cancer

What should be the appropriate consumption of PUFAs and correct ratio of omega-6:omega-3 in humans to prevent cancer? Several studies point to PUFA deficiency as a promoter of tumorigenesis, as well as physico-chemical membrane changes and a lower susceptibility to peroxidation [59,60]. Evidence also exists that in tumor cells, PUFAs can initiate cell death through the production of reactive oxygen species, which seems to be caspase-3 independent [61]. Too much omega-3 PUFA is also detrimental. For example, Burns and Spector showed that the capacity of endothelial cells and macrophages to release prostaglandins is reduced when they accumulate *n*–3 polyunsaturated

fatty acids and this might be important as prostaglandins produced from PUFAs reduce the adhesion of tumor cells to microvascular endothelium [54].

Based on 2 unique ALA deficiency case reports [62,63] and other studies reporting energy intakes cited by Sinclair et al [38], it is proposed that the ALA energy intake in humans should be between 1% and 1.5%, with a ratio of between 1:1 and 2.5:1 parent omega-6:omega-3 PUFAs. For a human consuming a diet of 2000 kcal that contains 65 g of fat, this would translate to approximately 5.8 g of LA and 3.3 g of ALA at an energy intake of 1.4% at an LA:ALA ratio of 1.8:1. One could also increase the LA:ALA ratio slightly to allow for the fact that extra LA is needed to reduce incorporation of any trans or oxidized fatty acids into cellular membranes through substrate competition.

Correct PUFA supplementation also shows promise as an adjunct in cancer treatment; for example, in conjunction with hyperbaric oxygen, chemotherapy, or radiation therapy whose success depends on the oxygen level in the cancer cell being sufficient to ensure that any remaining benign tumors, will not metastasize.

Conclusions

In our hypothesis, we have proposed that cancer is preceded by a period of cell hypoxia, which is caused by the long-term consumption of inappropriate PUFAs, such as trans fats and oxidized moieties, which are incorporated into cell membranes and interfere with the oxygen transmission into cells required for respiration. The exact mechanisms by which a prolonged period of mild to moderate hypoxia could trigger the typical metabolism of cancer cells are not known but might be a series of epigenetic changes similar to those described by Chen et al. for precancerous stem cells [64]. In addition, much more research needs to be performed concerning the effect of altered phospholipid structure in cell membranes regarding the effect of oxygen transmission across cell and organelle membranes to confirm other elements of our hypothesis.

Warburg found that the cancer process could be prevented if cellular oxygen deprivation could be reversed before a certain critical period, and stated, "We find by experiment about 35% inhibition of oxygen respiration already suffices to bring about such a transformation during cell growth" [17]. If cellular oxygen can be kept high enough and below this deprivation threshold, cancer cells should not be able to form.

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