

Fat, Fatty Acids, and Prostate Cancer: Statistics, Inconsistencies, and Confusion

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Abstract

Based on ecological studies and early epidemiological findings, a link has been proposed between dietary fats/fatty acids and the development of clinically apparent prostate cancer. Several hypotheses have been proposed to explain this link through biochemical mechanisms, although all remain unproven at this time. More recent epidemiological studies have further analyzed the dietary fat/fatty acid and prostate cancer link, and while suggestive, have returned largely inconsistent and inconclusive results. Results from animal and cell-culture models have been equally difficult to interpret, and these models have the additional complication that they may not be appropriate for studying the pathogenesis of human prostate cancer. In conclusion, current knowledge of dietary risk factors for developing prostate cancer is insufficient to recommend any dietary modifications at this time.

Keywords: *prostate cancer, dietary fat, fatty acids*

1 Introduction

Prostate cancer is the most common malignancy and the second leading cause of cancer death among men in the United States [1]. There are several elements that make prostate cancer rather unique among cancers. First, prostate cancer is a disease that is almost entirely unique to humans, occurring in other mammals at far lower rates than the occurrence levels seen in man [2]. Second, the levels of sub-clinical, latent prostatic carcinoma in humans is extremely high. Cadaver studies have demonstrated that 30-50% of men at age 50 and 50-80% of men greater than 80 years of age have histological evidence of prostate cancer [3]. Finally, prostate tumors, at least initially, tend to be extremely slow growing. The five year survival rate for new diagnoses is 89%, with a 100% survival rate for patients presenting with a tumor that is still localized to the prostate [1].

Despite the high rates of men with prostate cancer, only ~2% of men in the United States die of prostate cancer. Given the human predilection toward prostate cancer, a natural question that arises is what factors are important in determining which men will go on to develop clinical manifestations of prostate cancer, and which of these men will in turn go on to die from this disease?

Clues have been provided by studies that have found large differences in prostate cancer rates between different ethnic regions. Interestingly, migrants from regions of traditionally low prostate cancer risk, such as Japan or Poland, increase their risk of developing prostate cancer when moving into regions of traditionally high risk,

such as the U.S. [4]. This observation suggests that an environmental factor may be involved in prostate tumorigenesis. Ecological studies have found positive correlations between per-capita fat consumption, particularly animal fat, and age adjusted rates of prostate cancer, suggestive of a link between diet and prostate cancer [5, 6].

Further epidemiological studies have found that the frequency of small, latent prostatic carcinomas is relatively constant in all regions and age groups, while larger, latent carcinomas correlate with age, regional area, and increased mortality [7]. These findings suggest that the impact of diet on the tumorigenesis of prostate cancer may be on the transformation of the initial carcinoma into metastatic cancer [8].

2 Primer on Fat, Fatty Acids, and Fatty Acid Products

Fatty acids in the diet are found as either triacylglycerols (fat) or phospholipids. Triacylglycerols, which are the storage form of fatty acids, are composed of three fatty acids attached to one molecule of glycerol. Phospholipids, which are the major constituents of cellular membranes, consist of two fatty acids and a polar head group attached to a molecule of glycerol. The fatty acids in phospholipids and triacylglycerols can be saturated (containing no carbon-carbon double bonds), monounsaturated (containing one carbon-carbon double bond) or polyunsaturated (containing multiple carbon-carbon double bonds). In general, animals contain a higher proportion of saturated fat than plants. The polyunsaturated fatty acids (PUFA's) are further classified according to the location of their first carbon-carbon double bond with respect to the terminal methyl group. For example, an ω -3 PUFA has a double bond between the third and fourth carbons (fig. 1).

The ω -3 fatty acids consist of two groups, long chain ω -3 fatty

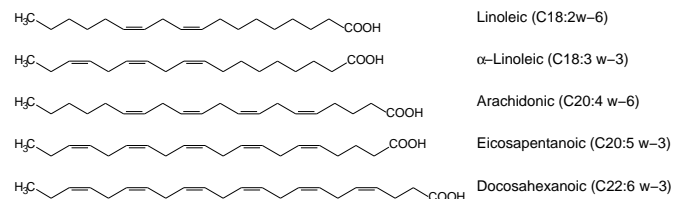


Figure 1: Structures and formulas of the most common polyunsaturated fatty acids

acids, and short chain ω -3 fatty acids. Long chain ω -3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are generally derived from marine sources. Shorter chain ω -3 fatty acids, such as α -linolenic acid (ALA), are generally derived from terrestrial sources. ω -6 fatty acids such as arachidonic acid (AA) and linoleic acid (LA) are found in both animal and plant sources. Two of these PUFA's, ALA and LA, cannot be synthesized by mammals and are called the essential fatty acids (EFA).

LA is especially important in the diet, as it can be metabolized to AA, which is the common precursor molecule to a group of compounds called the eicosanoids. Eicosanoids are hormone-like substances that act near their site of synthesis, and include prostaglandins, leukotriens, and thromboxanes. One role of eicosanoids are as key mediators of the inflammatory response, and inappropriate production of eicosanoids may represent a link between dietary fatty acid intake and prostate cancer tumorigenesis [9].

3 Epidemiological and Ecological Studies

A fair number of ecological and epidemiological studies examining dietary causes for prostate cancer have appeared over the last 30 years. Rather than reviewing all of these studies individually, this article will summarize the collective findings and common study design problems of the older studies, and then take a more in-depth view of the relevant recent literature. Readers interested in more detailed information on the older studies are referred to recent review articles (Kolonel *et al.* [4], Dwyer *et al.* [10]).

3.1 Older Findings

The initial ecological studies that have looked for links between dietary factors and prostate cancer have been fairly self consistent. In nine major ecological studies, all have found some correlation between prostate cancer and total fat intake, saturated fat intake, or meat consumption [4].

The findings of the epidemiological studies have, however, been far less consistent. Additionally, many of these earlier epidemiological studies are difficult to interpret and compare, as they did not use sufficiently detailed dietary protocols so as to permit calculation of the total caloric intake. In Western countries, dietary fat intake is highly correlated with total energy intake, which itself has been linked to cancer, so an increased dietary fat intake may also indicate a greater caloric consumption [4]. Of the 5 studies that did do adjustments for caloric intake, only one found a significant association with either total, saturated, or animal fat intake [4].

Many of these early studies also reported on the intake of specific food items (meat, eggs, and/or milk). Of these 10 odd studies, some reported positive correlations, many reported non-significant correlations, and one reported a negative correlation between these food items and prostate cancer [4].

Studies have also been done looking at specific types of fats and specific fatty acids. Of five case-control and 2 cohort studies looking for a relationship between monounsaturated fat, polyunsaturated fat and prostate cancer, the only one to find significant correlations was also the only one that did not account for caloric in-

take [4].

Several studies have also looked specifically at ALA [4, 11, 12]. Only one of the two epidemiological studies and two of the 4 biochemical analysis studies of stored serum samples have reported significant findings. Interestingly, none of these studies found any positive or negative correlation between long chain ω -3 fatty acids (derived from marine sources) and prostate cancer. The findings of these papers with respect to LA have been similarly mixed and inconclusive.

3.2 Recent Findings

More recently epidemiological studies have started to use more sophisticated diet analyses along with corrections for total caloric intake. The hope might of been that improved analyses and better dietary records could help resolve the contradictions reported in the earlier literature, but the article reviews that follow will show that no great improvements in terms of the repeatability of findings have been made.

The Giovannucci *et al.* [11], 1993 study, while covered in the previously mentioned review articles, has been of sufficient impact to merit further review here. This report covers a prospective study of 47,855 U.S. male medical professional participants, 300 of whom went on to develop prostate cancer. While only a marginally significant link was found between total fat and advanced prostate cancer after total caloric adjustments, the study did find a significant correlation between consumption of red meat and advanced prostate cancer. While the paper suggests that carcinogens in cooked meat may be responsible for the findings, it also acknowledges that the causative carcinogenic factor may also just correlate with red meat consumption. The most intriguing finding of this study, however, was a significant positive association between ALA and the risk of advanced prostate cancer, a finding which spurred the examination of specific fatty acids in laboratory models of prostate cancer. One important note to make about this study is that higher intake of total fat among its participants was also found to correlate with having fewer digital rectal examinations, smoking more, having a greater body mass, and exercising less, any of which may have confounded the report's findings.

In 1996, Andersson *et al.* [13] reported on a case control study of Swedish men with 256 cases and 252 controls. After adjusting for energy expenditure, they found no significant correlations between any nutrient and prostate cancer except for total caloric intake. This finding was not significantly changed after adjustments were made for height, weight, body mass index (BMI), or lean body mass (LBM). Since they found no significant difference in BMI between their case and control group, the authors hypothesized that total caloric intake may act as a dietary risk factor through an Insulin-like Growth Factor 1 (IGF-1) mediated mechanism (covered in more detail in section 4.1).

A 1997 report by Veierød, *et al.* [14] covered a prospective study of 25,708 Norwegian men, 72 of whom developed prostate cancer over the course of the study. This study found that BMI was significantly associated with prostate cancer in contrast to the Andersson *et al.* study. The study also found that total energy intake was highly correlated with total fat intake, as expected, and that after doing total caloric intake adjustments, neither saturated fat, monounsaturated fat, nor polyunsaturated fat had significant cor-

relations with prostate cancer. The most interesting, and strange, findings of this study were that skim milk significantly increased prostate cancer risk versus whole milk, and that, in contrast to the Giovannucci *et al.* report, the number of meals with meat per week were inversely correlated with prostate cancer.

Rounding out the Scandinavian studies is another 1997 study of Norwegian men (Harvei *et al.* [12]). This was a case control study of 141 matched sets of participants. The study utilized a biological analysis of stored serum samples and found a statistically significant correlation between serum ALA levels and prostate cancer. No differences were found between the case and control groups for blood levels of saturated fat, unsaturated fat, and LA. Additionally, no correlation was seen between dietary fat and the aggressiveness of cancer in the cases group. A limitation of this study was that, since it used set volumes of stored blood samples, only relative values and not absolute values for the different values could be compared. Relative values of fats and fatty acids in blood serum have not been looked at previously, and are therefore difficult to compare with previous work.

A 1998 report by Lee *et al.* [15] on a case control study covering 3 separate locations in China using 133 cases and 265 controls saw a significant positive association between total caloric intake and prostate cancer risk. This study also found highly significant positive associations for prostate cancer risk with total caloric intake adjusted saturated, unsaturated, and total fat intake. Interestingly, China is a region in which very low levels of prostate cancer have been traditionally seen.

Two reports on three studies were released by a Quebec group in 1998 and 1999. Bairati *et al.* [16] reported on a case control study of 1025 French Speaking Canadian participants, 427 with prostate cancer. They saw a small correlation with saturated fat, total animal fat, and prostate cancer risk. They however failed to adjust for total caloric intake. Interestingly, they saw no correlations between prostate cancer and either LA, linolenic acid, or total caloric intake. The second report from the group (Fradet *et al.* [17]) encompassed two separate studies. The first study was a case control study of 593 controls and 215 preclinical cases in Quebec. This study found a significant positive association between total energy intake and preclinical prostate cancer. No significant correlations between preclinical prostate cancer and total fat, types of fat, selected fatty acids, fats from animal sources, or fats from vegetable sources were found after adjusting for total caloric intake. In the second study, 142 Quebec patients with advanced prostate cancer were compared with 242 patients with early stage prostate cancer. When comparing these two groups, no correlations between the risk of advanced prostatic cancer and total energy intake, total fat, or unsaturated fat were found. They did however find a slight correlation between saturated fat and the risk of advanced prostatic cancer.

Returning back to Europe, 1999 saw a report by Schuurman *et al.* [18] of a case control study of males from the Netherlands which included 1525 controls and 642 cases. The report found no association between total energy intake and prostate cancer, nor total fat, total fatty acids, saturated fatty acids, trans-unsaturated fatty acids, and prostate cancer after adjusting for total energy intake. They did find a positive association with oleic acid, but interestingly reported an inverse association between prostate cancer and LA or linolenic acid.

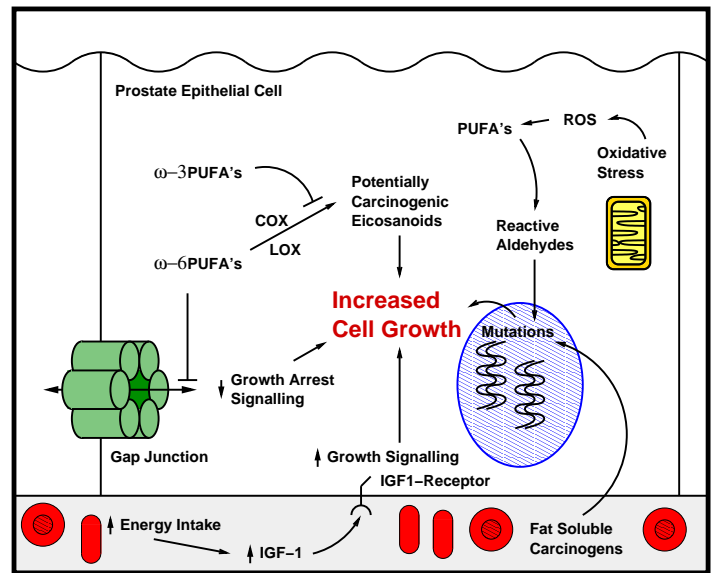


Figure 2: Some proposed mechanisms for a fatty acid role in the tumorigenesis of prostate cancer. (COX: Cyclooxygenase, IGF-1: Insulin-like Growth Factor-1, LOX: Lipoxygenase, PUFA: Polyunsaturated fatty acid, ROS: Reactive Oxygen Species)

Finally, Norrish *et al.* [19] report from New Zealand with a case control study using 317 prostate cancer cases and 480 controls. From a dietary analysis, they found similar total caloric intake, total fat intake, and dietary consumption of fish oils, specifically EPA and DHA, between the two groups. Interestingly, they also did serum tests for fatty acids and found increased levels of dietary fish oils, specifically EPA and DHA, were associated with a reduced risk of prostate cancer. They choose to blame the inconsistency between dietary records and serum levels on inherent limitations of dietary analysis.

4 Biological Evidence for a Fatty Acid Role

While the epidemiological studies have been far from conclusive, they have stimulated hypotheses and resulting laboratory based research looking for possible mechanisms whereby dietary factors could increase the risk of developing prostate cancer.

4.1 Proposed Mechanisms of Actions

One of the more common hypotheses for the dietary fat-prostate cancer link is that dietary fat may aid the development of prostate cancer through a mechanism involving oxidative stress [4] (fig. 2). Oxidative metabolism inherently produces some small amount of free radical oxygen species. In oxidative stress, the metabolic state of a cell runs at a level such that the cell can no longer neutralize all of the free radical oxygen species formed. These reactive oxygen species can then react with the double bonds of PUFA's, extracting hydrogen, and resulting in free radical fatty acids. The free radicals fatty acids can then in turn react with oxygen to form peroxide

radicals and initiate an oxidative chain reaction leading to more reactive species (such as reactive aldehydes). These reactive species can move to the nucleus and lead to DNA damage [20, 9]. While fatty acids are most likely involved in the chain of free radical reactions, theories on how increased fatty acid intake in the diet could lead to increased oxidative stress damage of DNA are quite speculative. Fat derived from plants, however, is usually accompanied by the anti-oxidant vitamin E, and this vitamin E could possibly serve in a protective role against free radical damage [4, 9].

Another theory proposed by several researchers is that long chain ω -3 PUFA's might displace ω -6 PUFA's such as AA in the cell membrane [19, 21, 22, 11]. Once in the membrane, these ω -3 PUFA's could exert a competitive inhibitory effect on enzymes such as cyclooxygenase and lipoxygenase. Since these enzymes regulate the synthesis of AA into several active eicosanoids, including prostaglandin E₂, leukotriens, and prostacyclins [8], and since eicosanoids have been shown to enhance *in vitro* tumor progression [9], it's plausible that ω -3 PUFA's may have an inhibitory effect on carcinogenesis.

Dietary fats may also be associated with prostate cancer through an IGF-1 mediated pathway [13] (fig. 2). Prostate epithelial cells have been shown to express IGF-1 receptors [23], and since IGF-1 is anti-apoptotic and mitogenic, tumorigenesis of prostate cancer could conceivably be via an IGF-1 related mechanism [23, 8]. In cell culture work, IGF-1 stimulates mitogenicity in a dose dependent manner in the presence of dihydrotestosterone (DHT, a required androgen for prostate cell viability) [23]. Additionally, IGF-1 has been implicated in promoting angiogenesis [24]. Since serum IGF-1 levels have been shown to be reduced by lowering energy intake in humans [13] along with in mouse and rat models [24], it seems reasonable that a high total caloric diet would increase serum IGF-1 levels and thereby increase prostate cancer risk. Further evidence for this proposal comes from the finding that serum IGF-1 levels in humans are strongly correlated with prostate cancer risk [23].

Additionally, a hypothesis has been proposed stemming from evidence that ω -6 PUFA's (such as AA and LA) can block cell to cell communication through gap junctions. Since these intercellular signals serve as an important modulator of cellular proliferation, blocking gap junctions may promote tumorigenesis. [25, 26] (fig. 2).

Finally, a possible explanation for all the confusion in the epidemiological literature has been proposed by the hypothesis that the putative prostate cancer risk factor may not be fat or a fatty acid, but rather a fat-soluble carcinogenic compound which associates to varying levels with animal fat in different geographic regions [8] (fig. 2).

4.2 *in vitro* model reports

The main bulk of the *in vitro* literature (and the only portion referred to here) has been in support of the eicosanoids inhibition hypothesis. It has been shown that ω -3 fatty acids appear to inhibit prostate cancer cell lines in culture, and that ω -6 fatty acids stimulate prostate cancer cell lines in culture [21]. However, not all researchers report consistent findings, and some have reported results for ω -3 fatty acids which may either be inhibitory or stimulatory depending on the concentration of the fatty acid applied to the cells [27].

In general, much of the *in vitro* model work can be regarded with some suspicion, as the appropriateness of most of the commonly available prostate cancer cell lines for studying the tumorigenesis of prostate cancer is questionable. Most of the widely used prostate cancer cell lines (such as PC3) represent androgen-independent, end stage prostate disease, and cannot be considered good models for studying the progression of latent prostate cancer to its clinical form. Additionally, neither of the two commonly used androgen sensitive cell-culture models (LNCaP and Dunning R3327-H) may be appropriate [28]. LNCaP was derived from a metastatic lesion and has an uncommon androgen receptor mutation, and the Dunning R3327-H tumor was developed from an advanced human prostate tumor.

4.3 *in vivo* model reports

One cannot question the appropriateness of the *in vitro* models without calling into greater suspicion the appropriateness of the *in vivo* models. A review of the recent literature will show multiple uses of the LNCaP or Dunning R3327-H cell lines (discussed in section 4.2) in subcutaneous xenographic SCID (severe compromised immunodeficient) rodent models, along with other mouse and rat models which involve inducing prostate cancer via an exogenous orthotopically applied mutagen [4].

Part of the difficulty of developing an appropriate animal model for prostate cancer has been that this disease is very distinct to the human species. In no other animal species does 50-80% of the males die with (but not of) prostate cancer. Additionally, since the pathogenesis of human prostate cancer is currently unknown, developing a completely appropriate animal model has not been possible.

Interestingly, transgenic models (such as the TRAMP mouse model [2]) have appeared over the last five years which follow the human course of prostate cancer from latent tumor to advanced metastatic disease fairly faithfully over the life-span of the animal. The transgenics have been created by attaching a prostate specific promoter to a known oncogene, and appear to be more appropriate models for the study of the pathogenesis of prostate cancer. To date, however, no dietary fat/fatty acid studies have employed these new models.

One recent study [24] of associations between dietary fat and prostate cancer in a mouse model casts additional skepticism on previous animal model work. This study used the previously discussed LNCaP human carcinoma xenographic SCID mouse model and Dunning R3327-H human adenocarcinoma xenographic rat model in an analysis of restricted calorie diets on tumor growth. In addition to restricting the diet to 30% of normal total caloric intake, they also played with the proportions of fat and carbohydrates in the diet. As expected, the reduced calorie diet produced a reduction in tumor growth versus controls. The interesting part was that all diets, when the total reduction in caloric intake was carefully controlled, produced similar decreases in prostate tumor growth. Since IGF-1 levels are reduced under conditions of energy restriction in rodent models, the findings of this study support the hypothesis of an IGF-1 role in prostate cancer development. Additionally, the consistent results at a given caloric intake regardless of the fat content of the diet call into question previous studies linking dietary fat and prostate cancer in rodent models which have not

carefully controlled total caloric intake.

In light of the questions regarding the appropriateness of the animal models and the design of the studies in the literature, this article will refer the interested reader to appropriate reviews [4, 20] rather than repeating more of this information here.

5 Conclusion

In summary, several hypotheses have been proposed linking dietary fat/fatty acid intake, and/or total caloric intake with the development of clinical apparent prostate cancer. These hypotheses stem from fairly sound ecological data, and epidemiological data which is suggestive, but inconsistent and difficult to interpret. Furthermore, *in vivo* and *in vitro* work have been consistent with the epidemiological data only in that it has been suggestive, yet inconsistent and difficult to interpret. In light of these findings, the author would agree with previously published reviews in that there is currently insufficient knowledge of dietary prostate cancer risk factors to recommend any dietary modifications [4, 10].

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