WEIGHT LOSS / EATING HABITS
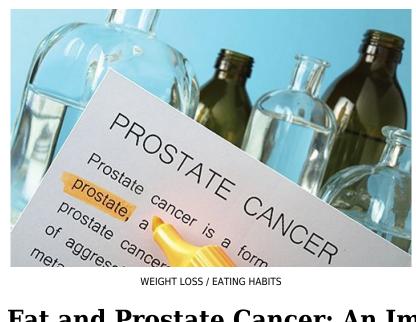
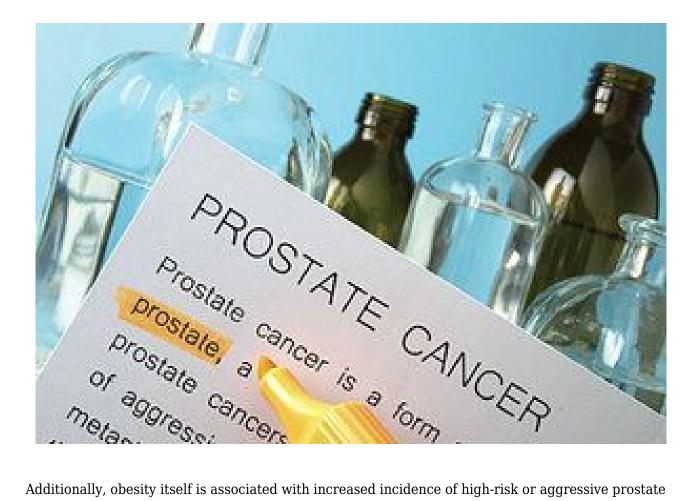# Dietary Fat and Prostate Cancer: An Important Update and Review of Mechanisms

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K.M. Di Sebastiano and M. Mourtzakis published a review paper examining the role of dietary fat on prostate cancer development and progression late last year that does a stellar job of summarizing the available data on fat and prostate cancer. Their review paper sheds light on the importance of counseling men on the dangers of consuming too much bad fat in regard to prostate cancer prevention and adjunctive management in prostate cancer survivors. Let's highlight the key findings from their literature review.

Dietary Fat as an Etiological Factor

Di Sebastiano and Mourtzakis suggest too much bad fat negatively influences the signal transduction pathway within prostate cells known as the insulin-like growth factor (IGF)-Akt signaling pathway. When this pathway is overstimulated or dysregulated, it is known to promote prostate cancer development and progression. However, saturated fat, trans fats and obesity itself have been shown to promote prostate cancer via other mechanisms as well, which are outlined below.

In general, the scientific literature shows that specific categories of fats – saturated and animal fats – appear to pose the greatest risk for prostate cancer development, while EPA (eicosapentaenic acid from fish and fish oil) may have a protective effect.

Additionally, obesity itself is associated with increased incidence of high-risk or aggressive prostate cancer, as well as increased incidence of prostate cancer recurrence. A great paradox of prostate cancer treatment is that androgen deprivation (or ablation) therapy tends to encourage more body-fat deposition, which in turn may promote prostate cancer recurrence. The authors conclude, "There are numerous nutritional factors associated with obesity and prostate cancer risk, including positive energy balance, red meat and dairy intake, saturated fat, trans-fatty acid intake and total dietary fat intake. Conversely, *n*-3 fatty acids have been identified as having a potentially protective effect against prostate cancer."

Mechanisms by Which Bad Fats Promote Prostate Cancer

Various mechanisms have been identified that potentially explain how bad fats or excessive animal fat can promote prostate cancer development and progression. These include changes in the insulin-like growth factor (IGF)-Akt pathway, androgen signaling, alterations in cell proliferation and angiogenesis, and via increased generation of reactive oxygen species (free radicals):

1. IGF-1-Akt Signaling Pathway

It has been identified that the IGF signaling pathway is one of the main regulating pathways in which dietary fat can promote prostate cancer development and progression. Dietary fat intake is positively correlated with circulating levels of IGF-1(insulin-like growth factor-1), which may ultimately result in increased signaling through the IGF signaling pathway.

The IGF system plays a critical role in cell proliferation, differentiation, apoptosis and transformation. Dysregulation of this system is a common finding in prostate cancer pathophysiology. Fat intake also tends to be related to lower amounts of insulin-like growth factor binding protein-3 (IGFBP-3), the major binding protein of IGF-1 in plasma. Lower blood levels of IGFBP-3 allow more IGF-1 to stimulate IGF-1 receptors, which likely overstimulates the IGF-1-Akt

pathway, encouraging prostate cancer development. Lower IGFBP-3 serum levels is independently associated with the risk of prostate cancer.

Dysregulation of the IGF-1-Akt signaling pathway also activates NF kappa beta in cancer cells, resulting in decreased cell death. More specifically, Akt activation promotes signaling in the IGF-1receptor / IRS-1 axis, which contributes to the dysregulation of NF kappa beta and, ultimately, cancer cell growth. The IGF-1R / IRS-1 axis also indirectly increases mTOR activity. The mTOR also promotes cell growth via specific signal transduction pathways. "Thus, increased dietary fat intake may potentially promote malignant cell growth through increased IGF-1 and decreased IGFBP-3, resulting in increased IGF-1 signaling through the IGF-1R, a receptor implicated in the transformation of healthy cells to cancerous cells and a mediator of cell growth through the IGF-1R / IRS-1 axis."

2. Androgen Signaling Pathway

Androgen signaling is another pathway by which dietary fat intake appears to promote prostate cancer development. In fact, some studies show that decreased dietary fat intake is associated with decreased androgen and testosterone levels, which subsequently improves signaling mediated through the IGF-1 signaling pathway.

Androgens play a key role in prostate development and function, but androgen signaling and, specifically, the androgen receptor, also known as nuclear receptor subfamily 3, group C, member 4, (NR3C4), is the principle stimulant of prostate cancer progression. Androgens stimulate prostate cancer cell growth via the Erk-2 pathway, where Erk-2 activation increases the androgen receptor complex content in the prostate cells. Androgens also increase IGF-1R expression, which is associated with prostate cancer development as previously described.

In the early stages of development, malignant prostate cancer cells require androgen stimulation for growth. However, increased androgen receptor growth eventually leads to a transition to hormone-resistant cancers, the more aggressive form of prostate cancer, and activation of heat shock protein (HSP) 90. HSP90 is a chaperone protein of the androgen receptor. All of these changes further stimulate signaling through the androgen receptor pathway, resulting in increasingly malignant behavior of prostate cancer cells.

High-fat diets have been shown to increase stimulation through the IGF-1 axis, as well as being associated with increased androgen and testosterone levels. Diets low in total and saturated fat and high in *n*-3 fatty acids counter this pathway by inhibiting IGF-1 binding and decreasing HSP90 association with the androgen receptor, which results in androgen receptor degradation, reduction of androgen receptor proteins, and reduction in the number of androgen receptor-regulated genes. All of these factors reduce prostate cancer development and prostate cancer progression.

3. Angiogenesis

Angiogenesis is the mechanism by which tumor cells encourage the synthesis of new blood vessels to feed more tumor growth. Angiogenesis greatly increases the metastatic potential of tumors and is associated with poor prognosis of many types of cancer. Of special note is the fact that *n*-3 fatty acid intake has been shown to inhibit malignant cell proliferation and angiogenesis. The *n*-3 fatty acids work both intrinsically (mitochondrial pathway) and extrinsically (death receptor pathway) to induce apoptosis (programmed cell death of cancer cells, but not healthy cells). Omega-3 fats appear to exert this anti-angiogenesis effect by inhibiting PI3K activity (phosphatidylinositol-3 kinase), which activates the Akt complex.

Activated Akt regulates a number of downstream signaling peptides that can directly affect apoptosis and the cell cycle. In short, activated Akt leads to decreased apoptosis, whereas inhibition of these pathways via *n*-3 fatty acids ultimately results in increased cell death of tumor cells.

4. Free Radicals or Reactive Oxygen Species

Total dietary fat and saturated fat also have been shown to enhance cell proliferation and angiogenesis through the generation of reactive oxygen species (ROS). ROS generated endogenously and externally are associated with cancer progression by inducing a number of cancerous changes within the cell. ROS alter the conformational structure of the p53 protein, resulting in a mutated phenotype of the protein. P53 protein is a key protein that directs the process of apoptosis of cancer cells.

Changes to the p53 protein inhibit the ability of cells to induce apoptosis, via intrinsic pathways, when cancer cells are emerging. These types of p53 mutations are specifically important in prostate cancer progression. Total dietary fat, especially *n*-6 fatty acids, as well as androgens, can serve as oxidants, directly increasing the level of ROS in the cells and its subsequent damage and consequences, including up-regulation of transcription factors that speed up cell replication (another risk factor in cancer development).

The authors also note that "oxidative stress has been shown to be higher in the benign epithelium of men with prostate cancer when compared to men without prostate cancer, while Lee, *et al.,* demonstrated that inactivation of glutathione-s-transferase pi, a pro-oxidant scavenging enzyme, is critical in the development of prostate cancer carcinogenesis. Specifically, dietary fat consumption may contribute to the carcinogenesis of prostate tissue via lipid peroxidation, thus resulting in increased oxidative stress."

Fat Intake and Cancer Survival

It is too early to confirm that bad fats promote cancer recurrence in prostate cancer survivors, but preliminary studies suggest fat intake, specifically saturated fat intake, may decrease disease-specific survival. In one study, Fradet and colleagues followed a group of men diagnosed with prostate cancer for an average of 5.2 years. After controlling for cancer grade, clinical stage, treatment age and total energy intake, men in the lowest tertile of saturated fat intake had a decreased risk of dying from prostate cancer, as compared to those in the highest tertile of saturated fat intake. Findings such as these may prompt health practitioners to encourage prostate cancer patients to reduce their intake of total animal fat (with the exception of fish) and saturated fat, while we await the findings of well-designed intervention studies needed to confirm if manipulating dietary fat can have positive effects on survival rates.

Other studies have combined a low-fat diet with supplementation of flaxseed, noting beneficial effects on prostate health. For instance, Demark-Wahnefried, *et al.,* demonstrated decreased proliferation rates in men supplemented with flaxseed, and that the low-fat-diet group had significantly reduced serum cholesterol levels following ~30 days of supplementation. Heymach, *et al.,* demonstrated that compared to the control arm, a low-fat diet, a flaxseed-supplemented diet and a low-fat diet with a flaxseed supplementation for 30 days each decreased a number of angiogenic factors, although results were greatest in the group consuming the low-fat diet alone.

Clinical Pearls

The emerging data tends to support the findings that dietary fat and, in particular, high intake of

animal and saturated fats, may be associated with prostate cancer risk. The IGF-Akt signaling pathway appears to be the key signaling pathway moderating malignant cell growth and changes in androgen receptor signaling. Overall, saturated fat and trans fatty acids appear to promote prostate cancer development, while omega-3 fats may exert a protective effect. For prostate cancer survivors, a diet low in fat and particularly low in saturated fat may be beneficial, as it may reduce tumor angiogenesis and cancer recurrence. The addition of flaxseed supplementation also may be beneficial in these cases.

In my view, the evidence linking a high-animal-fat / saturated-fat diet with increased prostate cancer risk is sufficient for us to advise men to make appropriate dietary changes that would eliminate or greatly reduce their intake of these fats. Reducing these fats also helps to reverse obesity, another documented risk factor for the development of advanced prostate cancer.

Reference

1. Di Sebastiano KM, Mourtzakis M. The role of dietary fat throughout the prostate cancer trajectory. *Nutrients,* 2014 Dec;6(12):6095-6109.

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