Bridging animal and human studies: what are the missing segments in dietary fat and prostate cancer?1,2

Jin-Rong Zhou and George L Blackburn

ABSTRACT  
Epidemiologic investigations have suggested an association of dietary fat intake with prostate cancer risk, especially risk of advanced prostate cancer. However, supporting evidence from animal studies is limited. Segments that would bridge animal and human studies on dietary fat and prostate cancer—which would determine the future directions of research—are missing. Such segments include 1) well-designed animal studies to evaluate whether dietary fat or fatty acid modulation, particularly by reducing dietary fat and supplementing n-3 fatty acids, reduces the progression of prostate cancer; 2) in vivo identification of intermediate biomarkers that are responsive to dietary fat and fatty acid treatment and may serve as surrogate endpoints in future clinical studies; 3) elucidation of mechanisms by which dietary fat or fatty acid modulation could prevent prostate cancer progression; 4) further epidemiologic studies to estimate dietary exposure more precisely to establish the correlation between dietary fat and risk of prostate cancer; 5) randomized clinical intervention trials evaluating whether dietary fat reduction combined with dietary n-3 fatty acid supplementation delays the recurrence of prostate cancer and improves survival in patients with clinical disease after therapeutic treatment, and whether it prevents or reduces the progression to clinically significant disease in men with latent disease; and 6) studies validating intermediate biomarkers as surrogate endpoints. Am J Clin Nutr 1997;66(suppl):1572S–80S.

KEY WORDS  
Dietary fat, fatty acid, prostate cancer, intermediate biomarker, human studies, animal studies

INTRODUCTION

If the intent of research on dietary fatty acids is to affect tumor progression in human cancer, priority must go to investigations related to changing the clinical outcome. This would be particularly true when funding is requested from the National Cancer Institute and the National Institutes of Health. The 1996 National Science and Technology Council Committee on Health, Safety, and Food identified nutrition as pivotal in optimizing health and productivity and in reducing the risk of diet-related disease including cancer (1). We have selected a major cancer type—prostate cancer—that may serve as a hypothesis-testing model to investigate fatty acids and tumor growth important to human health.

Results from epidemiologic investigations have suggested an association of dietary fat intake with prostate cancer risk, especially risk of advanced prostate cancer (eg, tumor growth and metastasis). However, supporting evidence from animal and in vitro studies is limited. It is unclear whether alteration in dietary fat patterns can affect prostate tumor progression in clinical or in vivo studies. Many mechanisms of action are possible, adding a further challenge to these types of studies. Some fatty acids have a tumor-promoting effect, whereas others have a tumor-inhibitory effect. Testing the fatty acid hypothesis will require both dose-response and qualitative studies. Reducing or changing the pattern of dietary fat may serve as an intervention regimen for preventing prostate cancer progression. Therefore, a series of in vitro laboratory, animal, and clinical studies are required to meet the criteria for substantial scientific evidence. In this article, we will attempt to identify the missing segments of the bridge between animal and human studies of dietary fat and prostate cancer to propose future directions of research.

PROSTATE CANCER

Prostate cancer is the most frequently diagnosed invasive cancer and the second leading cause of cancer-related deaths in US males. It was estimated that 300,000 new cases would be diagnosed and 40,000 men would die from the disease in 1995 (2). The incidence of clinically diagnosed prostate cancer (3) and the mortality of prostate cancer (2) show geographic variations even though the incidence of latent prostate carcinomas (carcinoma in situ with integrity of the basement membrane) is the same worldwide (4–6). Immigrants from low-incidence countries settling in high-incidence countries showed an increased clinically significant incidence of prostate cancer (7–11). A high-risk population (US black men) had a higher incidence rate of invasive carcinoma than did a low-risk population (Nigerian black men) (5). These observations suggest that lifestyle factors, such as diet and nutrition, contribute to the progression of small, latent, nonmetastatic tumors to clinically significant, invasive, metastatic lesions of prostate cancer.

Prostate cancer morbidity and mortality are mainly due to metastases and recurrence of the tumor. Recurrent prostate cancer cells are characterized as rapidly growing, poorly differentiated, and androgen-independent. The skeleton is the

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major site of metastasis for prostate carcinoma; ≈70% of patients with metastatic prostate cancer will develop bone metastasis (12).

**DIETARY FAT AND PROSTATE CANCER: A REVIEW**

**Interpretation of an association**

Criteria for establishing causal inferences, first suggested by Hill (13), are important to remember when interpreting an observed association. Associations may be due to factors such as chance, bias, confounding, reverse cause, cause, or a combination of these factors (14).

Efforts have been made to correlate dietary factors with prostate cancer risk and progression. A high dietary intake of fat or energy, such as the traditional Western total fat intake of ≈40% of energy, constitutes a major risk factor for prostate cancer (15–17); a significant correlation between high dietary fat intake and the incidence of advanced prostate cancer was suggested. The following sections will briefly review previous studies on dietary fat intake and prostate cancer risk.

**Descriptive studies**

Descriptive studies on dietary fat and prostate cancer risk are summarized in Table 1. Some studies suggest a positive association between prostate cancer risk and intake of total dietary fat (18, 19) or of saturated or animal fat (20, 22, 25), whereas others did not find a significant association of prostate cancer risk with intake of total dietary fat (20–22) or of saturated or animal fat (21, 23, 24). No studies showed negative associations. The most significant association was between intake of high dietary fat (especially animal fat) and the incidence of more aggressive phenotypes and prostate cancer mortality (18–20, 22, 25). In general, these data support the hypothesis that high dietary fat intake is associated with late prostatic carcinogenesis by promoting the progression from focal to clinical disease.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Descriptive studies of dietary fat and prostate cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Total dietary fat</td>
<td></td>
</tr>
<tr>
<td>Armstrong and Doll (18), 1975</td>
<td>International</td>
</tr>
<tr>
<td>Carroll and Khor (19), 1978</td>
<td>International</td>
</tr>
<tr>
<td>Giovannucci et al (20), 1993</td>
<td>Health Professionals Follow-up, 51,529 US men, 300 patients including 126 advanced cases</td>
</tr>
<tr>
<td>Severson et al (21), 1989</td>
<td>7999 Japanese ancestry in Hawaii, 174 cases</td>
</tr>
<tr>
<td>Snowdon et al (22), 1984</td>
<td>6763 white male Seventh-day Adventists, 99 fatal cases</td>
</tr>
<tr>
<td>Animal fat intake</td>
<td></td>
</tr>
<tr>
<td>Giovannucci et al (20), 1993</td>
<td>Health Professionals Follow-up, 51,529 US men, 300 patients including 126 advanced cases</td>
</tr>
<tr>
<td>Snowdon et al (22), 1984</td>
<td>6763 white male Seventh-day Adventists, prostate cancer, 99 fatal cases</td>
</tr>
<tr>
<td>Hsing and Comstock (23), 1993</td>
<td>17,633 white males, 149 fatal cases</td>
</tr>
<tr>
<td>Mills et al (24), 1989</td>
<td>78,000 Seventh-day Adventists, 180 cases</td>
</tr>
<tr>
<td>Le Marchand et al (25), 1994</td>
<td>20,316 men, 196 patients in Hawaii</td>
</tr>
<tr>
<td>Saturated fat intake</td>
<td></td>
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<tr>
<td>Giovannucci et al (20), 1993</td>
<td>Health Professionals Follow-up, 51,529 US men, 300 patients including 126 advanced cases</td>
</tr>
<tr>
<td>Severson et al (21), 1989</td>
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<td>Unsaturated fat intake</td>
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<td>Giovannucci et al (20), 1993</td>
<td>Health Professionals Follow-up, 51,529 US men, 300 patients including 126 advanced cases</td>
</tr>
<tr>
<td>Gann et al (26), 1994</td>
<td>120 pairs from Physicians' Health Study</td>
</tr>
<tr>
<td>Gann et al (26), 1994</td>
<td>120 pairs from Physicians' Health Study</td>
</tr>
</tbody>
</table>

* +, Significant positive association, P < 0.05; 0, no significant association.
Because fat intakes contain a mixture of fatty acids (trans, cis, saturated, monounsaturated, and polyunsaturated), the Health Professionals Follow-up Study investigated this topic (20). The risk of advanced prostate cancer was significantly associated with high intake of saturated fat, polyunsaturated fat, and—particularly—α-linolenic acid (18:3n-3). An inverse but not significant association was found between linoleic acid (18:2n-6) intake and prostate cancer. Comparisons of plasma fatty acid profiles of prostate cancer patients and control subjects in the Physicians’ Health Study showed that plasma 18:3n-3 was positively associated with prostate cancer risk and that this association was greater in men with low plasma 18:2n-6 concentrations (26). Thus, dietary intake of individual fatty acids, such as 18:2n-6 and 18:3n-3, may be important in prostate cancer progression from latent phenotype to clinically significant phenotype. Complex laboratory systems and new animal models are needed to guide the development and evaluation of intervention therapies. For example, transgenic mice or the new metamouse (bred specifically for tumor metastasis study) (27) may be an example of unique models to test the fatty acid hypothesis.

Case-control studies

Although prospective studies showed general association between intake of high dietary fat, especially animal fat, and increased risk in prostate cancer progression, results from case-control studies are inconsistent (Table 2). Most case-control studies found a significant association of prostate cancer risk with high dietary intake of total fat (27, 29, 31, 35, 37, 39), animal fat (28, 37, 40), and saturated fat (29, 31, 35, 38). Some studies, however, did not find a significant association (30, 32–34, 36). Kaul et al (30) reported the negative association of 18:2n-6 intake and prostate cancer risk in old men. Significant associations of advanced prostate cancer with dietary intake of total (38, 39), saturated, monounsaturated, and polyunsaturated fats (38) were also reported.

A major contributor to this inconsistent association is the methodologic limitation of case-control studies, which includes recall bias, validation of relatively short-period dietary recall in reflecting long-term dietary history, and selection of control subjects. A detailed discussion of the methodology of studies of dietary fatty acids and cancer in humans is given in this supplement by Byers and Gieseker (42).

Animal studies

The studies of the effects of dietary fat modulation on prostate tumor growth in different animal models are summarized in Table 3. Chemically induced carcinogenesis models and a xenograft prostate tumor model were used to evaluate the effects of high dietary fat intake on promoting prostatic carcinogenesis and stimulating prostate tumor growth, respectively. The results indicate that high dietary fat intake (as corn oil) significantly promotes the growth of both hormone-sensitive and hormone-insensitive transplantable human prostate tumors in nude mice (44–46). Wang et al (46) also found that dietary fat reduction resulted in reduced serum prostate-specific antigen (PSA) concentrations. In a rodent model, dietary n-6 polyunsaturated fatty acids, primarily 18:2n-6, promoted tumor growth, whereas in the xenograft model n-3 polyunsaturated fatty acids, primarily decosahexaenoic acid (22:6n-3) and eicosapentaenoic acid (20:5n-3) in fish oil or menhaden oil, significantly diminished tumorigenesis (44, 45).

No influence of dietary fat on prostatic carcinogens was found in chemically induced carcinogenesis models in rats (48–50). Pollard and Luckert (47) found that high dietary fat significantly promoted the testosterone-induced prostatic tumor growth in genetically susceptible rats.

ROLES OF INDIVIDUAL FATTY ACIDS IN PROSTATE CANCER PROGRESSION

Dietary linoleic and linolenic acids

Most epidemiologic studies evaluated the effects of total dietary fat on prostate cancer risk. Few studies have dealt with the association between prostate cancer risk and a fatty acid family or individual fatty acids. High intake of dietary 18:3n-3 was significantly associated with increased risk for development of advanced prostate cancer in the Health Professionals Follow-up Study (20). Results from the Physicians’ Health Study indicated that high plasma 18:3n-3 concentrations were associated with increased risk of prostate cancer and that this association was enhanced in men who had low plasma 18:2n-6 concentrations (26). Kaul et al (30) found that high dietary intake of 18:2n-6 was associated with reduced prostate cancer risk. Thus, dietary 18:3n-3 may function in promoting prostate cancer progression whereas dietary 18:2n-6 may protect 18:3n-3 from this tumor-promoting effect.

This speculation is supported by other epidemiologic evidence. African American prostate cancer patients have low 18:2n-6 intake compared with control subjects (30). The rates of prostate cancer mortality are high in North America and northwestern Europe, where the consumption of soybean or canola oil (major sources of 18:3n-3) are also high. The concentration of 18:3n-3 in adipose tissue of men in five European countries was found to be correlated with rates of prostate cancer in these countries (51).

However, in vitro laboratory and animal studies have shown that 18:2n-6 promotes prostate tumor growth (44, 45, 52), but the reason for this different effect is unknown. Little is known about the effects of dietary 18:3n-3 on prostatic tumor growth in animal models. More studies are needed in clinically relevant models to clarify the roles of dietary 18:3n-3, 18:2n-6, and their interactions on prostate cancer progression.

Dietary long-chain n-3 fatty acids

The role of dietary long chain n-3 fatty acids (mainly 22:6n-3 and 20:5n-3 in fish oil and menhaden oil) on tumorigenesis of both breast and colon cancers has been extensively studied. The results generally show that, compared with n-6 fatty acids, n-3 fatty acids significantly inhibit the growth of tumors of breast and colon in the rodent model and proliferation of cancer cell lines in vitro.

The role of n-3 polyunsaturated fatty acids in prostatic tumorigenesis has been difficult to evaluate because of the relatively limited data showing that animal prostatic tumors are sensitive to dietary fat. Transplantable human prostatic carcinoma cells in a nude mouse model system were used to evaluate the effects of n-3 fatty acids on prostate cancer tumorigenesis. Karmali et al (44) and Rose and Cohen (45)
### TABLE 2
Case-control studies of dietary fat and prostate cancer risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Significance</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total dietary fat intake</strong></td>
<td></td>
<td></td>
<td>--------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Graham et al (28), 1983</td>
<td>262 case subjects, 259 hospital control subjects, Buffalo, NY</td>
<td>+ Prostate cancer risk in men age &gt; 70 y</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Heshmat et al (29), 1985</td>
<td>181 black case subjects, 180 age- and race-related hospital control subjects, Washington, DC</td>
<td>+ Prostate cancer risk in young men (30–49 y) but not men &gt; 50 y</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Kaul et al (30), 1987</td>
<td>55 black case subjects, 55 age- and race-matched hospital control subjects, Washington, DC</td>
<td>0 Prostate cancer risk</td>
<td>0</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Kolonel et al (31), 1988</td>
<td>452 case subjects, 899 population control subjects, Hawaii</td>
<td>+ Prostate cancer risk in elderly men (&gt; 70 y) but not in younger men</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Mettlin et al (32), 1989</td>
<td>371 case subjects, 371 hospital control subjects, Buffalo, NY</td>
<td>0 Prostate cancer risk</td>
<td>0</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Mishina et al (33), 1985</td>
<td>100 case subjects, 100 healthy age-matched control subjects, Japan</td>
<td>0 Prostate cancer risk</td>
<td>0</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Ohno et al (34), 1988</td>
<td>100 benign prostatic hyperplasia case subjects, 100 age-matched hospital patients, Japan</td>
<td>0 Benign prostatic hyperplasia risk</td>
<td>0</td>
<td>Benign prostatic hyperplasia risk</td>
</tr>
<tr>
<td>Ross et al (35), 1987</td>
<td>284 case subjects (142 blacks, 142 whites), 284 age- and race-matched population control subjects, Southern California</td>
<td>+ Prostate cancer risk</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Talamini et al (36), 1986</td>
<td>166 case subjects, 202 hospital control subjects, Northern Italy</td>
<td>0 Prostate cancer risk</td>
<td>0</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Walker et al (37), 1992</td>
<td>166 black case subjects and age- and race-matched control subjects in South Africa</td>
<td>+ Prostate cancer risk</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>West et al (38), 1991</td>
<td>358 case subjects, 679 age-matched population control subjects, Utah</td>
<td>+ Aggressive prostate cancer in elderly</td>
<td>+</td>
<td>Aggressive prostate cancer in elderly</td>
</tr>
<tr>
<td>Whittemore et al (39), 1995</td>
<td>1655 case subjects (531 blacks, 515 whites, 2283 Chinese Americans, 326 Japanese Americans), 1645 age- and race-matched control subjects, United States and Canada</td>
<td>+ Total and advanced prostate cancer risk</td>
<td>+</td>
<td>Total and advanced prostate cancer risk</td>
</tr>
<tr>
<td><strong>Animal fat intake</strong></td>
<td></td>
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</tr>
<tr>
<td>Talamini et al (36), 1986</td>
<td>166 case subjects, 202 hospital control subjects, Northern Italy</td>
<td>+ Meat, milk and dairy products and prostate cancer risk</td>
<td>+</td>
<td>Meat, milk and dairy products and prostate cancer risk</td>
</tr>
<tr>
<td>Walker et al (37), 1992</td>
<td>160 black case subjects and age- and race-matched control subjects, South Africa</td>
<td>+ Prostate cancer risk</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td>Rotkin (40), 1977</td>
<td>111 case subjects, 111 age- and race-matched hospital control subjects, Los Angeles and Chicago</td>
<td>+ Prostate cancer risk</td>
<td>+</td>
<td>Prostate cancer risk</td>
</tr>
<tr>
<td><strong>Saturated fat intake</strong></td>
<td></td>
<td></td>
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<td>+</td>
<td>Prostate cancer risk</td>
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*continued*
found that compared with diets containing corn oil, diets containing n-3 fatty acids inhibited the growth of transplanted DU 145 human prostatic carcinoma cells in nude mice. However, it is unclear whether reduced tumor growth was due to the reduced tumor-promoting effect of 18:2n-6, the tumor-inhibitory effect of n-3 fatty acids, or the combined effects. The proliferation of both PC-3 and DU 145 cell lines in vitro was inhibited by 22:6n-3 and 20:5n-3 (52). Two epidemiologic studies showed a negative association of prostate cancer risk with seafood intake (33, 41). In summary, n-3 fatty acid supplementation may provide unique fatty acid patterns in the prevention and treatment of prostate cancer, but more data are needed.

Possible mechanisms

Known biochemical, endocrine, and molecular mechanisms do not adequately explain the role of dietary fat and individual fatty acids in prostate cancer progression. Several possibilities, based on biological functions of fatty acids, are presented here.

Eicosanoid regulation

One of the most attractive fatty acid hypotheses suggests that each polyunsaturated fatty acid has an effect on eicosanoid metabolism that determines its tumor-promoting potential. Laboratory results indicate that eicosanoids (both prostaglandins and leukotrienes) can affect cell proliferation, immune response, tumor cell invasion, and metastases (53). Dietary fatty acids, such as 18:3n-3 and 18:2n-6, control the synthesis of eicosanoids of different series via competing pathways and in turn exert different functions in tumorigenesis. Dietary n-3 fatty acids in fish oil (22:6n-3 and 20:5n-3) inhibit tumor cell growth partially because 20:5n-3 is a competitive inhibitor of cyclooxygenase, whereas 22:6n-3 inhibits the metabolism of arachidonic acid (20:4n-6) and thus dienoic prostaglandin synthesis (54, 55).

Cell membrane integrity

Polyunsaturated fatty acids, such as 18:3n-3 and 18:2n-6, are the components of cell membrane phospholipids. Changes in lipid composition of the diet readily alter the fatty acid patterns and the structure of cell membranes and could affect cell surface permeability and receptor activity or cell-cell interaction in the rodent mammary tumor model (56, 57). Certain membrane fatty acid alterations can also affect cell response to external stimuli, such as growth factors and hormones.

Lipid peroxidation and free radical formation

Oxidative stress is a metabolic state in which the cellular oxidative reactions are out of control. Under such conditions the superoxide may accumulate, leading to formation of the hydroxyl radical, a free radical that abstracts hydrogen from the double bonds of polyunsaturated fatty acids. A fatty acid thus becomes a free radical. Free radicals react easily with oxygen to form peroxide radicals, which initiate oxidative chain reactions. These reactions may result in cellular damage of DNA, proteins, and carbohydrates. Feeding of either low-fat or energy-restricted diets to rats results in reduced oxidative DNA damage in the rodent mammary tumor model. Because oxidative DNA damage is suggested to have a role in carcinogenesis, this may be one mechanism by which dietary reduction of fat can reduce cancer risk. A possible mechanism by which dietary fish oil inhibits mammary tumorigenesis is that fish oil supplementation may increase accumulation of lipid peroxidation products in the tumor tissue (58, 59). These peroxidative products may decrease cell proliferation or increase cell death.

Sex hormone metabolism

Sex hormones may play an important role in prostate cancer initiation and promotion. Cell division in the prostate is controlled by testosterone after intracellular conversion to its reduced form, dihydrotestosterone, by 5α-reductase. High dietary fat, high animal fat in particular, may increase circulating
TABLE 3
Animal studies of dietary fats and fatty acids and prostate tumor growth

<table>
<thead>
<tr>
<th>Tumor types and study</th>
<th>Tumor and animal</th>
<th>Fat type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Clinton et al (43), 1988</td>
<td>Dunning transplantable prostate carcinomas, rat</td>
<td>CO (low or high)</td>
<td>Fat-free diet inhibited tumor growth; fat intake of 0.5–20% did not (as measured both by percentage of energy intake and by percentage of weight of food intake)</td>
</tr>
<tr>
<td>Karmali et al (44), 1987</td>
<td>DU 145, nude mice</td>
<td>20.5% FO + 3% CO compared with 23.5% CO</td>
<td>FO reduced tumor growth compared with CO</td>
</tr>
<tr>
<td>Rose and Cohen (45), 1988</td>
<td>DU 145, nude mice</td>
<td>Menhaden oil + CO compared with CO</td>
<td>n-3 Fatty acid inhibited tumor growth compared with CO</td>
</tr>
<tr>
<td>Wang et al (46), 1995</td>
<td>LNCaP, nude mice</td>
<td>CO (2.3–40.5% of energy)</td>
<td>Fat reduction slowed tumor growth and reduced serum prostate-specific antigen concentrations</td>
</tr>
<tr>
<td>Induced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollard and Luckert (47), 1985</td>
<td>Testosterone-induced, rat</td>
<td>CO (low or high)</td>
<td>High-fat diet promoted testosterone-induced tumor growth</td>
</tr>
<tr>
<td>Pour et al (48), 1991</td>
<td>BOP-induced testosterone-promoted, rat</td>
<td>CO (5% or 24.6%)</td>
<td>Dietary fat did not influence the incidence of prostatic tumor</td>
</tr>
<tr>
<td>Shirai et al (49), 1991</td>
<td>MNU or BOP-induced testosterone-promoted, rat</td>
<td>CO (low or high)</td>
<td>High-fat did not influence tumor growth</td>
</tr>
<tr>
<td>Takai (50), 1991</td>
<td>DMAB-induced, rat</td>
<td>Normal or high fat</td>
<td>High-fat diet did not enhance prostate tumor development</td>
</tr>
</tbody>
</table>

1 CO, corn oil; FO, fish oil; MNU, N-methylnitrosourea; BOP, N-nitrosobis(2-oxopropyl)amine; DMAB, 3,2'-dimethyl-4-aminobiphenyl.

testosterone, which results in stimulated 5α-reductase expression, elevated intracellular dihydrotestosterone, increased cell division, oncogene activation and tumor suppressor gene inactivation, and subsequent prostate cancer tumorogenesis (60). Urinary concentrations of androgens and estrogens decreased in a group of white and black men who had decreased their dietary fat intake (61). Hamalainen et al (62) found that reduced dietary fat (from 40% to 25% energy as fat) with a higher ratio of polyunsaturated to saturated fatty acids (from 0.15 to 1.22) resulted in decreased serum concentrations of testosterone, free testosterone, and androstenedione.

Regulation of tumor invasion and metastasis

Epidemiologic investigations suggested that environmental factors responsible for clinically significant prostate cancer operate as tumor progressors rather than tumor initiators (6). Thus fatty acids may be more strongly associated with the incidence of advanced prostate cancer than of total prostate cancer. Penetration of the basement membrane and the extracellular matrix by cancer cells through proteolytic degradation was suggested to be the first step in tumor invasion and metastasis, the processes involved in advanced prostate cancer. Among proteolytic enzymes, metalloproteinases and urokinase-type plasminogen-activator play crucial roles in the degradation of basement membrane and extracellular matrix and subsequent cell invasion and metastasis. Active metalloproteinases are also necessary for establishment of tumor growth and invasion at metastatic sites distant from prostate. The effects of dietary fat and individual fatty acids on the expression and the activity of proteolytic enzymes in prostate cancer tumor have not been studied.

Few studies have investigated the effects of fatty acids on regulating the activity of metalloproteinases and urokinase-type plasminogen-activator in mammary tumors. γ-linolenic acid inhibits urokinase-type plasminogen-activator activity (63). A diet containing a large amount of 18:2n–6 was shown to promote tumor growth and metastases in the rodent mammary tumor model (64, 65) and stimulate the invasion of breast cancer cells through the basement membrane in vitro (66). This stimulatory effect of 18:2n–6 on tumor cell invasion was associated with an enhancement of type IV collagenase (metalloproteinase-9) expression (mRNA) and activity (65, 67); 20:5n–3 supplementation suppresses mammary tumor growth and metastases and reduces tumor metalloproteinase-9 expression (68).

GAPS AND FUTURE DIRECTIONS OF RESEARCH IN BRIDGING ANIMAL AND HUMAN STUDIES

A growing body of evidence suggests a tumor-promoting effect of increased dietary fat intake and a possible tumour-inhibitory effect of specific dietary fat patterns on prostate cancer progression. However, a large gap in data exists between animal and human studies that is a barrier to advancing the fatty acid-tumor progression hypothesis. Identification of these missing segments will provide the direction of future research in the area of dietary prevention and treatment of prostate cancer.

The questions that need to be answered include the following: What is the effect on prostate tumor growth in animals of dietary fat reduction combined with supplementation of n-3 fatty acids? How can this information be applied to human
trials? What intermediate biomarkers are sensitive to dietary fat or fatty acid modulation and can serve as surrogate endpoints for human intervention studies?

**Animal studies: missing segments and future study**

Only a few animal studies have been conducted to investigate the effects of dietary fat on prostate cancer progression. Therefore, future research will need to include the following areas (see also Birt (69) and Ip (70) in this supplement):

**Development of suitable animal models of prostate carcinogenesis**

Although xenograft models can be used to study the effect of dietary intervention on the growth of prostate cancer, these models are not suitable for metastasis study. There is no suitable animal model for de novo prostate carcinogenesis, which is needed for prevention study. Recently, a new mouse model, called metastom, was developed for studying metastases of a variety of tumor types (27). Use of this model to study the effects of dietary fat modulation on prostate cancer metastases should be highly encouraged.

**Effects of individual fatty acids on prostate cancer progression**

Epidemiologic investigations suggest a positive association between dietary 18:3n−3 intake and advanced prostate cancer and a possible beneficial effect of dietary 18:2n−6 intake, whereas animal studies showed a tumor-promoting effect of dietary 18:2n−6. Existing evidence does not explain this phenomenon. More animal studies are needed to address the effects of dietary 18:3n−3, 18:2n−6, and their interaction on prostate cancer progression. Also, future human studies should provide detailed information on dietary intake of these and other fatty acids as well as other dietary components.

**Effects of dietary fatty acid concentrations and ratios on prostate cancer progression**

The plausibility of using dietary fat reduction or modulation of dietary fat patterns as an intervention regimen warrants a high priority of study. A hypothesis based on existing evidence is that dietary fat reduction combined with increased dietary long-chain n−3 fatty acids will inhibit the growth of prostate tumor. A series of animal studies are required to test this hypothesis.

Several concerns should be addressed in animal experiments: 1) The type of dietary fat used to prepare low-fat and high-fat diets for animal studies: corn oil rich in 18:2n−6 was usually used in diet preparations. However, 18:2n−6 in corn oil may have tumor-promoting effects besides its contribution of energy to tumor promotion. Therefore, a fat without tumorigenic effect should be used as a neutral fat to adjust energy intake. 2) The amount of dietary fat used: a threshold of tumor-promoting effect may exist for dietary fat. The possibility of such a threshold must be investigated. 3) Energy intake’s effect on tumor growth: energy intake and weight gain of the animal should be controlled. The experiments should be designed to avoid possible influences of these variances on experimental endpoints or intermediate biomarkers.

**Mechanism of action and validation of intermediate biomarkers**

Although several possibilities are postulated, relatively little is known about cellular and molecular events or the mechanism by which the dietary fat and fatty acids may promote or prevent prostate cancer progression. Biochemical, cellular, or molecular markers are needed as surrogate endpoints for evaluating the efficacy of dietary intervention. By using animal models, we can evaluate the mechanism of action and the sensitivity and specificity of those intermediate markers on treatment.

**Human studies: missing segments and future study**

Animal studies are expected to provide data about the efficacy of dietary fat reduction and n−3 fatty acid supplementation on inhibiting prostate tumorigenesis, explain possible mechanisms, and validate intermediate biomarkers. Further clinical studies are required to demonstrate the public health effect on prostate cancer progression of this intervention regimen.

The efficacy of intervention by total fat reduction combined with dietary n−3 fatty acid supplementation could be evaluated in two series of studies with randomized experimental design: one series would study the effect on delayed recurrence of prostate cancer and improved survival in patients with clinical disease and after prostatectomy or radiation therapy; the other series would evaluate the efficacy of the intervention in preventing or reducing the progression to clinically significant disease in men with latent disease.

Well-characterized epidemiologic studies will also be necessary to further explore the relation between fat intake (as well as intake of other dietary factors) and the risk of latent or clinically significant prostate cancer. Efforts should be made to estimate dietary exposure more precisely than done hitherto to establish whether quantity or type of dietary fat represents a risk factor for prostate cancer progression.

**Intermediate biomarkers**

Molecular, endocrine, and cellular biomarkers are needed to provide clinically relevant endpoints to avoid the excessively long study periods and high costs associated with the use of cancer incidence reduction as an endpoint, particularly with relatively slow-growing tumors such as prostatic adenocarcinoma. These biomarkers need to be specific and sensitive, and capable of determining the extent of tumorigenesis and the efficacy of dietary fat reduction or fatty acid modulation on prostate cancer progression.

**Serum prostate-specific antigen**

Serum PSA is a possible intermediate biomarker because elevated serum PSA concentrations are correlated with the progression of prostatic adenocarcinoma (71). Dietary fat reduction reduces plasma PSA concentrations in a rodent model. However, PSA is not specific to neoplasia and there are no data suggesting that the concentration is directly related to the degree of neoplasia progression. Density (72) and velocity of PSA rise (71) and the ratio of free to total PSA (73) may be better indicators of prostate cancer progression than is serum PSA alone.

**Cellular fatty acids and eicosanoid metabolites**

Tumors have unique profiles of eicosanoids, cellular fatty acids, and phospholipids. The amount of cellular fatty acids
and eicosanoid metabolites may be related to the mechanism by which dietary fat reduction and fatty acid modulation regulate prostate cancer progression.

Sex hormones

The change of blood sex hormone concentrations (androgens and estrogens) and related enzyme activities (5α-reductase) may be modulated by dietary fat or fatty acids. Another sex hormone–related biomarker is tissue androgen receptor expression (mRNA, protein, and binding activity).

Angiogenesis index

Angiogenesis, the generation of new blood vessels in tumor, is directly associated with the potential of tumor progression and invasion and metastases. Determination of the angiogenesis index (the density of microvessels) will provide direct evidence for regulation of dietary fat reduction and fatty acid modulation on tumor invasion and metastasis.

REFERENCES


