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Fat, Meat, and Prostate Cancer

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INTRODUCTION

For more than 25 years, epidemiologic studies have reported on the relation of dietary fat to the risk of prostate cancer. Indeed, fat per se, or food sources of fat, has probably been the most studied of all dietary factors with regard to this cancer site. Despite this extensive investigative effort, the role of dietary fat in prostate cancer remains unclear.

The hypothesis that dietary fat increases the risk of prostate cancer grew out of early ecologic studies that showed a positive correlation between prostate cancer mortality and per capita intake of fat, meat, and milk in international comparisons (1, 2). These findings were consistent with the recognition that prostate cancer risk is modifiable, as evidenced by such observations as the changing incidence and mortality rates in Japanese migrants to Hawaii and the substantial variations in incidence among ethnically similar populations in different geographic locations, e.g., Chinese men in different countries of Asia and the United States (3, 4).

Fat and meat are considered together in this presentation because most research has been done in Western populations (United States, Canada, and Europe) where meat is an important contributor to total and saturated fat intake. Many investigators, therefore, interpreted associations with meat intake to reflect an effect of dietary fat. However, other constituents of meat could also contribute to a carcinogenic effect, as discussed below.

FAT

Because fat is such a major contributor to energy intake in Western populations, these two dietary components tend to be highly correlated and an independent effect of fat may be difficult to establish. Early epidemiologic studies of diet and prostate cancer were based on dietary assessment methods that did not permit the calculation of total caloric intake, so that neither the effect of energy nor adjustment for energy intake was possible. This limitation has been overcome in many recent studies in which dietary histories were sufficiently complete for the computation of total caloric intakes. Although a positive effect of energy per se was reported in a few of these investigations (5–7), including one study of latent prostate cancer (8), most studies found no effect of energy independent of fat (9–15). Nevertheless, it is noteworthy that experimental studies in rodents have shown a reduction in prostate tumor growth from energy restriction (16).

In epidemiologic studies of prostate cancer, fatty acids have been classified in several different ways, including total fat, animal versus vegetable fat, and saturated versus unsaturated fat. Unsaturated fatty acids have sometimes been grouped into monounsaturated versus polyunsaturated fats, and polyunsaturated fatty acids have been further subdivided into ω-6 and ω-3 fatty acids. Fatty acids can differ in their biologic properties depending on the degree of saturation and length of the carbon chain. Thus, not all fat components would be expected to carry the same risk for cancer.

Total, saturated, and animal fat

Data from several ecologic studies have shown positive correlations ($r \geq 0.6$) between per capita intake of total, saturated, or animal fat and prostate cancer incidence or mortality (1, 2, 17–19). The findings for these fat components from case-control and cohort studies are summarized in table 1. Although several case-control studies found positive associations (odds ratio (OR) ≥1.3) between total fat intake and the risk of prostate cancer (7, 9, 10, 20–22, 24, 27, 29), only slightly fewer failed to find this relation (5, 12–14, 23, 26, 30). Most studies found stronger associations for saturated or animal fat than for total fat (9, 11, 20, 24, 25, 28, 30). Of the five case-control studies in table 1 that examined total fat intake with adjustment for total energy intake (5, 7, 10, 12, 13), only two (7, 10) found an increased risk. Similarly, of the eight case-control studies that examined animal or saturated fat with adjustment for total energy intake (5–7, 10–13, 31), only two (10, 11) showed an increased risk.

Because cohort studies of diet and cancer avoid the problem of recall bias and are less prone than case-control studies to other selection biases, they are generally given more weight in overall assessments of the literature. Three such studies, all of which adjusted for energy intake (15, 33, 34), examined total fat and prostate cancer; two of these studies (33, 34) found a positive association (relative risk ≥ 1.3). Four cohort studies examined animal or saturated fat and prostate cancer (15, 32–34), all with adjustment for energy intake. Only one of these studies (33) found a positive asso-

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Abbreviation: OR, odds ratio.

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TABLE 1. Summary of results from case-control and cohort studies of total/saturated/animal fat and prostate cancer

Study (reference no.) and year	Location	No. of subjects	Fat variable	Risk ratio*	Energy adjustment	Notes
		Case-control studies				
Graham et al. (20), 1983	New York	262 cases; 259 hospital controls	Total Animal	1.9 3.2†	No No	Men aged ≥70 years
Heshmat et al. (21), 1985	Washington, DC	180 cases; 180 hospital controls	Total Saturated	Positive Positive	No No	Consumption during ages 30–49 years
Ross et al. (22), 1987	California	284 cases (142 black, 142 white); 284 population controls (142 black, 142 white)	Total	Black 1.9† White 1.6	No	
Ohno et al. (23), 1988	Kyoto, Japan	100 cases; 100 hospital controls	Total	0.8	No	
Kolonel et al. (24), 1988	Hawaii	452 cases (multiethnic); 899 population controls (multiethnic)	Total Saturated	1.5 1.7	No No	Men aged ≥70 years; adjusted for ethnicity
Mettlin et al. (25), 1989	New York	371 cases; 371 hospital controls	Animal	1.5	No	Men aged <69 years
Fincham et al. (26), 1990	Alberta, Canada	382 cases; 625 population controls	Total Animal	0.8 1.0	No	
West et al. (27), 1991	Utah	358 cases; 679 population controls	Total Saturated	1.7; 2.9 1.3; 2.2	No No	All tumors and aggressive tumors, respectively; men aged 68–74 years
Bravo et al. (28); 1991	Madrid, Spain	90 cases; 180 hospital controls	Animal	2.6†	No	
Walker et al. (29), 1992	Soweto, South Africa	166 cases; 166 neighborhood controls	Total	2.6†	No	
Whittemore et al. (11), 1995	California; Hawaii; Vancouver, Canada; Toronto, Canada	1,655 cases (531 black, 515 white, 609 Asian); 1,645 controls (540 black, 504 white, 601 Asian)	Saturated	2.0†; 2.8†	Yes Yes	All tumors and advanced tumors, respectively; adjusted for ethnicity
Rohan et al. (6), 1995	Ontario, Canada	207 cases; 207 population controls	Saturated Animal	0.6 0.7	Yes Yes	
Andersson et al. (5), 1996	Sweden	526 cases; 536 population controls	Total Animal	1.1; 1.2 1.1, 1.2	Yes Yes	All tumors and advanced tumors, respectively
Ghadirian et al. (12), 1996	Montreal, Canada	232 cases; 231 population controls	Total Saturated Animal	0.8 0.7 0.8	Yes Yes Yes	

Table continues

ciation with saturated fat, but two (32, 33) reported positive associations with animal fat. Although most studies did not stratify the cases by stage or other measures of disease progression, it is notable that the association with total and saturated fat was stronger for the advanced cases in some reports (9, 11, 27, 33).

Two recent studies reported on the relation of dietary fat to latent prostate cancer (8, 15). Neither study found a significant association between total or saturated fat and prostate cancer after adjustment for energy intake.

Unsaturated fat

The data regarding unsaturated fat are more limited. A few ecologic studies examined monounsaturated and polyunsaturated fat intake based on per capita intake data (19, 35) or analysis of fatty acids in adipose tissue (36); none of these studies found more than weak correlations. The results from case-control and cohort studies are shown in table 2. Three case-control studies (27, 30, 39), one of which adjusted for energy intake (39), found positive associations ($p \geq 1.3$) of monounsaturated fat intake with prostate cancer risk, but five others (5, 6, 12, 13, 31), all of which adjusted for energy intake, did not. Of the three cohort studies that examined monounsaturated fat (15, 33, 34), all found positive associations after adjustment for energy intake. Of the two reports on latent prostate cancer (8, 15), one found a positive association with intake of monounsaturated fat; a similar effect was seen for the non-latent tumors in this study.

Three case-control studies (12, 27, 31), two of which (12, 31) included energy adjustment, found positive associations between polyunsaturated fat intake, or measurement in blood samples, and prostate cancer, whereas four studies (5, 6, 13, 30), three of which included energy adjustment (5, 6, 13), did not. Two reports based on latent prostate cancer (8,

TABLE 1. Continued

Study (reference no.) and year	Location	No. of subjects	Fat variable	Risk ratio*	Energy adjustment	Notes
			Case-control studies			
Key et al. (13), 1997	England	328 cases; 328 population controls	Total Saturated	0.9 1.1	Yes Yes	
Harvei et al. (30), 1997	Norway	141 cases; 141 controls	Total Saturated	1.1 1.6	NA‡ NA	Analysis of fatty acids in prediagnostic serum phospholipids
Lee et al. (10), 1998	China (12 cities)	133 cases; 265 neighborhood controls	Total Saturated	3.6† 2.9†	Yes Yes	
Hayes et al. (9), 1999	Georgia; Michigan; New Jersey	932 cases (449 black, 483 white); 1,201 population controls (543 black, 658 white)	Total Animal	1.4†; 2.0† 1.5†, 2.6†	No No	All tumors and advanced tumors, respectively; adjusted for race
Deneo-Pellegrini et al. (7), 1999	Montevideo, Uruguay	175 cases, 233 hospital controls	Total Saturated	1.8 0.9	Yes Yes	
Tzonou et al. (31), 1999	Athens, Greece	320 cases; 246 hospital controls	Saturated	1.1	Yes	Odds ratio for one standard deviation increment in nutrient intake based on the controls
Villeneuve et al. (14), 1999	Canada (8 provinces)	1,623 cases; 1,623 population controls	Total	1.2	No	
			Cohort studies			
Mills et al. (32), 1989	United States	14,000 Seventh-Day Adventist men; 180 cases	Animal (as a percentage of calories)	1.4	Yes	
Giovannucci et al. (33), 1993	United States	51,521 professional men; 279 cases	Total Saturated	1.3; 1.7 0.8; 1.0	Yes Yes	All tumors except stage A; and stage C and D and fatal tumors, respectively
			Animal	1.6	Yes	Stage C and D and fatal tumors
Veierod et al. (34), 1997	Norway	25,708 men; 72 cases	Total Saturated	1.3 0.7	Yes Yes	
Schuurman et al. (15), 1999	The Netherlands	58,279 men; 642 cases	Total Saturated	1.1 1.2	Yes Yes	All tumors (similar findings for advanced tumors)

* Odds ratio or relative risk for highest relative to lowest quantile.
† Statistically significant, $p < 0.05$.
‡ NA, not applicable.

15) found no association of polyunsaturated fat intake with prostate cancer risk. One of these studies (15) also examined *trans* unsaturated fatty acids and found no effect on prostate cancer risk.

Analyses based on groupings of fatty acids, such as polyunsaturated fat, could mask an effect specific to a single fatty acid. Several recent studies have examined specific polyunsaturated fatty acids, based either on dietary intake data or biochemical measurements in blood or adipose tissue (5, 15, 30, 33, 37–40). The results for the major polyunsaturated fatty acid, linoleic acid (ω-6), and its derivative, α-linolenic acid (ω-3, obtained from terrestrial food sources), as well as for two of the major long-chain ω-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid, found in fish oils) are also shown in table 2. Most studies found no increased risk associated with linoleic acid (5, 15, 30, 33, 39, 40), but five (30, 33, 37, 39, 40) of seven (5, 15, 30, 33, 37, 39, 40) studies that examined α-linolenic acid found a positive association. Some of the discrepancies in the results of different studies could be related to the use of different data sources (diet histories, adipose tissue, erythrocyte membranes, serum phospholipids, plasma cholesterol ester fatty acids). In one study, linoleic, but not α-linolenic, acid was associated with a statistically nonsignificant increased risk of latent prostate cancer (odds ratio = 1.6 for highest relative to lowest intake quartile) (8).

Eicosapentaenoic acid was associated with decreased risk (odds ratio ≤ 0.7) in two case-control studies based on biochemical analyses (37, 38), though three other studies, including two cohort studies, did not show this relation (15, 30, 40). Notably, neither of two studies that estimated eicosapentaenoic acid intake from diet histories found any effect (15, 38). Findings for docosahexaenoic acid are similar to those for eicosapentaenoic acid, with the exception of one study (30) which found an inverse relation for the former but not the latter fatty acid.

MEAT

The data on meat and prostate cancer are more consistent than those on fat. The findings from case-control and

TABLE 2. Summary of results from case-control and cohort studies of unsaturated fat and prostate cancer

Study (reference no.) and year	Location	No. of subjects	Fat variable	Risk ratio*	Energy adjustment	Notes
			Case-control studies			
West et al. (27), 1991	Utah	358 cases; 679 population controls	Monounsaturated Polyunsaturated	1.9†; 3.6† 1.9†; 2.7	No No	All tumors and aggressive tumors, respectively; men aged 68–74 years
Rohan et al. (6); 1995	Ontario, Canada	207 cases; 207 population controls	Monounsaturated Polyunsaturated	0.8 1.2	Yes Yes	
Andersson et al. (5), 1996	Sweden	526 cases; 536 population controls	Monounsaturated Polyunsaturated Linoleic acid α-Linoleic acid	1.1; 1.2 1.0; 1.0 1.2; 1.2 0.9; 0.8	Yes Yes Yes Yes	All tumors and advanced tumors, respectively
Ghadirian et al. (12), 1996	Montreal, Canada	232 cases; 231 population controls	Monounsaturated Polyunsaturated	0.8 1.5	Yes Yes	
Godley et al. (37), 1996	North Carolina	89 cases; 38 clinic controls	Linoleic acid α-Linoleic acid Eicosapentaenoic acid Docosahexaenoic acid	3.5†; 2.5 1.7; 2.7 0.7; 0.5 0.4; 1.1	NA‡ NA NA NA	Analysis of fatty acids in erythrocyte membranes and adipose tissue, respectively
Key et al. (13), 1997	England	328 cases; 328 population controls	Monounsaturated Polyunsaturated	0.9 0.9	Yes Yes	
Harvei et al. (30), 1997	Norway	141 cases; 141 controls	Monounsaturated Polyunsaturated Linoleic acid α-Linoleic acid ω-3 PUFA Eicosapentaenoic acid Docosahexaenoic acid	1.3 1.1 0.9 2.0† 1.1 1.2 0.7	NA NA NA NA NA NA NA	Analysis of fatty acids in prediagnostic serum pholspholipids
Lee et al. (10), 1998	China (12 cities)	133 cases; 265 neighborhood controls	Unsaturated	3.3†	Yes	
Tzonou et al. (31), 1999	Athens, Greece	320 cases; 246 hospital controls	Monounsaturated Polyunsaturated	1.1 1.8†	Yes Yes	Odds ratio for one standard deviation increment in nutrient intake based on the controls

Table continues

cohort studies are summarized in table 3. Sixteen (7, 9, 25, 28, 29, 32–34, 40, 42, 44–46, 48, 50, 52) of the 22 studies in the table show a positive relation, with all but one (42) showing risk ratios of 1.3 or more. In addition, several ecologic studies have reported a similar positive relation (1, 2, 53). Most studies reported on meat as a single category. Of the eight studies in table 3 that distinguished red meat as a group, or that included specific red meat items (mostly beef or pork) (7, 9, 33, 34, 40, 42, 47, 52), all but one (47) found positive associations, six of which showed risk ratios of 1.3 or more. Two reports (7, 52) examined processed meats, a dietary source of exposure to nitrites; neither study found an association of prostate cancer with this food item.

The basis for this association between prostate cancer and high consumption of red meat is not known. Initially, the finding was thought to reflect a high exposure to dietary fat, especially saturated fat, since meat and dairy products are the major contributors to fat intake in the western diet. However, because the findings on dietary fat and prostate cancer, as reviewed above, are inconsistent, other explanations for the association need to be considered. There are several possibilities: 1) In the American diet, red meat is a major source of zinc, which is essential for testosterone synthesis and may have other effects in the prostate (see the review of selenium and zinc in this issue of *Epidemiologic Reviews*). 2) Diets high in meat and other animal products may be relatively deficient in certain anticarcinogenic constituents found primarily in plant foods (see the reviews of fruits and vegetables, and phytochemicals also in this issue of *Epidemiologic Reviews*). 3) Most intriguingly, many meats are cooked at high temperatures, such as by pan-frying, grilling, or barbecuing. Cooking meats at high temperatures can result in the formation of heterocyclic amines which are potent carcinogens in animals (54), including the rat prostate (55). Furthermore, when meats are cooked on charcoal grills, rendered fat is pyrolized by the coals, leading to the deposition of polycyclic aromatic hydrocarbons, which are also carcinogenic in animals, on the outer surface of the meat (56). Because the levels of these compounds in the diets of individuals cannot be easily assessed, few epidemiologic studies have yet reported on their relation to

TABLE 2. Continued

Study (reference no.) and year	Location	No. of subjects	Fat variable	Risk ratio*	Energy adjustment	Notes
			Case-control studies			
Norrish et al. (38), 1999	Auckland, New Zealand	285 cases; 427 population controls	Eicosapentaenoic acid	0.6†; 0.5†	No	Analysis of fatty acids in erythrocyte phosphatidylcholine; all tumors, and advanced tumors, respectively (similar results with energy-adjustment based on dietary intake)
			Docosahexaenoic acid	0.6†; 0.7	No	
		317 cases; 480 population controls	Eicosapentaenoic acid	1.0	Yes	Based on dietary intake
			Docosahexaenoic acid	1.1	Yes	
De Stefani et al. (39), 2000	Montevideo, Uruguay	217 cases; 431 hospital controls	Monounsaturated	1.9	Yes	
			Linoleic acid	0.7	Yes	
			α-Linoleic acid	3.9†	Yes	
			Cohort studies			
Giovannucci et al. (33), 1993	United States	51,521 professional men; 279 cases	Monounsaturated	1.9; 1.6	Yes	All tumors except stage A; and stage C and D and fatal tumors, respectively
			Linoleic acid	0.9; 0.6	Yes	
			α-Linoleic acid	1.3; 3.4†	Yes	
Gann et al. (40)	United States	14,916 male physicians; 120 cases	Linoleic acid	0.6	NA	Analysis of plasma cholesterol ester fatty acids
			α-Linoleic acid	2.1	NA	
			Eicosapentaenoic acid	0.9	NA	
Alberg et al. (41), 1996	Maryland	25,802 men; 43 cases	Polyunsaturated (ω-6)	No association	NA	Analysis of fatty acids in prediagnostic serum
			Polyunsaturated (ω-3)	No association	NA	
Veierod et al. (34), 1997	Norway	25,708 men; 72 cases	Monounsaturated	1.4	Yes	
			Polyunsaturated	1.4	Yes	
Schuurman et al. (15), 1999	The Netherlands	58,279 men; 642 cases	Monounsaturated	1.3	Yes	All tumors (similar results for advanced tumors)
			Polyunsaturated	0.8	Yes	
			Linoleic acid	0.8	Yes	
			α-Linoleic acid	0.8	Yes	
			Eicosapentaenoic acid	1.0	Yes	
			Docosahexaenoic acid	1.0	Yes	

* Odds ratio or relative risk for highest relative to lowest quantile.
† Statistically significant, $p < 0.05$.
‡ NA, not applicable.

cancer. In a recent study on prostate cancer, heterocyclic amine intake from cooked meat was estimated; however, the study did not lead to a clear result (57).

ANIMAL AND IN VITRO STUDIES

Despite difficulties in developing a suitable animal model for the study of prostate cancer, several animal and in vitro studies support the fat-cancer hypothesis (58). In one of the earliest studies, a high fat diet was found to increase prostate cancer incidence and to shorten the latency period in Lobund-Wistar rats treated with exogenous testosterone to induce the tumors (59). Conversely, prostate tumor growth rate was reduced by a fat-free diet in Dunning rats (60) or by lowering dietary fat intake in athymic nude mice injected with LNCaP cells (a human prostate cancer cell line) (61). However, some other studies in rodent models failed to reproduce these findings (62, 63). In a recent report (16), tumor growth of androgen-responsive carcinomas in rats was shown to be reduced by restriction of energy rather than fat. With regard to specific types of fat, fish oils containing high levels of ω-3 fatty acids, such as eicosapentaenoic and docosahexaenoic acids, generally suppressed prostate tumor growth in rodents, whereas other polyunsaturated fatty acids, including linoleic (ω-6) and α-linolenic (ω-3), promoted tumor growth (64, 65). Since most animal studies have been conducted in rodents, whose prostate glands differ anatomically from that of humans, extrapolation of these findings to humans is particularly tenuous.

BIOLOGIC MECHANISMS

A number of plausible mechanisms by which dietary fat could contribute to carcinogenesis in the prostate gland have been proposed (58): 1) oxidation of polyunsaturated fatty acids leads to the formation of lipid radicals and hydroperoxides that can produce DNA damage; 2) a high fat diet

TABLE 3. Summary of results from case-control and cohort studies of total meat or red meat and prostate cancer

Study (reference no.) and year	Location	No. of subjects	Meat variable	Risk ratio*	Notes
		Case-control studies			
Rotkin (42), 1977	California; Illinois	111 cases; 111 hospital controls	Beef/pork	1.2	Odds ratio estimated from the data
Schuman et al. (43), 1982	Minnesota	223 cases; 223 neighborhood controls	Meat	No association	
Mishina et al. (44), 1985	Japan	100 cases; 100 population controls	Meat	2.0	
Talamini et al. (45), 1986	Pordenone, Italy	166 cases; 202 hospital controls	Meat	1.7	
Mettlin et al. (25), 1989	New York	371 cases; 371 hospital controls	Meat	1.5	Men aged <69 years
Bravo et al. (28), 1991	Madrid, Spain	90 cases; 180 hospital controls	Meat	2.3†	
Walker et al. (29), 1992	Soweto, South Africa	166 cases; 166 neighborhood controls	Meat	2.0†	
Talamini et al. (46), 1992	Northern Italy	271 cases; 685 hospital controls	Meat	1.4	
Grönberg et al. (47), 1996	Sweden	406 cases; 1,208 hospital controls	Beef	0.6	
Ewings and Bowie (48), 1966	England	159 cases; 325 hospital controls	Meat	2.7	
Key et al. (13), 1997	England	328 cases; 328 population controls	Meat	0.6	
Hayes et al. (9), 1999	Georgia; Minnesota; New Jersey	932 cases (449 black, 483 white); 1,201 population controls (543 black, 658 white)	Meat Red meat	1.4† 1.8† 1.4† 2.0†	All tumors (adjusted for race) Advanced tumors (adjusted for race) All tumors (adjusted for race) Advanced tumors (adjusted for race)
Deneo-Pellegrini et al. (7), 1999	Montevideo, Uruguay	175 cases; 233 hospital controls	Meat Red meat	1.6 1.7	Adjusted for total energy
Villeneuve et al. (14), 1999	Canada (8 provinces)	1,623 cases; 1,623 population controls	Meat	1.0	
		Cohort studies			
Hirayama (49), 1979	Japan	122,261 men; 63 fatal cases	Meat	0.8	
Snowden et al. (50), 1984	California	6,763 Seventh-Day Adventist men; 99 fatal cases	Meat	1.3	
Mills et al. (32), 1989	California	14,000 Seventh-Day Adventist men; 180 cases	Meat	1.4	
Hsing et al. (51), 1990	Minnesota; northeast US	17,663 Lutheran men; 149 cases	Meat	0.8	
Giovannucci et al. (33), 1993	United States	51,521 professional men; 126 stage C and D tumors and fatal cases	Red meat	2.6†	Adjusted for total energy
Le Marchand et al. (52), 1994	Hawaii	20,316 men (multiethnic); 198 cases	Beef	1.6†	Adjusted for ethnicity
Gann et al. (40), 1994	United States	14,916 male physicians; 120 cases	Red meat	2.5	
Veierod et al. (34), 1997	Norway	25,708 men; 72 cases	Main meals with meat Main meals with hamburger or meatballs	0.4 3.1†	

* Odds ratio or relative risk for highest relative to lowest quantile.
† Statistically significant, $p < 0.05$.

increases circulating levels of endogenous androgens that may contribute to the development of prostatic tumors (see the review on hormonal risk factors in this issue of *Epidemiologic Reviews*; 3) polyunsaturated fatty acids inhibit gap-junctional communication between cells, which is essential for normal control of tissue growth; 4) fatty acids can alter the activities of signal transduction molecules that are necessary for cellular growth control; 5) eicosanoids (prostaglandins and leukotrienes) are formed from arachidonic acid, and may influence prostate tumor cell growth; and 6) fatty acids may decrease the immune responsiveness of prostatic tissue.

Heterocyclic amines and polycyclic aromatic hydrocarbons may induce cancer directly by formation of DNA adducts, though supportive data are limited and other factors may be involved (54, 66). Biologically plausible mechanisms for the carcinogenic effects of other meat constituents can be found in the reviews noted in the section above on Meat.

ASSESSMENT

Conclusions

Figure 1 summarizes the relative risks/odds ratios for the various studies in tables 1–3. The findings from case-control studies are distinguished from those of cohort studies, and statistically significant risk ratios are noted. As seen in figure 1, most studies of total and saturated or animal fat reported risk ratios greater than 1.3, though none of the results from cohort studies were statistically significant. The substantial proportion of studies with a positive finding, however, makes it difficult to dismiss the possibility that total or saturated fat may play a role, perhaps indirect, in the etiology of prostate cancer. Attributable risk estimates from two reports (11, 67) suggest that about 20–25 percent of the incidence of prostate cancer among US Caucasian-Americans and African-Americans, and about 5–10 percent among Asian-Americans, may be due to high levels of saturated fat intake. However, less than 10 percent of the African-American versus Caucasian-American, and only about 15 percent of the Caucasian-American versus Asian-American, differences in incidence of prostate cancer could be attributed to differences in their saturated fat intakes (11).

The findings for monounsaturated fat suggest a possible positive relation to prostate cancer, though the number of studies is fewer than for total or saturated fat. For total polyunsaturated fat, the risk ratios are more evenly spread above and below 1.0, though two case-control studies reported odds ratios greater than 2.0. The inconsistency in the overall findings for polyunsaturated fat may reflect different effects for specific fatty acids, as the results for α-linolenic acid are supportive of a positive association, whereas those for eicosapentaenoic acid suggest a possible inverse association. Furthermore, the ratio of fat types,

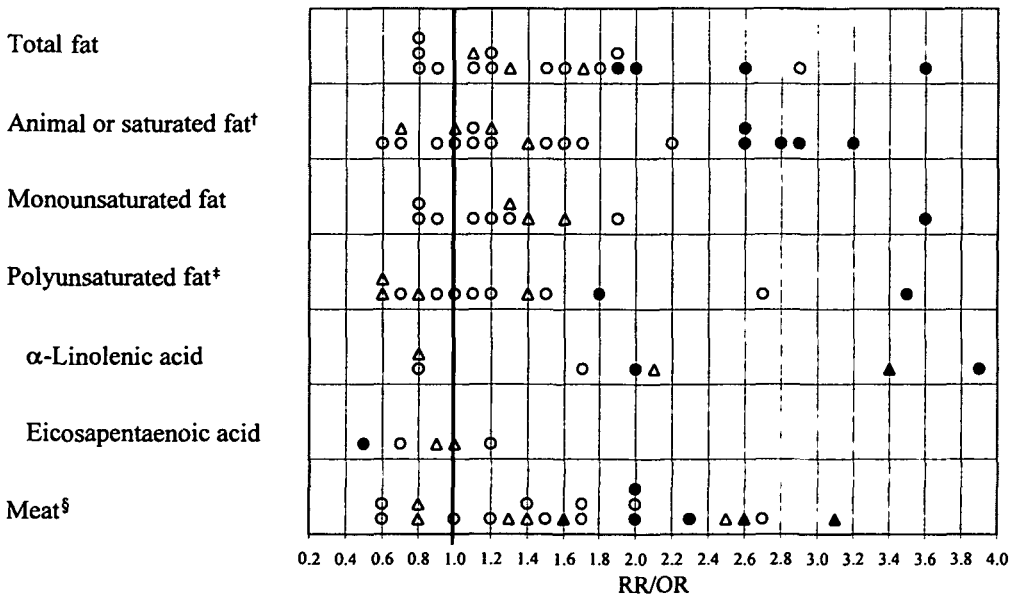

FIGURE 1. Summary of relative risks (RR)/odds ratios (OR) for high vs. low intake or tissue levels of fat from case-control and cohort studies.* Key: ○ = case-control study, OR not statistically significant; ● = case-control study, OR statistically significant ($p < 0.05$); △ = cohort study, RR not statistically significant; ▲ = cohort study, RR statistically significant ($p < 0.05$). *When values for all tumors and aggressive or advanced tumors were provided in the same study, the value for aggressive/advanced tumors was selected. †When values for both animal fat and saturated fat were provided in the same study, the value for saturated fat was selected. ‡When values for individual fatty acids, but not polyunsaturated fat as a group, were provided in a study, the value for linoleic acid, the major polyunsaturated fatty acid, was selected. One study (37) provided values for eicosapentaenoic acid based on both dietary intake and biomarker assay; the biomarker value was selected. §When values for individual meats, but not meat as a group, were provided in a study, beef was selected; if meats were grouped into categories, red meat was selected.

such a ω-6 to ω-3 polyunsaturated fatty acids, or possibly saturated to unsaturated fatty acids, may be more critical, as suggested in one report (30). The data on meat, like total fat, are heavily weighted with studies showing a positive relation to prostate cancer. All of the statistically significant findings are risk ratios above 1.3 and include the results from three cohort analyses. As noted earlier, the meat effect could reflect several constituents other than fat, including compounds produced during the cooking process.

Research needs

It does not seem likely that incremental improvements in the methods of dietary assessment in the next several years will substantially clarify the relations discussed in this review. More specific examination of particular subgroups of fats, such as the ratio of ω-6 to ω-3 fatty acids or the balance of saturated and unsaturated fats in the diet, may yield useful insights. Although fatty acids can be measured in serum, other biomarkers that could better reflect long-term and absolute fat intake (especially if they could distinguish fat intake at different periods of life) would be useful; such markers have yet to be identified. Research efforts to determine the role of diet, especially dietary fat, in explaining the large interracial differences in prostate cancer incidence should continue. More studies that distinguish between latent and overt cases should be encouraged, as only the latter have health consequences, and the proportion of very early prostate cancers being identified through the widespread use of prostate-specific antigen screening has greatly increased (68). If clinical tumors evolve from latent tumors, then the identification of factors that promote the progression of latent tumors should be of paramount interest. Because dietary fat appears to act as a cancer promoter (69), it could play a role in this sequence. However, the findings of one cohort study that compared latent with nonlatent tumors (15) suggested that the relation of fat to prostate cancer does not differ substantially between these two groups of cases.

Studies that carefully examine interactions between dietary fat and other dietary or nondietary risk factors may help clarify some of the specific effects of fat on carcinogenesis in the prostate. This research should include investigations of gene-environment interactions, such as may occur between intake of specific fat components or red meat consumption (including methods of preparation) and polymorphisms in genes encoding cytochrome P450 and other enzymes involved in the metabolism of heteocyclic amines, polycyclic aromatic hydrocarbons, and fatty acids (e.g., *CYP1A2*, *NAT2*, *GSTP1*). Although analyses of some candidate polymorphisms did not show significant relations to prostate cancer risk in a recent study (70), interactions with dietary exposures were not included. Studies with sufficient power to examine such interactions will require very large sample sizes that should be available in the next several years from some of the ongoing cancer cohorts in the United States and Europe.

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