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REVIEW ARTICLE

Dietary Fatty Acids and Cancer

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Abstract: In this review, the influence of dietary fat on the development of cancer is discussed. In epidemiological studies, a relationship between dietary fat and breast cancer has been found in correlational studies, but prospective studies do not support a role for dietary fat. Prospective epidemiological studies examining the role of dietary fat in the development of colon, pancreatic, and prostate cancers have produced conflicting results. The Women's Health Initiative intervention studies did not show any statistically significant effects of dietary fat on the development of either colon or breast cancer in women. In experimental studies, dietary fat generally enhances chemically-induced skin, liver, pancreatic, and mammary carcinogenesis, whereas conflicting results have been observed in colon carcinogenesis. Dietary fat appears to act primarily during the promotional stage of carcinogenesis in all of these models except the liver, where the effect of dietary fat is primarily on initiation.

Keywords: Fat, Cancer, Carcinogenesis, Epidemiological studies, Correlational studies, Dietary fat.

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1. INTRODUCTION

Cancer is currently the second leading cause of death in the United States. It is estimated that about 1,762,000 people will be diagnosed with cancer in the United States in 2019 and that about 606,880 will die from it [1]. One of the primary mechanisms for reducing cancer deaths is by altering the diet, and one proposed way is by decreasing the consumption of dietary fat. In this review, the role of dietary fat on the development of human and experimental cancer will be discussed. Because of the large number of studies published, reviews will be cited where possible. Relevant studies were identified using PubMed (U.S. National Library of Medicine, Bethesda, MD) and Google Scholar (Google LLC, Mountain View, CA).

Numerous epidemiological and experimental animal studies have examined the effect of dietary fat on human cancer. Several correlational studies have noted an increase in the rates of colon, breast, and other cancers in areas where dietary fat consumption is high [2]. Additionally, studies with immigrant populations have identified dietary fat intake as a causative factor in the development of these cancers [2].

2. COLON CANCER

Colorectal cancer is the third leading cause of death from cancer in both men and women. An estimated 145,000 cases will be diagnosed in 2019, and 51,000 people will die from it [1]. Epidemiological studies have not reached a clear consensus about the influence of dietary fat. Case-control studies overall have not found a positive association with dietary fat, although many have observed a positive association with meat intake [3]. Prospective epidemiological studies have conflicting results (Table **1**): some studies found a positive association [4 - 7], others saw no effect [8 - 25], and others saw an actual protective effect of high fat intakes [26 - 28]. In several of these studies, the consumption of red meat was found to be significantly correlated with colon cancer risk, but independent of fat intake. The International Agency for Research on Cancer recently classified red meat as probably carcinogenic to humans and processed meat as carcinogenic to humans, with the colon being the main target organ [29, 30]. In the Women's Health Initiative intervention study published in 2006 [31], 19,500 women lowered their fat intake by about 10% compared to 29,000 women who did not alter their diet, for a follow-up period that averaged 8 years. The intervention group had a higher relative risk of 1.08, which was not statistically significant, indicating that a diet lower in fat did not inhibit the development of colon cancer in this study.

Studies in experimental animals have produced differing results. A variety of chemicals have been used to induce colon tumors, usually in rats or mice. These include 1,2-dimethylhydrazine [DMH] and its metabolites azoxymethane [AOM] and methylazoxymethanol [MAM]; 3,2'-dimethyl-4-aminobiphenyl [DMAB]; methylnitrosourea [MNU]; and N-methyl-N'-nitro-N-nitrosoguanidine [MNNG] [32 - 35]. DMH and

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AOM have been used most frequently to study nutritional effects. Both can induce colon tumors by single [36 - 40] or multiple [41 - 45] injections. The Min mouse, which has a mutation in the mouse homolog of the Adenomatous Polyposis Coli [APC] gene, develops small intestinal and colon tumors spontaneously and has been used as a model of colon carcinogenesis [46]. Mice with mutations at other locations of the APC gene have also been developed [47]. In addition to tumors, putative preneoplastic lesions, Aberrant Crypt Foci [ACF], are induced by colon carcinogens [48]. ACF, which are identified by fixing the colon in formalin and then staining with methylene blue, are stained darker and are larger than normal crypts [48]. Some but not all studies have shown that ACF correlate well with the later appearance of adenocarcinomas [49 - 52].

Animal studies examining the effect of dietary fat have used a variety of protocols, and the results obtained often have been dependent on the investigator's protocol. In these studies, rats or mice were subjected to multiple doses of a colon carcinogen, with the dietary fat content being varied isocalorically during, and frequently before or after, the carcinogen injections. Some of these studies found an enhancement when the dietary fat content of the diet was increased, but others saw no effect or even an inhibition of tumor development [43, 53 - 62]. High-fat diets were found to influence the early stages of carcinogenesis more than the later stages [63]. In several studies where fat was found to enhance colon carcinogenesis, fat was either added to an unrefined [chow] diet or was substituted for carbohydrate on a weight basis, so that the ratio of calories to essential nutrients was altered; therefore the effect could have been due to a lower consumption of essential nutrients rather than to an effect of fat [41, 42, 64 - 70]. In the Min model, high-fat diets were found to increase colon carcinogenesis in two studies but not another [71 - 73]. Increasing the fat content of the diet has been found to increase the number of ACF induced by colon carcinogens in several but not all studies [61, 74 - 84]. The type of fat unsaturated *vs.* saturated in the diet also produced conflicting results [59, 80, 85, 86]. ω-3 fatty acids can also influence colon carcinogenesis: feeding fish oil, microalgal oil, or flaxseed oil in place of corn oil, or eicosapentaenoic acid in place of linoleic acid, decreases the development of DMH- or AOM-induced colon tumors, but adding menhaden oil to a low-fat diet does not affect colon carcinogenesis [61, 87 - 96]. A transgenic model [fat-1 mouse] that has high endogenous levels of ω-3 fatty acids was found to have lower induction of colon tumors induced by AOM and dextrane sodium sulfate [97]. Olive oil, which is high in ω-9 fatty acids, was also found to inhibit colon carcinogenesis when substituted for polyunsaturated fatty acids [92].

Table 1. Dietary fat and colorectal cancer: Prospective studies.

Investigators	Subjects	Years of Follow-up	Effect of Dietary Fat
Hirayama [26]	265,118 subjects in Japan	13	Significant negative effect for meat
Stemmermann *et al.* [27]	7,074 Hawaiian-Japanese men	15	Significant negative effect
Garland *et al.* [8]	1,954 men in Chicago	19	No significant effect
Phillips & Snowdon [9]	25,493 Seventh Day Adventists in California	21	No significant effect
Willett *et al.* [4]	88,751 female nurses in USA	6	Significant positive effect for total, animal, monounsaturated, and saturated fat, and for red meat
Giovannucci *et al.* [5]	7,284 male health professionals	2	Significant positive effect for total, animal, monounsaturated, and saturated fat, and for red meat
Thun *et al.* [10]	764,343 men and women	6	No significant effect of fat or red meat
Goldbohm *et al.* [11]	58,279 men and 62,573 women in Netherlands	3.3	No significant effect
Giovannucci *et al.* [12]	47,949 male health professionals	6	No significant effect of fat, but significant positive correlation with red meat
Bostick *et al.* [13]	35,215 women in Iowa	4	No significant effect
Gaard *et al.* [14]	50,535 men and women in Norway	11	No significant effect of fat, but significant positive correlation with sausage intake
Chyou *et al.* [28]	7,945 Japanese-American men in Hawaii	27-30	Significant negative correlation with total and monounsaturated fat for colon but not rectal cancer
Kato *et al.* [15]	14,727 women in New York and Florida	7	No significant effect of fat or meat
Singh & Fraser [6]	32,051 7th Day Adventist men and women in California	6	Significantly increased risk with red, white or total meat intake
Pietinen *et al.* [16]	27,111 male smokers in Finland	8	No significant effect of fat or meat
Jarvinen *et al.* [17]	9959 Finnish men and women	27-32	High cholesterol intake was associated with increased risk, but not consumption of total, saturated, monounsaturated or polyunsaturated fat
Terry *et al.* [18, 19]	61,463 women in Sweden	9.6	No significant effect of intake of fat or a “Western” diet
Flood *et al.* [20]	45,496 women in USA	8.5	No significant effect of fat or meat consumption
Chao *et al.* [314]	148,610 men and women in USA	9, 19	Significant increase with red and processed meat consumption; poultry and fish consumption protective

(Table 1) contd.....

Investigators	Subjects	Years of Follow-up	Effect of Dietary Fat
Robertson *et al.* [21]	1,520 men and women in USA	1, 4	No significant effect of fat or red meat consumption
Oba *et al.* [22]	13,894 men and 16,327 women in Japan	8	No significant effect of dietary fat; significant increase from processed meat consumption
Lin *et al.* [23]	37,547 women in USA	8.7	No significant effect of dietary fat
Sanjoaquin *et al.* [24]	10,998 men and women in the United Kingdom	17	No significant effect of animal fat intake
Dahm *et al.* [25]	153,000 men and women in the United Kingdom	7-23	No significant effect of dietary fat
Butler *et al.* [7]	61,321 Singapore Chinese	9.8	Positive association between total and saturated fat and localized cancer in women only

Table 2. Dietary fat and breast cancer: Prospective studies.

Investigator	Subjects	Years of Follow-Up	Effect of Dietary Fat
Jones *et al.* [112]	5,485 women in USA	10	No significant effect
Willett *et al.* [113]	89,538 female nurses in USA	4	No significant effect
Mills *et al.* [114]	20,341 Seventh Day Adventist women in California	6	No significant effect
Knekt *et al.* [115]	3,988 women in Finland	20	No significant effect
Howe *et al.* [116]	56,837 Canadian women	5	Slightly elevated risk
Graham *et al.* [117]	18,586 women in New York State	7	No significant effect
Kushi *et al.* [118]	34,388 women in Iowa	4	No significant effect
Willett *et al.* [119]	89,494 female nurses in USA	8	No significant effect
van den Brandt *et al.* [120]	62,573 women in Netherlands	3.3	No significant effect
Toniolo *et al.* [121]	14,291 women in New York City	6	No significant effect; but significant positive correlation with red meat
Gaard *et al.* [122]	31,209 women in Norway	7-13	No significant effect for fat or saturated fat; but significant positive correlation with meat and monounsaturated fat
Wolk *et al.* [131]	61,471 women from central Sweden	4.2	Positive correlation with polyunsaturated fat; negative association with monounsaturated fat
Holmes *et al.* [123]	88,795 female nurses in USA	14	No significant effect of total fat or specific fatty acids
Velie *et al.* [124]	40,022 women in 29 centers throughout USA	5.3	No overall association; but among women with no history of benign breast disease, positive association between total and unsaturated fat intake and breast cancer risk
Thiebaut *et al.* [125]	65,879 women in Europe	3.4	Small positive association between fat intake and breast cancer risk
Terry *et al.* [126]	61,463 women in Sweden	9.6	No association between “Western” dietary pattern and breast cancer risk
Byrne *et al.* [127]	44,697 female nurses in USA	14	No effect of fat in women with no history of benign breast disease
Voorrips *et al.* [133]	62,573 women in Netherlands	6.3	No effect for total fat; positive association with conjugated linoleic acid; negative association with monounsaturated fat
Wirfalt *et al.* [132]	12,803 women in Sweden	Up to 8	Positive association with total, monounsaturated, and polyunsaturated fat
Horn-Ross *et al.* [137]	111,526 women in California	2	No effect for total fat, saturated fat, linoleic acid, or oleic acid
Cho *et al.* [130]	90,655 premenopausal female registered nurses in one of 14 states within the United States	8	Positive association with intake of animal fat but not total fat or vegetable fat
Gago-Dominguez *et al.* [136]	35,298 Singapore Chinese women aged 45-74 years	Up to 7	No effect for total, saturated, monounsaturated, or polyunsaturated fat; decreased risk with marine n-3 fatty acid intake
Bingham *et al.* [139]	25 630 men and women aged 45–74 years from Norfolk, UK	Up to 9	Positive association with total and saturated fat intake when measured using food diaries but not when using food frequency questionnaires
Kim *et al.* [128]	80,375 female nurses in USA	20	No effect of total fat or specific types of fat
Lof *et al.* [135]	49,261 women in Sweden	13	No association with total, saturated, polyunsaturated, and monounsaturated fat intakes

(Table 2) contd.....

Investigator	Subjects	Years of Follow-Up	Effect of Dietary Fat
Thiebaut *et al.* [134]	188,736 postmenopausal women	4.4	Positive association with total, saturated, polyunsaturated, and monounsaturated fat intakes
Linos *et al.* [129]	39,268 premenopausal female nurses in USA	7	Increased consumption of total fat during adolescence, but not saturated, monounsaturated, or polyunsaturated fat, increased risk
Murff *et al.* [143]	74,942 women from Shanghai, China	7-11	No significant effect of n-3 or n-6 polyunsaturated fatty acid intake, but high ratio of n-6 to n-3 increased risk
Sczaniecka *et al.* [142]	30,252 women in USA	6	Total saturated and monounsaturated fat intakes associated with increased risk but not trans or polyunsaturated fat; individual fatty acids had heterogeneous effects
Farvid *et al.* [141]	88,804 female nurses in USA	20	Positive association with animal fat intake but not other types of fat
Boeke *et al.* [140]	187,898 female nurses in USA		No influence on risk of lethal breast cancer

Several mechanisms by which dietary fat may influence colon cancer have been proposed. Bile acids, particularly hydrophobic bile acids, have been proposed to play a role in colon carcinogenesis [98 - 100]. Bile acids, particularly secondary bile acids, have promoting activity in the colon [101 - 103]; their concentration in the feces has been found to be increased by dietary fat in some but not all studies [41, 104 - 107]. Effects on the colon microbiome could also play a role in the development of colon cancer [108].

3. BREAST CANCER

Breast cancer is the second leading cause of death from cancer in women. An estimated 271,000 cases will be diagnosed in 2019, and 42,000 people will die from it [1].

Numerous epidemiological studies have attempted to identify factors which influence breast cancer risk in humans. Established breast cancer risk factors include age of first pregnancy, body mass index, age at menarche or menopause, and family history of breast cancer [109]. The effect of dietary fat has been studied in correlational, case-control, and prospective epidemiological studies. Studies examining international correlations between dietary fat intake and breast cancer risk, and migrant studies have reported a positive association between dietary fat intake and breast cancer risk [110]. A meta-analysis of 27 case-control studies found no significant association between breast cancer risk and saturated fat intake [111]. Most prospective studies did not find any link between total dietary fat intake and the development of breast cancer [112 - 143] (Table **2**). Furthermore, a combined analysis of many of these prospective studies did not find any evidence of a link between total dietary fat intake and breast cancer risk, although an elevated risk was observed with higher consumption of polyunsaturated fat [111]. The Women's Health Initiative intervention study [described in the preceding section on colon cancer] examined the effect of low-fat diets on the development of breast cancer [144]. Although dietary fat did not significantly affect the development of breast cancer, there was a relative risk of 0.91 in the low-fat intervention group.

The effect of dietary fat on mammary carcinogenesis in experimental animals has been examined extensively: over 100 experiments have been conducted [145 - 148]. The primary model used is a rat model [usually the Sprague-Dawley strain] in which mammary tumors are induced by DMBA or MNU. Genetically-engineered models have also been developed, including models in which the Erbb2 gene or simian virus 40 [SV40] T/t-antigens are overexpressed in mammary epithelial cells [149]. The use of these animal models is advantageous because tumor latency, tumor size, and tumor progression can easily be quantified by palpation of mammary tumors as they appear. Increasing the fat content of the diet clearly enhances the development of mammary tumors [145 - 147]. In the rat model, a high-fat diet increases tumorigenesis both when it is fed during and after carcinogen administration, and when it is fed only after carcinogen injection. More recent studies have examined the role of high-fat diets fed before and/or during gestation, and/or during lactation, or during puberty on mammary carcinogenesis in the offspring. Increasing the level of unsaturated fat (*e.g.* corn oil) during gestation and lactation increased the number of mammary tumors developing in the offspring, whereas monounsaturated fat olive oil had less of an effect, and saturated fat lard produced conflicting results [150 - 153]. Feeding high-fat diets during puberty was sufficient to enhance mammary carcinogenesis [154, 155]. Feeding a diet high n-3 fatty acids decreases experimental mammary carcinogenesis in experimental animals [145 - 147, 156 - 158]. A meta-analysis of experimental animal studies found that n-6 fatty acids strongly enhanced carcinogenesis, saturated fatty acids were weaker at enhancing carcinogenesis, monounsaturated fatty acids had no effect, and n-3 fatty acids weakly but non-significantly inhibited carcinogenesis [147].

4. PANCREATIC CANCER

Pancreatic cancer is the fourth leading cause of death from cancer in both men and women. An estimated 56,000 cases will be diagnosed in 2019, and 45,000 people will die from it [1].

For the pancreas, international comparisons do not show as strong of a trend as with colon or breast cancer [159]. Overall, neither case-control nor prospective studies that examined total fat intakes observed an effect [160]. However, diets high in polyunsaturated fat were found to have an inverse association in a meta-analysis, whereas diets high in saturated fatty acids or monounsaturated fatty acids had no effect [161]. Studies examining the consumption of cholesterol tend to show a positive correlation, however [162, 163]. Several prospective studies have examined the relationship of meat consumption with pancreatic cancer; a meta-analysis of these studies observed a positive association [164].

Dietary fat has been studied extensively in animal models of pancreatic cancer. A common model is induction of pancreatic tumors by azaserine; however, azaserine produces tumors in acinar cells [165], whereas the primary site in humans is the ductal cell. Tumors can be produced in pancreatic ductal cells in rats, by DMBA [166], or in hamsters, by the chemicals N-nitroso-bis-[2-oxypropyl]amine [BOP] and N-nitroso-bis-[2-hydroxypropyl]amine [BHP] [165]. A number of transgenic models have been developed [165, 167]. A number of models used regulatory elements from the rat elastase gene, which targets acinar cells. These constructs produced acinar tumors or mixed acinar/ductal tumors [165, 167]. Another model uses an oncogenic K-ras [$KRAS^{G12D}$] inserted into the endogenous K-ras locus [168]. The gene has a Lox-STOP-Lox [LSL] construct inserted upstream. These mice are interbred with mice containing the Cre recombinase downstream from a pancreatic specific promoter, either PDX-1 or P48. The PDX-1-Cre;LSL-$KRAS^{G12D}$ mice develop pancreatic intraepithelial neoplasia [PanINs], which progress over time [168]. In addition, when these mice are crossed to mice containing p53 mutations or Ink4a/Arf deficiency, the rapid development of pancreatic adenocarcinomas is observed [169, 170].

Dietary fat has been found to influence tumorigenesis in mice, rats, and hamsters. In rats, feeding high-fat diets after, or during and after, the injection of azaserine enhances the development of pancreatic tumors and putative preneoplastic lesions [171 - 179]. Pancreatic carcinogenesis induced in rats by N-nitroso[2-hydroxypropyl][2-oxopropyl]amine [180] or by DMBA [181] is also enhanced by feeding high-fat diets. In hamsters, BOP-induced pancreatic carcinogenesis is also increased by feeding high-fat diets [177 - 179, 182 - 186]. Roebuck and colleagues [171, 173, 176] found that polyunsaturated fat, but not saturated fat, enhanced pancreatic carcinogenesis, and that a certain level of essential fatty acids is required for the enhancement of pancreatic carcinogenesis. Increased linoleic acid was also found to increase metastases to the liver in hamsters [187]. Appel *et al.* [188], however, found that increasing the linoleic acid content of the diet did not increase pancreatic carcinogenesis in either rats or hamsters. Birt *et al.* [185] found that feeding a saturated fat [beef tallow] enhanced pancreatic carcinogenesis in hamsters greater than a polyunsaturated fat [corn oil]. In transgenic models, increasing dietary corn oil led to a higher incidence and size of pancreatic ductal neoplasia in elastase-Kras mice [189] and in PDX-1-Cre;LSL-$KRAS^{G12D}$ mice [190].

Studies using fish oil or n-3 fatty acids have produced differing results, depending on the experimental protocol. Substituting fish oil for oils high in polyunsaturated fats decreases [191, 192] or does not affect [193] the development of azaserine-induced preneoplastic lesions in rats. Adding fish oil to a diet containing adequate polyunsaturated fatty acids enhances azaserine-induced carcinogenesis in rats and BOP-induced carcinogenesis in hamsters [194 - 196]. However, Heukamp *et al.* [197] found that increasing dietary n-3 fatty acids inhibited the incidence but not the number of liver metastases in BOP-treated hamsters compared to hamsters fed a low-fat diet or a diet enriched in n-3, n-6 and n-9 fatty acids; the incidence of pancreatic adenocarcinomas did not differ among the diets. Also, Strouch *et al.* [198] found that increasing dietary n-3 fatty acids inhibited precancerous lesions similar to PanINs in elastase-mutant Kras transgenic mice.

Finally, it has been observed in 2-year carcinogenesis studies in which corn oil gavage has been used as the vehicle for the carcinogen that a higher incidence of pancreatic acinar cell adenomas is present in corn oil gavage-treated male Fischer-344 control rats than in untreated controls [199, 200]. This association was not observed in female rats or in male or female $B6C3F_1$ mice.

Mechanisms by which dietary fat may influence pancreatic carcinogenesis include modification of cholecystokinin [CCK] secretion [201], effects of fatty acids on pancreatic cell growth [202], or epigenetic modifications [203].

5. PROSTATE CANCER

Prostate cancer is the second leading cause of death from cancer in men. An estimated 175,000 cases will be diagnosed in 2019, and 31,000 men will die from it [1].

A number of case-control and prospective studies have examined the role of dietary fat in prostate cancer. Most case-control studies have observed a positive correlation between the intake of total and saturated fat and the development of prostate cancer, although others did not see an effect [204, 205]. Increased total and saturated fat intakes were associated with a higher risk of advanced prostate cancer in case-control studies [206]. Several prospective studies have been performed, with most observing no effect; a meta-analysis also did not find an effect of total, saturated, monounsaturated, or polyunsaturated intake [207, 208].

In experimental animal models, several studies have found that high-fat diets enhance the growth of transplantable prostate tumors, but these inconsistent effects are seen in chemically-induced prostate carcinogenesis models [209 - 216].

6. LIVER CANCER

Liver cancer is the fifth leading cause of death from cancer in males, and is 7^{th} in females [1]. Estimated 42,030 new cases of liver cancer including intrahepatic bile duct cancers were expected to occur in the US during 2019; and estimated 31,780 liver cancer deaths 10,180 women, 21,600 men were expected. Liver cancer incidence rates are about 3 times higher in men than in women and have tripled since 1980. From 2006 to 2015, the overall incidence rate increased by 3% per year.

Non-alcoholic fatty liver disease [NAFLD] is strongly associated with obesity and metabolic syndrome [217, 218]. The incidence of NAFLD has been dramatically increasing. NAFLD has been found to increase the risk of liver cancer [219].

One of the contributors to the development of obesity may be a higher consumption of dietary fat. Epidemiological studies have shown that the consumption of a higher percentage of fat in the diet correlates with the incidence of obesity [220]. High-fat diets have also been found to induce obesity in animal models [220, 221]. However, the incidence of obesity in the USA has increased dramatically over the past 50 years, from 13% in 1960 to 38% in 2014 [222, 223], whereas the percentage of dietary fat in the American diet has decreased from 45% in 1965 to 37.5% in 1971 and 33.6% in 2011 [224].

Many early experimental animal studies of dietary fat and cancer used the liver as the target organ. In these studies, aromatic amines and azo dyes were frequently used to induce hepatocellular carcinomas. In later studies, the effects of dietary fat on initiation and promotion in the liver or in transgenic models were examined. In initiation-promotion protocols, the administration of a single subcarcinogenic dose of a carcinogen such as diethylnitrosamine [DEN] or DMBA along with a proliferative stimulus such as partial hepatectomy followed by the long-term feeding of chemicals such as phenobarbital, 2,3,7,8-tetrachlorodibenzo-p-dioxin, or polyhalogenated biphenyls leads to a high incidence of hepatocellular adenomas and carcinomas [225, 226]. In addition, foci of putative preneoplastic hepatocytes appear before the development of gross tumors. These foci, known as altered hepatic foci or enzyme-altered foci, contain cells which exhibit qualitatively altered enzyme activities or alterations in one or more cell functions [225]. The enzymes most frequently studied include γ-glutamyl transpeptidase [GGT] and Placental Glutathione-S-Transferase [PGST], which are normally not present in adult liver but which are often present in foci; and ATPase and glucose-6-phosphatase, which are normally present but which are frequently missing from foci [227, 228]. Altered hepatic foci can also be identified on hematoxylin and eosin stained tissue [229, 230]. The appearance of foci has been correlated with the later development of malignant neoplasms [231, 232]. Transgenic mouse models of liver carcinogenesis have also been developed [233, 234].

The first studies examined the effect of dietary fat on the induction of hepatocellular carcinomas by complete hepatocarcinogens. In the liver, increasing the fat content of the diet enhances the development of 2-acetylaminofluorene [AAF]-, p-dimethylaminoazobenzene [DAB]-, and aflatoxin B_1 [AFB]-induced tumors and GGT-positive foci in rats [235 - 239]. Furthermore, hepatocarcinogenesis by DAB is enhanced by feeding a diet which contains a greater proportion of polyunsaturated fatty acids [240, 241]. In these studies, however, the diets were administered at the same time as the carcinogen injections, so that the stage of carcinogenesis which was affected could not be determined.

Other studies have examined whether this enhancement of hepatocarcinogenesis is caused by an effect on the initiation of carcinogenesis, the promotion of carcinogenesis, or both. Misslbeck *et al.* [242] found that increasing the corn oil content of the diet after the administration of 10 doses of aflatoxin increased the number and size of GGT-positive foci, but Baldwin and Parker [243], using a similar protocol, found no effect of dietary corn oil. Glauert and Pitot [244] similarly found that increasing the safflower oil or palm oil content of the diet did not promote DEN-induced GGT-positive foci or greatly affect phenobarbital promotion of GGT-positive foci. The promotion of GGT-positive foci by dietary tryptophan also was not affected by dietary fat [245]. Newberne *et al.* [246] found that increasing dietary corn oil [but not beef fat] during and after the administration of AFB increased the incidence of hepatic tumors, but not when the diets were fed only after AFB administration. Baldwin and Parker [243] also found that increasing the corn oil content of the diet before and during AFB administration increased the number and volume of GGT-positive foci. When rats are fed diets high in polyunsaturated fatty acids [but not in saturated fatty acids] before receiving the hepatocarcinogen DEN, they develop more GGT-positive and ATPase-negative foci than rats fed low-fat diets [247]. The feeding of diets high in corn oil but not lard enhanced the initiation of PGST-positive foci induced by azoxymethane [AOM] [248]. Finally, the feeding of a high-fat diet inhibited the initiation of hepatic tumors induced by DEN [249]. The results of these experimental animal studies suggest that the enhancement of chemically-induced hepatocarcinogenesis by dietary fat is primarily due to an effect on initiation, and that polyunsaturated fats have a greater effect than do saturated fats.

Other studies have fed diets sufficiently high in fat to induce nonalcoholic steatohepatitis [250, 251]. Liquid high-fat diets increased the numbers of DEN-initiated PGST-positive foci in rats compared to rats fed a liquid control diet [252, 253]. In male C57Bl/6J mice, feeding high-fat diets induced liver tumors, as compared to mice fed a standard chow diet [251]. Therefore, the induction of steatohepatitis appears to alter the effect of high-fat diets.

7. SKIN CANCER

Skin cancer is the most common form of cancer in the United States. Most basal cell and squamous cell carcinomas are easily curable, but 96,000 cases of melanoma will be diagnosed in 2019, with 7,000 deaths [1].

Using case-control and cohort study designs, Granger *et al.* [254] found that increased dietary fat consumption protected against the development of skin cancer. Davies *et al.* [255] and Gamba *et al.* [256], however, found that dietary fat did not influence non-melanoma skin carcinoma development. Recently, Park *et al.* [257] found that polyunsaturated fat consumption increased the risk for skin cancer in a prospective study.

Mouse skin is one of the oldest and most widely-used systems for studying chemical carcinogenesis, including multistage carcinogenesis. Two-stage carcinogenesis initiation-promotion was first observed in mouse skin and involves initiation by a sub-carcinogenic dose of radiation or of a chemical such as a Polycyclic Aromatic Hydrocarbon [PAH] followed by the long-term administration of croton oil or its active ingredient 12-O-tetradecanoylphorbol-13-acetate [TPA] [258]. More recently, transgenic skin carcinogenesis models have been developed [259, 260].

Most studies examining dietary fat have studied complete carcinogenesis by PAH or ultraviolet light. Early studies demonstrated that high-fat diets enhanced skin carcinogenesis induced by tar [261] or PAH [262 - 268]. In studies where skin tumors were induced by ultraviolet [UV] light, Mathews-Roth and Krinsky [269] and Vaid *et al.* [270] found that high-fat diets increased skin carcinogenesis, whereas Black *et al.* [271] found that high-fat diets did not increase skin carcinogenesis, but that feeding a saturated fat inhibited tumorigenesis. Lou *et al.* [272] found that mice fed a diet high in ω-3 fatty acids developed fewer UVB-induced skin tumors than mice fed a diet high in ω-6 fatty acids. In a transgenic model, skin tumors in mice overexpressing the oncogenic human papillomavirus type 16 were increased when the mice were fed a diet high in n6-polyunsaturated fatty acids [corn oil] [273].

The effect of fatty acids on the initiation and promotion of skin carcinogenesis has also been studied. Certain fatty acids--oleic acid and lauric acid--were found to have promoting activity when applied daily to mouse skin after a single application of 7,12-dimethylbenz[a]anthracene [DMBA]; stearic acid and palmitic acid did not have any effect [274]. When diets varying in their fat content were fed during the promotion stages of DMBA-initiated, TPA-promoted mouse skin carcinogenesis, high-fat diets were found to enhance the promotion of skin carcinogenesis in some studies [275, 276] but not in others [277, 278]. High-fat diets also partially offset the tumor inhibitory effects of caloric restriction [279]. Locniskar *et al.* [280] found that substituting menhaden oil for corn oil or coconut oil did not affect skin tumor promotion by TPA. When benzoyl peroxide was used as the promoting agent, mice fed mainly coconut oil had the highest tumor incidence and mice fed corn oil had the lowest tumor incidence, with those fed mainly menhaden oil having intermediate tumor incidence [281]. In a study using mezerein as the promoting agent, high-fat diets did not increase the skin carcinogenesis [282]. High-fat diets were found to not affect or slightly inhibit initiation [275, 283], and substituting coconut oil for corn oil did not influence UV-induced skin carcinogenesis [284].

8. LUNG CANCER

Lung cancer is the leading cause of death from cancer in both men and women. 228,000 cases of lung cancer will be diagnosed in 2019, and 142,000 people will die from it [1].

Lung cancer risk was not found to be significantly affected by total dietary fat in prospective studies, but several case-control studies have observed an association [285 - 289], although several investigators indicated that their results may have been affected by confounding from smoking. In pooled analyses, neither total nor polyunsaturated fat was found to affect lung cancer risk [290, 291].

In experimental animal models, dietary fat enhanced BP- or BOP-induced carcinogenesis in hamsters [183, 292], whereas in mice a high-fat diet did not affect spontaneous carcinogenesis in one study [267] and produced different results in 2-amino-3, 8-dimethylimidazo [4,5-f] quinoxaline [MeIQx]-induced tumors [293, 294]. Tumor metastasis of Lewis lung carcinoma cells was increased by high-fat diets [295 - 297].

9. OTHER CANCERS

Fewer studies have been conducted for other major forms of human cancer. For endometrial cancer, several but not all case-control studies have noted an association with dietary fat; a meta-analysis did not observe an association [298]. Similarly, no association was observed in prospective studies. No significant effects were observed with either plant fat or animal fat intake [298]. Case-control studies examining dietary fat and bladder cancer showed an association in some but not all studies; a prospective study did not observe a correlation between dietary fat intake and the development of bladder cancer [299]. Dietary fat has been found to be a risk factor for ovarian cancer in some epidemiological studies but not in others [300 - 309]. The development of esophageal cancer was found to be increased by dietary fat in two case-control studies [310, 311].

SUMMARY AND CONCLUSION

Clearly, there is much variability in studies of dietary fat and cancer, both in epidemiological and experimental studies. Because of this variability, particularly in prospective epidemiological studies, recommendations for preventing human cancer should not include decreasing the fat content of the diet. This is reflected in recent recommendations for reducing cancer risk by dietary means. For example, in 1997 the American Institute for Cancer Research stated to “limit consumption of fatty foods, particularly those of animal origin” [312]. In their updated 2007 report [313], however, there is no specific recommendation for dietary fat. In addition, the American Cancer Society no longer specifically recommends lowering fat intake and instead advises individuals to “consume a healthy diet with an emphasis on plant sources” [314].

LIST OF ABBREVIATIONS

AAF	=	2-acetylaminofluorene
ACF	=	Aberrant Crypt Foci
AFB	=	Aflatoxin B_1
AOM	=	Azoxymethane
APC	=	Adenomatous Polyposis Coli
BOP	=	N-nitrosobis[2-oxopropyl]amine
BP	=	Benzo[a]pyrene
DAB	=	p-dimethylaminoazobenzene
DEN	=	Diethylnitrosamine
DMBA	=	7,12-dimethylbenz[a]anthracene
DMH	=	1,2-dimethylhydrazine
GGT	=	γ-glutamyl transpeptidase
LXR	=	Liver X Receptor
MAM	=	Methylazoxymethanol
MNU	=	Methylnitrosourea
PAH	=	Polycyclic Aromatic Hydrocarbon[s]
PanIN	=	Pancreatic Intraepithelial Neoplasia
PGST	=	Placental Glutathione S-transferase
PKC	=	Protein Kinase C
PPAR	=	Peroxisome Proliferator-activated Receptor
TPA	=	12-O-tetradecanoylphorbol-13-acetate

DISCLOSURE

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