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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.

Article History

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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]. 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-dimethyl-hydrazine [DMH] and its metabolites azoxymethane [AOM] and methylazoxymethanol [MAM]; 3,2'-dimethyl-4-amino-biphenyl [DMAB]; methylnitrosourea [MNU]; and N-methyl-N-nitro-N-nitrosoguanidine [MNNG] [32 - 35]. DMH and...
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.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Subjects</th>
<th>Years of Follow-up</th>
<th>Effect of Dietary Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirayama [26]</td>
<td>265,118 subjects in Japan</td>
<td>13</td>
<td>Significant negative effect for meat</td>
</tr>
<tr>
<td>Stemmermann et al. [27]</td>
<td>7,074 Hawaiian-Japanese men</td>
<td>15</td>
<td>Significant negative effect</td>
</tr>
<tr>
<td>Garland et al. [8]</td>
<td>1,954 men in Chicago</td>
<td>19</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Phillips &amp; Snowdon [9]</td>
<td>25,493 Seventh Day Adventists in California</td>
<td>21</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Willett et al. [4]</td>
<td>88,751 female nurses in USA</td>
<td>6</td>
<td>Significant positive effect for total, animal, monounsaturated, and saturated fat, and for red meat</td>
</tr>
<tr>
<td>Giovannucci et al. [5]</td>
<td>7,284 male health professionals</td>
<td>2</td>
<td>Significant positive effect for total, animal, monounsaturated, and saturated fat, and for red meat</td>
</tr>
<tr>
<td>Thun et al. [10]</td>
<td>764,343 men and women</td>
<td>6</td>
<td>No significant effect of fat or red meat</td>
</tr>
<tr>
<td>Goldbohm et al. [11]</td>
<td>58,279 men and 62,573 women in Netherlands</td>
<td>3.3</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Giovannucci et al. [12]</td>
<td>47,949 male health professionals</td>
<td>6</td>
<td>No significant effect of fat, but significant positive correlation with red meat</td>
</tr>
<tr>
<td>Bostick et al. [13]</td>
<td>35,215 women in Iowa</td>
<td>4</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Gaard et al. [14]</td>
<td>50,535 men and women in Norway</td>
<td>11</td>
<td>No significant effect of fat, but significant positive correlation with sausage intake</td>
</tr>
<tr>
<td>Chyou et al. [28]</td>
<td>7,945 Japanese-American men in Hawaii</td>
<td>27-30</td>
<td>Significant negative correlation with total and monounsaturated fat for colon but not rectal cancer</td>
</tr>
<tr>
<td>Kato et al. [15]</td>
<td>14,727 women in New York and Florida</td>
<td>7</td>
<td>No significant effect of fat or meat</td>
</tr>
<tr>
<td>Singh &amp; Fraser [6]</td>
<td>32,051 7th Day Adventist men and women in California</td>
<td>6</td>
<td>Significantly increased risk with red, white or total meat intake</td>
</tr>
<tr>
<td>Pietinen et al. [16]</td>
<td>27,111 male smokers in Finland</td>
<td>8</td>
<td>No significant effect of fat or meat</td>
</tr>
<tr>
<td>Jarvinen et al. [17]</td>
<td>9959 Finnish men and women</td>
<td>27-32</td>
<td>High cholesterol intake was associated with increased risk, but not consumption of total, saturated, monounsaturated or polyunsaturated fat</td>
</tr>
<tr>
<td>Terry et al. [18, 19]</td>
<td>61,463 women in Sweden</td>
<td>9.6</td>
<td>No significant effect of intake of fat or a “Western” diet</td>
</tr>
<tr>
<td>Flood et al. [20]</td>
<td>45,496 women in USA</td>
<td>8.5</td>
<td>No significant effect of fat or meat consumption</td>
</tr>
<tr>
<td>Chao et al. [314]</td>
<td>148,610 men and women in USA</td>
<td>9, 19</td>
<td>Significant increase with red and processed meat consumption; poultry and fish consumption protective</td>
</tr>
</tbody>
</table>
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</tr>
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<tbody>
<tr>
<td>Robertson et al. [21]</td>
<td>1,520 men and women in USA</td>
<td>1, 4</td>
<td>No significant effect of fat or red meat consumption</td>
</tr>
<tr>
<td>Oba et al. [22]</td>
<td>13,894 men and 16,327 women in Japan</td>
<td>8</td>
<td>No significant effect of dietary fat; significant increase from processed meat consumption</td>
</tr>
<tr>
<td>Lin et al. [23]</td>
<td>37,547 women in USA</td>
<td>8.7</td>
<td>No significant effect of dietary fat</td>
</tr>
<tr>
<td>Sanjoaquin et al. [24]</td>
<td>10,998 men and women in the United Kingdom</td>
<td>17</td>
<td>No significant effect of animal fat intake</td>
</tr>
<tr>
<td>Dahm et al. [25]</td>
<td>153,000 men and women in the United Kingdom</td>
<td>7-23</td>
<td>No significant effect of dietary fat</td>
</tr>
<tr>
<td>Butler et al. [7]</td>
<td>61,321 Singapore Chinese</td>
<td>9.8</td>
<td>Positive association between total and saturated fat and localized cancer in women only</td>
</tr>
<tr>
<td>Jones et al. [112]</td>
<td>5,485 women in USA</td>
<td>10</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Willett et al. [113]</td>
<td>89,538 female nurses in USA</td>
<td>4</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Mills et al. [114]</td>
<td>20,341 Seventh Day Adventist women in California</td>
<td>6</td>
<td>No significant effect</td>
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<td>Knuckt et al. [115]</td>
<td>3,988 women in Finland</td>
<td>20</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Howe et al. [116]</td>
<td>56,837 Canadian women</td>
<td>5</td>
<td>Slightly elevated risk</td>
</tr>
<tr>
<td>Graham et al. [117]</td>
<td>18,586 women in New York State</td>
<td>7</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Kushi et al. [118]</td>
<td>34,388 women in Iowa</td>
<td>4</td>
<td>No significant effect</td>
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<tr>
<td>van den Brandt et al. [120]</td>
<td>62,573 women in Netherlands</td>
<td>3.3</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Toniolo et al. [121]</td>
<td>14,291 women in New York City</td>
<td>6</td>
<td>No significant effect; but significant positive correlation with red meat</td>
</tr>
<tr>
<td>Gaard et al. [122]</td>
<td>31,209 women in Norway</td>
<td>7-13</td>
<td>No significant effect for fat or saturated fat; but significant positive correlation with meat and monounsaturated fat</td>
</tr>
<tr>
<td>Wolk et al. [131]</td>
<td>61,471 women from central Sweden</td>
<td>4.2</td>
<td>Positive correlation with polyunsaturated fat; negative association with monounsaturated fat</td>
</tr>
<tr>
<td>Holmes et al. [123]</td>
<td>88,795 female nurses in USA</td>
<td>14</td>
<td>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</td>
</tr>
<tr>
<td>Velie et al. [124]</td>
<td>40,022 women in 29 centers throughout USA</td>
<td>5.3</td>
<td>No significant effect of total fat or specific fatty acids</td>
</tr>
<tr>
<td>Thiebaut et al. [125]</td>
<td>65,879 women in Europe</td>
<td>3.4</td>
<td>Small positive association between fat intake and breast cancer risk</td>
</tr>
<tr>
<td>Terry et al. [126]</td>
<td>61,463 women in Sweden</td>
<td>9.6</td>
<td>No association between “Western” dietary pattern and breast cancer risk</td>
</tr>
<tr>
<td>Byrne et al. [127]</td>
<td>44,697 female nurses in USA</td>
<td>14</td>
<td>No effect of fat in women with no history of benign breast disease</td>
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<td>Voorrips et al. [133]</td>
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<td>12,803 women in Sweden</td>
<td>Up to 8</td>
<td>Positive association with total, monounsaturated, and polyunsaturated fat</td>
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<td>Horn-Ross et al. [137]</td>
<td>111,526 women in California</td>
<td>2</td>
<td>No effect for total fat, saturated fat, linoleic acid, or oleic acid</td>
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<tr>
<td>Cho et al. [130]</td>
<td>90,655 premenopausal female registered nurses in one of 14 states within the United States</td>
<td>8</td>
<td>Positive association with intake of animal fat but not total fat or vegetable fat</td>
</tr>
<tr>
<td>Gago-Dominguez et al. [136]</td>
<td>35,298 Singapore Chinese women aged 45-74 years</td>
<td>Up to 7</td>
<td>No effect for total, saturated, monounsaturated, or polyunsaturated fat; decreased risk with marine n-3 fatty acid intake</td>
</tr>
<tr>
<td>Bingham et al. [139]</td>
<td>25,630 men and women aged 45–74 years from Norfolk, UK</td>
<td>Up to 9</td>
<td>Positive association with total and saturated fat intake when measured using food diaries but not when using food frequency questionnaires</td>
</tr>
<tr>
<td>Kim et al. [128]</td>
<td>80,375 female nurses in USA</td>
<td>20</td>
<td>No effect of total fat or specific types of fat</td>
</tr>
<tr>
<td>Lof et al. [135]</td>
<td>49,261 women in Sweden</td>
<td>13</td>
<td>No association with total, saturated, polyunsaturated, and monounsaturated fat intakes</td>
</tr>
</tbody>
</table>

### Table 2. Dietary Fat and Breast Cancer: Prospective Studies.

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</table>
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 at 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-oxopropyl]amine [BOP] and N-nitroso-bis-[2-hydroxypropyl]amine [BHP] [165]. A number of transgenic models have been developed [165, 167]. Another model uses an oncogenic K-ras [KRASG12D] 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-KRASG12D 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-KRASG12D 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 B6C3F1 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 7th 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
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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AAF</td>
<td>2-acetylaminofluorene</td>
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<td>ACF</td>
<td>Aberrant Crypt Foci</td>
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<td>AFB</td>
<td>Aflatoxin B1</td>
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<td>AOM</td>
<td>Azoxymethane</td>
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<tr>
<td>APC</td>
<td>Adenomatous Polyposis Coli</td>
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<tr>
<td>BOP</td>
<td>N-nitrosobis[2-oxopropyl]amine</td>
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<tr>
<td>BP</td>
<td>Benz[a]pyrene</td>
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<tr>
<td>DAB</td>
<td>p-dimethylaminobenzene</td>
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<td>DEN</td>
<td>Diethylnitrosamine</td>
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<td>DMBA</td>
<td>7,12-dimethylbenz[a]anthracene</td>
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<tr>
<td>DMH</td>
<td>1,2-dimethylhydrazine</td>
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<td>GGT</td>
<td>γ-glutamyl transpeptidase</td>
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<tr>
<td>LXR</td>
<td>Liver X Receptor</td>
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<td>MAM</td>
<td>Methylazoxymethanol</td>
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<td>MNU</td>
<td>MethylNitrourrea</td>
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<tr>
<td>PAH</td>
<td>Polycyclic Aromatic Hydrocarbon(s)</td>
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<tr>
<td>PanIN</td>
<td>Pancreatic Intraepithelial Neoplasia</td>
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<tr>
<td>PGST</td>
<td>Placental Glutathione S-transferase</td>
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<tr>
<td>PKC</td>
<td>Protein Kinase C</td>
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<tr>
<td>PPAR</td>
<td>Peroxisome Proliferator-activated Receptor</td>
</tr>
<tr>
<td>TPA</td>
<td>12-O-tetradecanoylphorbol-13-acetate</td>
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