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Is dietary fat, vitamin D, or folate associated with pancreatic cancer?

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Abstract

Although potentially modifiable risk factors for pancreatic cancer include smoking, obesity, and diabetes, less is known about the extent to which diet affects cancer risk. Recent studies have demonstrated some consistency for dietary fat being associated with elevated pancreatic cancer risk, particularly from animal sources. However, less is known about which fatty acids pose the greatest risk. Vitamin D, due to its endogenous production following UV-B exposure, is a unique risk factor in that researchers have created several methods to assess its exposure in humans. Studies that measured vitamin D exposure differently have shown inconsistent results. Dietary studies suggest protective associations, whereas studies of circulating 25-hydroxyvitamin D status show null or positive associations with low or very high concentrations, respectively. Several, but not all epidemiologic studies provide evidence of an inverse relationship between total and/or dietary folate and risk of pancreatic cancer. Protective associations for circulating folate are more often observed among populations with inadequate status. This article reviews the current epidemiological and experimental evidence investigating the relationship of dietary fat, vitamin D, and folate with pancreatic cancer. Additionally the mechanisms by which these risk factors may contribute to cancer, the methodological challenges involved with assessing risk, and other obstacles encountered when ascertaining the magnitude and direction of these three exposures are discussed.

Keywords

pancreatic cancer; dietary fat; vitamin D; folate; nutritional risk factors

INTRODUCTION

The relatively low incidence of pancreatic cancer, compounded by its poor survival and rapid fatality in diagnosed cases, has made it a difficult disease for epidemiologists to examine dietary risk factors. Large studies, including recent pooled efforts that harmonize data using appropriate statistical methods, have helped increase the power to identify factors associated with small magnitudes of risk in the range of 20 to 30% that are typical of nutritional exposures.

The common methodological challenges faced when examining the association between dietary factors and pancreatic cancer risk include selection, survival, and recall biases,

reverse causation, and surrogate reporting. Selection bias can occur among both cases and controls, particularly if participation rates are low. Most pancreatic cancer studies have included diverse non-minority populations: therefore, there is an under representation of populations that have the highest cancer rates and may have decreased access to medical care¹, particularly in the United States. Survival bias, which is especially significant given the high mortality rate observed in pancreatic cancer, may arise when survivors are more likely to be cases in a study than those who did not live as long. The chances of recall bias are increased in case control studies because of inaccurate recollection of pre-disease dietary intake. Reverse causation is a bias related to the symptoms of a disease influencing the direction of an observed association that is a potential concern for dietary studies of pancreatic cancer with retrospective assessment of exposure. For example, if a subject with pancreatic cancer experiences unpleasant side effects following ingestion of dietary fat (as is common with pancreatic cancer), they may subsequently decrease their dietary fat intake. Later, when recalling their pre-disease fat consumption for a retrospective study, they may understate their usual fat intake because of their newly adapted, fat-evading behavior. Consequently the association observed by the researcher will be inaccurate. Surrogate reporting of intake has been used in some case-control studies since rapid progression of the disease prevents cases from reporting their intake at the time of the study. Due to concerns of validity and reliability of dietary intake, and an increasing number of studies using ultra-rapid case ascertainment, this practice has become less common. Prospective studies are less prone to these problems because diet and biomarkers that reflect nutritional status can be assessed before disease symptoms present. Prospective studies also have internal validity, as cases arise from the larger population.

Inconsistencies across studies examining the association of dietary risk factors and pancreatic cancer include both measurement of exposure and study design differences. Measurement error may result from inaccurate reporting of dietary intake related to variability of accurate self-reporting, and limitations inherent of instruments used to assess dietary intake. A wide range of intake of the nutrient of interest is desirable in order to compare different levels of exposure and establish a corresponding association, particularly with extremes in intake. Accounting for known risk factors (such as age, smoking, obesity, and diabetes) for pancreatic cancer in study design, or adjusting for them in using appropriate statistical methods, is important in order to control for confounding². In this review we will discuss the current epidemiological and experimental evidence concerning the relationship between dietary fat, vitamin D, and folate with regard to pancreatic cancer risk, as well as the hypothesized mechanisms for these relationships.

DIETARY FAT

Several mechanisms may explain an association between high dietary fat consumption and increased pancreatic cancer risk. As fat enters the duodenum within chyme, cholecystokinin is released, which in turn stimulates the secretion of pancreatic enzymes, such as lipases, to facilitate digestion of these fats. However, when large amounts of fatty acids enter the duodenum over long periods of time, pancreatic hypertrophy or hyperplasia can occur³. As a result, the pancreas may become vulnerable to carcinogens, and subsequent uncontrolled growth of abnormal cells may result³. Although such a mechanism has been observed in animal studies, it remains unclear whether this occurs in humans. It has also been hypothesized that higher intake of fat and certain fatty acids may promote excretion of bile acid into the pancreatic duct⁴. Bile acids have been shown to stimulate cyclooxygenase-2 (COX-2) release, and have been observed to act as tumor promoters *in vivo* and *in vitro*. COX-2 has been reported in higher concentrations in human pancreatic adenocarcinoma, and is also upregulated by both unconjugated and conjugated bile acids⁴. The head of the pancreas may be especially susceptible to this mechanism, due to its close proximity to the

biliary ducts and gallbladder⁴. Saturated fat has been associated with insulin resistance in several randomized controlled trials⁵⁻⁷, and diabetes or insulin resistance has been associated with pancreatic cancer⁸. The mechanism by which diabetes affects pancreatic cancer risk may involve metabolic, immunologic, and hormonal alterations in the body. Prolonged hyperinsulinemia increases endogenous levels of insulin-like growth factor-1 (IGF-1) which may promote cancer growth and development⁹.

Ecologic^{10,11}, case-control¹²⁻¹⁵, and cohort studies¹⁶⁻²⁰ have examined the relationship of dietary fat and pancreatic cancer.

One ecologic study examined animal fat consumption data from the Food Balance Sheet of the Food and Agriculture Organization and pancreatic cancer incidence data from the World Health Organization between 1964 and 1994 in 35 countries, including 7 countries in North and South America, 19 in Europe, 7 in Asia, and 2 in Oceania¹⁰. Statistically significant positive associations were observed between animal fat consumption and pancreatic cancer incidence in both men ($r = 0.40-0.74$) and women ($r = 0.50-0.66$). Adjusting for population smoking, energy, meat and vegetable consumption, and alcohol intake did not alter these relationships. However, after stratifying for smoking, this association was only observed in countries with low prevalence of cigarette smoking (<2273 cigarettes/adult/year) compared to countries with high prevalence of cigarette smoking (>2273 cigarettes/adult/year)¹⁰. Another ecologic study that examined global pancreatic cancer incidence and dietary fat observed similar associations, but the results were not adjusted for confounding¹¹. “Ecological fallacy”, which arises when researchers make inferences about individuals based on data collected at a population level (i.e. average per capita intake and cancer rates in a country), can occur in this type of study since fat intake is not directly measured on individuals and linked to disease.

Among case-control studies examining total dietary fat, statistically significant positive associations were observed in several studies¹²⁻¹⁴, and one study reported an inverse association¹⁵. When examining specific classes of fatty acids, increases in pancreatic cancer risk have been associated with saturated fatty acids(SFA)¹²⁻¹⁴, monounsaturated fatty acids(MUFA)^{12,14}, and polyunsaturated fatty acids(PUFA)¹³. One study observed inverse associations for SFA and MUFA¹⁵. In a population-based case-control study in the San Francisco Bay Area, significant positive associations for butter (highest vs. lowest quartile: odds ratio, OR = 2.4, 95%CI: 1.6-3.5), dairy other than butter (OR = 2.6, 95%CI: 1.8-3.7), as well as several other high fat or processed meat items were observed¹². A similar study showed positive associations for 8 individual saturated fatty acids (highest vs. lowest quartile: OR range = 1.6-2.6), monounsaturated palmitoleic acid (OR = 1.6, 95%CI: 1.2-2.1), polyunsaturated linolenic acid (OR = 1.4, 95%CI: 1.1-1.9) and an inverse association for n-3 fatty acids (OR = 0.47, 95%CI: 0.25-0.90)¹⁴. In a US based study that recruited cases from hospitals in the Minneapolis metropolitan area, an association was detected for total fat (highest vs. lowest quartile: OR = 2.16, 95%CI: 0.91-5.27), and stronger and more significant associations were observed for SFA (OR = 2.47, 95%CI: 1.07-5.86) and PUFA (OR = 2.47, 95%CI: 1.07-5.86)¹³. Lastly, a case-control study of eight Canadian provinces reported inverse relationships between pancreatic cancer risk and intake of SFA (highest vs. lowest quartile: OR = 0.67, 95%CI 0.50-0.91) and MUFA (OR = 0.72, 95%CI 0.53-0.98)¹⁵.

Cohort studies are better suited to examine the relationship between dietary fat and pancreatic cancer. Among prospective cohort studies examining dietary fat and pancreatic cancer, statistically significant positive associations were observed with total fat¹⁶, SFA^{17,16,18}, MUFA¹⁸, and butter consumption¹⁷, but two studies reported no association between dietary fat intake and pancreatic cancer^{19,20}. In a study of male Finnish smokers

aged 50 to 69 in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study cohort (ATBC), positive associations were observed between saturated fat intake (highest vs. lowest quintile: hazards ratio, HR = 1.60, 95% CI: 0.96-2.64, p-trend=0.02), butter consumption (HR = 1.40, 95% CI: 0.87-2.25, p-trend=0.04, and cream (HR = 1.50, 95% CI: 0.90-2.43, p-trend=0.06) and risk of exocrine pancreatic cancer¹⁷. In contrast, the Nurses Health Study cohort (NHS) showed no statistically significant relationship between total fat, different types of fat or fatty acids, or food source of fat consumed (vegetable vs. animal) and risk of pancreatic cancer¹⁹. Participants in the NHS appeared to have a lower median saturated fat intake compared to studies that demonstrated an association. In the Netherlands Cohort Study, no association was reported between total fat intake and pancreatic cancer risk²⁰. The Multiethnic Cohort study demonstrated no significant association between overall fat consumption and pancreatic cancer, however the percent energy of fat from red and processed meat showed a 44% elevated risk [highest vs. lowest quintile: relative risk, RR=1.44, 95% CI 1.18-1.76]⁹. The largest cohort study to date (n=525,473) examining dietary fat and pancreatic cancer, the National Institutes of Health-AARP Diet and Health Study, demonstrated statistically significant elevated pancreatic cancer risk for total fat intake (highest vs. lowest quintile: HR = 1.23, 95% CI: 1.03-1.46), SFA (HR = 1.36, 95% CI: 1.14-1.62), and MUFA (HR = 1.22, 95% CI: 1.02-1.46). Additionally, a strong positive relationship was observed for saturated fat originating from animal sources (HR = 1.43, 95% CI: 1.20-1.70)¹⁸. The strength of this study includes the large number of cases (n = 1337) and wider range of fat intake from a large variety of food sources. The NIH-AARP cohort also demonstrated an increased risk in saturated palmitic acid (HR = 1.33, 95% CI 1.11-1.58), saturated stearic acid (HR = 1.31, 95% CI 1.10-1.56), monounsaturated palmitoleic acid (HR = 1.34, 95% CI: 1.12-1.59), and polyunsaturated arachidonic acid (HR = 1.33, 95% CI: 1.12-1.58). This analysis also showed a positive association between n-3 fatty acids (HR = 1.21, 95% CI: 1.02-1.44) and pancreatic cancer, however no association was found for the ratio of the consumption of n-3 to n-6 PUFA¹⁸.

Overall, higher total fat and fat from animal products have been associated with higher risk of pancreatic cancer in many^{10,12,16-18}, but not all^{15,19,21} epidemiological studies. Due to the increasing number of available cohort studies, larger sample sizes, and ranges of fat intake in these studies, a relatively consistent association between dietary fat and pancreatic cancer might be emerging. The strongest evidence has been observed for intake of saturated fat and fat from animal sources. Across study and population types, as well as individual fatty acid profiles, significant positive relationships persist. Weaker evidence suggests total fat, MUFA, and PUFA intake may be associated with pancreatic cancer.

VITAMIN D

In most people, the majority of vitamin D is produced endogenously from dermal exposure to solar UVB light (280-320 nm), promoting cutaneous production of the precursors to 25-hydroxyvitamin D [25(OH)D]. Dietary sources of vitamin D include cholecalciferol(D₃) from animal foods such as fatty saltwater fish, liver, and eggs, and ergocalciferol(D₂) from plants used in pharmaceutical preparations and fortified foods (D₂ and D₃)²². Vitamin D is metabolized to its active form, 1,25 dihydroxycholecalciferol [1,25(OH)₂D] via 1- α -hydroxylase, the rate limiting step of the vitamin D conversion pathway. 25(OH)D is the best measure of vitamin D status as it represents vitamin D from both diet and sun exposure. Conversely, the active form of vitamin D, 1,25(OH)₂D, is highly regulated and is not an indicator of overall status. Once converted to 1,25(OH)₂D, vitamin D does not enter systemic circulation and remains in the local tissue as a steroid hormone involved in intracellular signaling pathways, cellular growth, cell differentiation, adhesion, and apoptosis. It carries out these effects by binding to the intracellular vitamin D receptor

(VDR) located on the nucleus, which in turn activates or suppresses the expression of targeted genes²³.

The role of vitamin D in pancreatic carcinogenesis is supported by experimental evidence. Expression of 25(OH)D₃-1 α -hydroxylase, the enzyme that catalyses the conversion of 25(OH)D to 1,25-dihydroxy vitamin D [1,25(OH)₂D], has been observed in ductal cells in the pancreas, as well as in normal and adenocarcinomatous tissue. Pancreatic cancer cell line growth is inhibited by 25(OH)D^{24,3}. Analogues of 1,25(OH)₂D inhibit pancreatic cancer cell proliferation, induce differentiation, promote apoptosis in vitro^{25,26}, and inhibit pancreatic tumor growth in vivo²⁶. This has been demonstrated when a chemotherapeutic agent such as gemcitabine is administered²⁷. Vitamin D is also involved in the regulation of insulin synthesis, binding, and responsiveness²⁸, which is relevant to pancreatic carcinogenesis since diabetes, higher glucose, and insulin concentrations have been implicated in pancreatic cancer development²⁹.

Some ecologic studies have suggested correlations between living in areas of high sun exposure and reduced pancreatic cancer death rates in Caucasian³⁰, Japanese³¹, and African American populations³². However, within the United States pancreatic cancer rates do not exhibit a striking North-South gradient³³. A reduced risk of pancreatic cancer was observed in a study relating UV-B exposure data from NASA's Total Ozone Mapping Spectrometer (TOMS) to cancer incidence data from the North American Association of Central Cancer Registries. Non-Hispanic white participants in this study residing in the northern U.S. (lower UV-B exposure) were at a higher risk of pancreatic cancer incidence than participants in southern states (higher UV-B exposure) [RR = 1.09, 95%CI: 1.05-1.14 for males, 1.17, 95%CI: 1.13-1.22 for females]³⁰. In another ecologic study using incidence data for 175 countries from the International Agency for Research on Cancer (IARC) Global Cancer (GLOBOCAN) database, countries at higher latitudes demonstrated higher pancreatic cancer incidence rates in men ($R^2 = 0.51$) and women ($R^2 = 0.32$)³⁴. Another ecologic study in Australia showed reduced pancreatic cancer mortality with vitamin D-effective ultraviolet radiation, which is associated with latitude³⁵. Although causality cannot be determined in ecologic studies, these studies have encouraged further investigation into the relationship between vitamin D status and pancreatic cancer incidence.

Epidemiologic studies examining the association between vitamin D and pancreatic cancer risk have reported less consistent results. Among studies that investigated vitamin D intake, one case-control study reported a positive association between high vitamin D intake from foods and pancreatic cancer risk in men but not women [highest (>450 IU/day) vs. lowest (<150 IU/day): OR = 2.6, 95%CI: 1.1-6.0]³⁶, while a cohort study observed an inverse relationship for both men [highest (>600 IU/day) vs. lowest (<150 IU/day): RR = 0.49, 95%CI: 0.29-0.82] and women (RR=0.76, 95%CI: 0.42-1.38)³⁷. Two prospective studies reported risks using a score based on six determinants to predict vitamin D status. The Health Professionals Follow-up Study (HPFS) reported an inverse relationship between participants' vitamin D score and cancer of the digestive system (esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts) (highest vs. lowest decile: RR = 0.55, 95%CI: 0.41-0.74)³⁸. In a combined analysis of the Nurses' Health Study cohort (NHS) and the HPFS cohort, an inverse relationship between vitamin D status score and pancreatic cancer risk was reported (highest vs. lowest quintile: RR = 0.65, 95%CI: 0.50-0.86)³⁹. A limitation to these studies is that none of them measured vitamin D status or 25(OH)D concentrations directly on individuals and examined the association with pancreatic cancer.

Three prospective studies have examined circulating 25(OH)D and pancreatic cancer risk⁴⁰⁻⁴². In the ATBC cohort of male Finnish smokers, men with higher vitamin D status demonstrated an unexpected statistically significant three-fold increase in pancreatic cancer

risk (highest vs. lowest quintile: OR=2.92, 95%CI: 1.56-5.48, p-trend=0.001)⁴⁰. These results might not be generalizable to populations that include non-smokers, women, or individuals residing at geographic latitudes lower than Finland, who may have a higher vitamin D status. In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) conducted within the US, the ATBC findings were not confirmed overall, however, a statistically significant four-fold increase in risk (highest vs. lowest quartile: OR=4.03, 95%CI: 1.38-11.79) was observed among participants residing in states of more northern latitudes compared to those living in more southern states⁴¹. A large subsequent pooled analysis that included eight cohorts (including ATBC and PLCO) within the National Cancer Institute's Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) demonstrated a statistically significant 2-fold increase in risk among subjects with circulating 25(OH)D concentrations >100 nmol/L compared to those with concentrations of 50 to <75nmol/L (OR=2.12, 95%CI: 1.23, 3.64). No significant associations were observed for participants with lower vitamin D status. The association persisted when each individual cohort was removed from the analysis, and was independent of race, sex, obesity and diabetes mellitus⁴².

The strengths these three studies share include measurement of 25(OH)D before the onset of disease, and implementation of matching by month or season of blood collection to minimize exposure misclassification, as circulating 25(OH)D concentrations may vary by season. Most importantly, circulating 25(OH)D is considered the best biomarker reflecting vitamin D status, as it includes vitamin D endogenously synthesized from solar exposure, as well as from foods and supplement use⁴³. Although vitamin D status was measured at only one point in these investigations, several studies indicate that a single sample provides a reliable measure of long term vitamin D status⁴⁴⁻⁴⁶.

The studies from ATBC, PLCO, and the VDPP all suggest positive associations between subjects residing at higher latitudes and pancreatic cancer risk, but differ in their degrees of external validity and measured 25(OH)D concentrations. Compared to previous studies, the VDPP had a large number of cases (n=952), a wider range of vitamin D concentrations, and included cohorts from several geographical regions and ethnic populations. Although multiple ethnic groups were included in this study, the majority are Caucasian and the number participants of other ethnicities was too small for stratified analyses. Men from the ATBC study had lower average vitamin D concentrations compared to the US-based cohorts, few exceeding the 100 nmol/L level defined in the VDPP. Although positive associations were observed in these Finnish smokers, the vitamin D concentrations were in a range where positive associations were not observed in the VDPP study. Lastly, while the ATBC study demonstrated a significant positive trend with increasing quintiles of 25(OH)D concentrations, the VDPP study showed a threshold pattern with only participants with the highest 25(OH)D concentrations(>100 nmol/L) having an elevated risk.

The biological basis that might explain the positive association that was observed in these studies remains speculative as there is an incomplete understanding of vitamin D's role in pancreatic carcinogenesis. The active form of vitamin D is a steroid hormone. It is possible that the vitamin D receptor-1,25(OH)₂D₃ complex interacts with genes and other endogenous hormones that influence growth factors that promote tumor growth in the pancreas microenvironment⁴⁷. Alternatively, it is plausible that an unknown risk factor correlated with sun exposure or mechanisms related to solar UV-B radiation may account for the observed associations in epidemiologic studies.

In summary, studies investigating vitamin D and pancreatic cancer risk have reported mixed findings. Ecologic, case-control, and cohort studies that use methods of indirect measurement of vitamin D status generally suggest an inverse relationship between vitamin

D intake and risk, whereas studies that measure circulating 25(OH)D in cohort studies report no association with low concentrations with some suggestion of positive associations with high concentrations. The mechanisms relating higher vitamin D status with increased pancreatic cancer risk are not well understood and remain speculative at this time. More experimental studies focusing on the role of vitamin D receptors in pancreatic carcinogenesis are needed in order to reach conclusions about the role of vitamin D in pancreatic cancer etiology.

FOLATE

Following mandatory folic acid fortification of whole grain in 1998, the average folate intake in the United States rose significantly⁴⁸. Since then, concern has been raised as to whether folic acid has contributed to increased cancer risk among those living in the United States and Canada, and whether other countries should adopt similar fortification policies⁴⁹. Although the protective effect that folic acid exhibits on neural tube defect (NTD) incidence is well known, the long term consequences of high levels of folate in humans remain unclear.

Folate is a water-soluble B vitamin whose deficiency plays a role in the development of several disorders in humans, including adverse pregnancy outcomes such as NTDs, anemia, cardiovascular disease, and cancer⁴⁹. The synthetic form of folate is folic acid, the fully oxidized monoglutamyl form of folate. Folic acid is used in supplements and added to fortified foods⁴⁹.

It has been hypothesized that folate influences carcinogenesis through its role in methylation reactions, nucleotide synthesis, and DNA repair⁵⁰. Low folate levels may result in decreased S-adenosyl-methionine (SAM), a primary donor for DNA methylation⁵⁰. The genetic instability that occurs as a result of hypomethylation might in turn affect the expression of oncogenes and tumor suppressor genes⁵¹. Additionally, functional polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene may affect cancer susceptibility⁵¹. MTHFR is the enzyme that converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the circulating form of folate⁵¹. Thus, MTHFR has been shown to play an essential role in the availability and distribution of folate metabolites for DNA synthesis⁵¹. Polymorphisms in the gene responsible for MTHFR may alter the availability and distribution of folate metabolites in the body, and may affect cancer risk⁵¹. Although there are several hypothesized mechanisms for a protective effect of folate on cancer, the time of exposure appears to be important. Folate deficiency in rapidly replicating cells, such as tumors, will result in poor DNA replication and inhibition of growth⁴⁹. This is the mechanism by which antifolate cancer chemotherapy agents slow tumor growth⁴⁹. In the case of a pre-existing neoplasm such as a precancerous lesion in the colon, supplementation of folic acid may provide a neoplasm with the necessary metabolites to facilitate DNA synthesis and promote tumor growth⁴⁹.

Seminal to the concern in the scientific community over changes in cancer rates following folic acid fortification of whole grain are the results of animal studies, ecologic studies, and randomized clinical trials, most of which have focused on the effect of folate on colorectal cancer incidence. For example, in an experimental study in mice, researchers observed that dietary folate administered prior to initiation of neoplastic lesions suppressed the development of ileal polyps, but administration after neoplasm initiation promoted polyp growth⁵². In an ecologic study, a brief and temporary increase in colorectal cancer incidence immediately followed folic acid fortification in the United States and Canada. Abrupt reversals in previously decreasing trends of colorectal cancer incidence occurred, and then returned to their normal downward trend at a rate of 4-6 cases per 100,000 individuals above

their pre-fortification rates. The investigators hypothesized that folic acid fortification may have been responsible for the transient increase in colorectal cancer rates, as the brief rise was concurrent with the initiation of mandatory fortification in both countries⁵³. In a double-blind, placebo-controlled, randomized clinical trial performed on patients with a recent history of colorectal adenomas, participants assigned to receive 1 gram of folic acid per day did not demonstrate a decreased risk of colorectal adenoma compared to a placebo group overall. An increase in adenoma multiplicity was observed among those in the intervention group. Incidence rates for precancerous lesions in this study were higher, but not statistically significant, among participants receiving folic acid, suggesting that instead of reducing colorectal adenoma risk as expected, folic acid may have increased risk⁵⁴. Subsequent randomized clinical trials failed to show any benefit or harm from folic acid supplementation^{55,56}. Although these studies did not focus on pancreatic cancer, they do highlight the uncertainties associated with the role of folate on tumorigenesis, and the potentially profound impact fortification practices may have on public health.

Prospective studies examining folate and pancreatic cancer have primarily focused on four folate indicators: dietary folate, supplemental folate, total folate intake (dietary and supplemental), and circulating folate and other one-carbon metabolites.

Several⁵⁷⁻⁵⁹, but not all^{60,61} cohort studies provide evidence of an inverse relationship between total and/or dietary folate and risk of pancreatic cancer. In a study of the ATBC cohort of male Finnish smokers, a strong inverse association with pancreatic cancer was observed among subjects with high total folate intake [highest vs. lowest quintile: HR = 0.52; 95% CI, 0.31-0.87, p-trend=0.05]. However, 90% of participants in this study had less than adequate folate status, and 25% of these participants were considered folate deficient⁵⁷. In the NHS and the HPFS, total folate intake was not associated with risk of pancreatic cancer (highest vs. lowest quartile: RR = 1.03; 95% CI, 0.42-1.03), however a suggestive inverse relationship was observed for dietary folate (RR = 0.66; 95% CI, 0.31-0.87)⁶⁰. In a population-based study of the Swedish Mammography Cohort and the Cohort of Swedish Men, both total folate intake [highest (>350 µg/day) vs. lowest (<200 µg/day): RR = 0.33; 95% CI, 0.15-0.72] and dietary folate (RR = 0.25; 95% CI 0.11-0.59) were inversely associated with pancreatic cancer risk⁵⁸. Total folate intake was weakly associated with an increased pancreatic cancer risk in the Netherlands Cohort (highest vs. lowest quintile: HR = 1.37; 95% CI .97-1.94)⁶¹. In the PLCO cohort, a significant inverse relationship between dietary folate and pancreatic cancer risk was observed in women (highest vs. lowest quartile: HR = 0.47; 95% CI 0.23-0.94), but not men (HR = 1.20; 95% CI 0.70-2.04). Similar relationships were observed with total folate (for women: HR = 0.65; 95% CI 0.37-1.14, for men: HR = 0.95; 95% CI 0.59-1.54). The explanation for this gender disparity may lie in the higher reported intake of folate by women in this study, and a greater proportion of men than women with self-reported diabetes. This condition may have influenced their dietary intake, and consequently accounted for this discrepancy⁵⁹. Additionally, the wide ranges and high values of total folate, especially for women, distinguish this prospective cohort study from previous studies.

Several studies have examined folic acid supplement use and pancreatic cancer risk. In the ATBC cohort, supplemental folate use was related to a non-significant greater risk of pancreatic cancer (RR = 1.60; 95% CI 0.92-2.77) compared with no supplemental folate use⁵⁷. In the NHS and HPFS cohorts, non-significant increases in pancreatic cancer risk were reported for supplemental folate in a pooled multivariate analysis of increasing categories of intake⁶⁰. In the PLCO study, no association was observed for folic acid supplements⁵⁹. Among studies examining folic acid supplementation, there is no substantial evidence indicating that folic acid supplementation influences pancreatic cancer risk.

The association between circulating folate and pancreatic cancer risk has been investigated in three nested case-control studies. In the ATBC cohort, a statistically significant inverse relationship was observed for participants with elevated serum folate (highest vs. lowest tertile: OR = 0.45; 95% CI = 0.24-0.82). Of note, the majority of subjects in this study had less than adequate folate status⁶². In another study that pooled data from four US cohorts, no association was observed overall for plasma folate (highest vs. lowest quartile: OR = 1.20, 95% CI 0.76-1.91), however a non-significant inverse association was observed in subjects who were not taking multivitamins (OR = 0.55; 95% CI 0.24-1.25)⁶³. Finally, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort plasma folate was associated with a U-shaped risk⁶⁴. These findings may suggest that circulating folate is inversely related to pancreatic cancer risk among subjects who have inadequate folate status; however there is a paucity of studies examining this relationship.

The investigation of the influence of folate on pancreatic cancer risk has its own set of challenges. For instance, the food fortification practices and policies across countries are worthy of consideration. To our knowledge, only one prospective cohort study⁵⁹ has examined data collected exclusively following folic acid fortification of whole grains. Another study collected data while fortification was implemented⁶³, and other studies were performed on cohorts that were not exposed to folic acid fortification^{57,58,60,61}. There is greater probability of confounding in dietary assessment of folate and folic acid compared to measuring circulating folate. Additionally, measurement of micronutrients such as folate from food frequency questionnaires may be a source of error.

Although several well-designed studies examining folate and pancreatic cancer indicate an inverse relationship may exist, evidence suggesting a possible association between colorectal cancer and exposure to folic acid warrant due diligence in surveillance of post fortification cancer incidence rates. Among studies examining total or dietary folate and pancreatic cancer risk, when inverse relationships were observed, the strength of the relationship was generally more pronounced for dietary folate. Some epidemiologic evidence suggests that supplemental folate increases pancreatic cancer risk, however this relationship remains speculative. Lastly, while fewer studies have examined circulating folate, some evidence suggests that circulating folate may be inversely associated with risk among subjects who are folate inadequate. Given the evidence of the propensity of folate to promote tumor growth, more epidemiologic studies, especially prospective cohorts following folic acid fortification, are needed to help determine the direction and magnitude of the relationship between folate and pancreatic cancer risk.

CONCLUSION

The existing evidence examining the relationship of pancreatic cancer and dietary fat seems to suggest an association for saturated fat over other types of fat, as well as for fat from animal sources. Inverse associations have been observed in ecologic, case-control, and cohort studies that assess vitamin D indirectly. Conversely, prospective cohort studies that measured circulating vitamin D demonstrate no association for pancreatic cancer with low concentrations and suggestive positive associations with higher concentrations. More experimental evidence concerning the role of gene expression and vitamin D receptors may be necessary to explain these contradictory findings. Finally, the inverse association between pancreatic cancer risk and folate was pronounced for folate from dietary sources, but remains inconsistent. Due to increasing concern about the role of folate in neoplasm growth, further post-fortification cohort studies examining the long term effects of folic acid exposure are necessary. Although gaps remain in our knowledge of these risk factors and their respective relationships to pancreatic cancer, the aforementioned experimental and epidemiologic evidence in this review has undoubtedly advanced our understanding of the

influence that dietary fat, vitamin D, and folate have on both individual and population health.

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