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Diet and pancreatic cancer: many questions with few certainties

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Abstract. – *Background, Objectives:* **Pancreatic cancer ranks fourth for cancer mortality for men and women in the United States.**

This is a particularly devastating cancer since the case-fatality proportion approaches 90% within 12 months following diagnosis. Therefore, understanding the etiology and identifying the risk factors are essential for the primary prevention of this deadly disease.

Of the few potentially modifiable risk factors that have been identified, cigarette smoking, history of diabetes mellitus, and obesity seem to be among the most consistent, but the effect of dietary factors is still unclear. The aim of our study is to review of the literature examining the potential role of carbohydrates, fatty acids, meat, fruit and vegetables, alcohol.

Discussion: **Although large prospective cohort studies with questionnaire based analyses will continue to have much to offer in defining predisposing factors for difficult diseases, such as pancreatic cancer, unfortunately dietary questionnaires do not reflect the bioavailability of the nutrients from various foods, the level of absorption from the digestive tract, or individual differences in metabolism.**

Conclusions: **Greater use of participant-derived biological samples, banked plasma, germline DNA, and tumour tissue samples may help to the understanding of pancreatic cancer pathogenesis.**

Key Words:

Pancreatic neoplasms/epidemiology, Etiology prevention and control, body weight, Diet, Food habits

Introduction

Pancreatic cancer ranks fourth for cancer mortality for men and women in the United States. It is the eighth most common cause of cancer death in Europe. The incidence of pancreatic cancer is higher in men compared with women and in blacks compared to whites. In both Europe and the US 5-year survival rates are only 4-5%[1].

This is a particularly devastating cancer since the case-fatality proportion approaches 90% within 12 months following diagnosis. Therefore, understanding the etiology and identifying the risk factors are essential for the primary prevention of this deadly disease[1-3].

Of the few potentially modifiable risk factors that have been identified, cigarette smoking, history of diabetes mellitus, and obesity seem to be among the most consistent[1], but the effect of dietary factors is still unclear[4-6] and in spite of reported in other cancer diseases[7-9].

Genetic Susceptibility to Environmental and Metabolic Injuries

It is widely acknowledged that genetic, epigenetic, and environmental factors influence the onset of pancreatic cancer. Germ-line mutations, acquired mutations and epigenetic modifications of gene expression increase susceptibility of pancreatic cells to injury from environmental and metabolic factors. They alter cellular responses to environmental factors and reduce the ability of

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the cells to effectively manage and contain the damage through repair mechanisms and cell-death pathways. Since early diagnosis is difficult and the mortality rate is high, it is important to identify individuals with high risk for pancreatic cancer. In this regard, specific genetic alterations have been linked to different degrees of tumor progression[10].

Familial Cancer Syndromes

From an epidemiologic perspective, most pancreatic cancer appears to be sporadic.

Rare germ-line mutations lead to familial cancer syndromes that may include pancreatic cancer but they are thought to account for only a very small proportion of the cases (Table I).

All of these syndromes are linked to failure to repair DNA damage or cell-cycle control mechanisms, functions that are required by all cells.

Peutz-Jeghers syndrome, a cancer syndrome caused by mutations in the *SKD11/LKB1* genes, increases the risk of pancreatic cancer as much as 132 times: it also increases risk of other types of gastrointestinal cancers, ovary, testes, lung, breast and endometrial cancers[3].

Hereditary non-polyposis colorectal cancer syndrome, caused by mutations in several DNA mismatch repair genes including *MLH1* and *MSH2*, increases the risk of cancer in the colon, small bowel, stomach, hepatobiliary system, breast, ureter, pancreas and others[4]. The *familial atypical multiple mole melanoma syndrome,* caused by mutations in the tumor suppressor genes *p16 INK4a/MTS1* genes, increases the risk of cancer in the pancreas, skin, lung, breast, and endometrium[5-6].

The *hereditary breast ovarian cancer syndrome*, caused by mutations in the *BRCA1* and *BRCA2* genes, which are tumor suppressor genes responsible for DNA repair, especially double-stranded breaks, increases the risk of breast, ovary, pancreas, prostate, colon, gallbladder, and others[9-11].

Hereditary pancreatitis, caused by mutations in the PRSS1 gene, is a disorder that increases the risk of cancer in the pancreas only.

Peutz-Jeghers syndrome and hereditary pancreatitis frequently surface as conferring the greatest risk, whereas BRCA2 mutations are the most common inherited disorder. A gene whose penetrance is modified by the presence of environmental factors, including smoking and dietary habits, may explain the difference in risk between the densely aggregated and less densely aggregated families.

Acquired Genetic Mutations and Gene Polymorphism: the Role of CYP, SULT, NAT

Jones et al[11] identified core signaling pathways that were altered by genetic mutations or chromosomal loss in human pancreatic cancer. A comprehensive genetic analysis was performed sequencing more than 20,000 protein-coding genes, and obtaining a high-density single nucleotide polymorphism analysis to analyze loss of heterozygosity, reflecting the loss of major pieces of individual chromosomes. The Authors suggest that, on average, pancreatic cancers contained at least 63 genetic alterations linked to 12 core cellular signaling pathways including PI3k/Akt, k-ras, etc. Each of these 12 pathways was altered in 67% to 100% of pancreatic tumors.

Table I. Cancer syndromes associated with elevated pancreatic cancer risk.

Syndrome	Gene type	Gene(s) and chromosomal location	Estimated relative risk	Frequency insporadic cases
Peutz-Jeghers syndrome	Tumor suppressor	STK11/LKB1, 19p 13.3	132	4%
Hereditary pancreatitis	Cationic trypsinogen	PRSS1, 7q35	20 or more	N/A
Familial atypical multiple mole melanoma (FAMMM)	Tumor suppressor	P16INK4a/ MTS1, 9p21	13-22	98%
Hereditary breast/ovarian cancer (HBOC)	Tumor suppressor	BRCA1, 17q21-24 BRCA2, 13q12-13	2.3-6 for BRCA1 3-10 for BRCA2	N/A for BRCA1 ~7% for BRCA2
Hereditary nonpolyposis colorectal cancer (HNPCC)	Mismatch repair	MSH2, 2p22-21 MLH1, 3p21.3	Unknown	4-11%
Familial adenomatous polyposis (FAP)	Tumor suppressor	APC, 5q21	~5	40%

In addition, to germline defects, there are several common polymorphisms in genes that control detoxification of environmental carcinogens: cytochrome P450 (CYP) 1A2, N-acetyltransferase (NAT) and sulfotransferase (SULT) are enzymes involved in the detoxification as well as bioactivation of carcinogenic aromatic amines (AAs), heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons NOCs[9-11]. Usually, these carcinogens are activated by N-hydroxylation catalyzed by hepatic CYP[11]. Alternatively they are either N-acetylated or N-sulfated by NAT or SULT, respectively, for detoxification. However, following N-hydroxylation, they can be O-acetylated or O-sulfated by the same enzymes, yielding highly reactive intermediates capable of binding to DNA, therefore, leading to tumourigenesis[15,16]. CYP, NAT and SULT gene polymorphism may alter the risk of pancreatic cancer and be influenced by smoke and dietary components. A host of dietary factors are known to modify several of the detoxification pathways and may also contribute to the onset of pancreatic cancer.

Chronic Flogosis and the Risk of Pancreatic Cancer

It is generally accepted that chronic pancreatitis is a significant risk factor for pancreatic ductal adenocarcinoma cancer[17]. The duration of inflammation seems to be the major factor involved in the transition of benign to malignant condition. Chronic pancreatitis may precede pancreatic cancer by a decade or more[18-19].

In hereditary chronic pancreatitis families the disorder is caused by gain of function in the cationic trypsinogen gene (PRSS1) leading to a very high risk of pancreatic cancer. Other types of early onset chronic pancreatitis, including cystic fibrosis and tropical pancreatitis, determinate high risk of pancreatic cancer years after the inflammation is established.

Inflammation may lead to carcinogenesis through multiple molecular mechanisms: nitric oxide, free radicals, cyclooxigenase-2, etc. In addition to reactive compounds that can cause DNA damage, chronic inflammation increases the rate of cell division and proliferation releasing growth factor and activating embryonic signaling pathways that may facilitate the survival and expansion of premalignant clones[17-19].

Long term heavy alcohol consumption is the major cause of chronic pancreatitis. In the United States and other developed countries, 65 to 90 percent of cases of chronic pancreatitis are linked to alcohol consumption. Therefore, prevention or treatment of alcoholic pancreatitis may reduce the incidence of pancreatic cancer in this country[22].

Diet, Lifestyle and Pancreatic Cancer

Smoking is a well documented environmental risk factor for the development of pancreatic adenocarcinoma. The relation between diet and pancreatic cancer comes from its long-recognized interrelationships with diabetes and obesity and, thus, caloric intake and expenditure. However the effect of dietary factors is still unclear[4-6].

We will examine the most recent literature inheriting the association of heavy carbohydrates, fat, alcohol consumption, high body mass index (BMI), and high caloric intake with an increased risk of pancreatic cancer in humans with reference on important prospective cohort studies.

The NIH-AARP Diet and Health Study

The NIH-AARP (NIH American Association of Retired Persons) Diet and Health Study was established in 1995-1996 to investigate lifestyle exposures, especially diet, in relation to cancer incidence.

A self-administered baseline 124-item food frequency questionnaire (FFQ) was mailed to 3.5 million AARP members with ages between 50 and 71 years who resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI). The questionnaire was returned by 617, 119 members, and 567,169 participants completed the questionnaire satisfactorily. Cancer incidence in the cohort was ascertained by linkage to cancer registries covering the eight states, as well as Arizona, Texas, and Nevada. Vital status was ascertained annually by linkage to the Social Security Administration Death Master File, as well as by cancer registry linkage. The NIH-AARP Diet and Health Study were approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI). All participants gave informed consent by virtue of completing the questionnaire.

The Multiethnic Cohort (MEC) Study

The MEC study was established to investigate lifestyle exposures, especially diet, in relation to cancer incidence. In brief, between 1993 and 1996, 215,000 men and women 45-75 y old were

recruited to the cohort. Most of the study participants belonged to 1 of the 5 targeted racial-ethnic groups: African Americans (16%), Japanese Americans (26%), Latinos (22%), Native Hawaiians (6%), and whites (23%). Participants initially completed a self-administered, comprehensive food frequency questionnaire that included a detailed dietary assessment (of over 180 food items) and sections on demographic factors; body weight and height; lifestyle factors other than diet, including smoking history; history of medical conditions; and family history of cancer. Follow-up of the cohort entails computerized linkages to cancer registries and death certificate. As explained in the invitation to participate, return of a completed questionnaire indicated a subject's written informed consent.

Glycemic load, Glycemic Index and Pancreatic Cancer

The insulin/insulin-like growth factor (IGF) axis may play a role in the observed correlation between obesity, diabetes and mortality from several cancers.

The IGF axis consists of growth factors (IGF-1, IGF-2, and insulin), cell surface receptors (IGF-1R and IGF-2R), binding proteins (IGFBP-1 to IGFBP-6), IGFBP proteases and IGFBP-interacting molecules that regulate the IGF axis. The IGF axis is implicated in the regulation of cell growth, differentiation, apoptosis, and transformation in many tissues including the exocrine pancreas. Unbalance of these processes may lead to uncontrolled cell proliferation and carcinogenesis promotion. There are some evidences that insulin acts as a growth promoter and mitogen for the pancreas mucosal cells "*in vitro*"[23,24]. There are studies that suggest a relation between low plasma IGFBP-1 levels[25], high serum levels of IGF-I and IGFBP-3[26] and an increased risk of developing pancreatic cancer. Conversely, two studies do not find association between the risk of pancreatic cancer and pre-diagnostic plasma levels of IGF-I, IGF-II, or IGFBP-3[27,28].

Other recent studies suggest a role of high insulin concentrations, glucose intolerance, and insulin resistance in pancreas carcinogenesis, even without a diagnosis of diabetes mellitus[29-31]. However, the epidemiological relation of dietary factors increasing blood insulin concentrations and risk of pancreatic cancer is still unclear.

In the literature measures commonly used to evaluate the impact of dietary carbohydrates are glycemic load (GL) and glycemic index (GI).

The *Glycemic index* is a measure of the postprandial glycemic effects of individual food items compared with the glucose response of a reference food, usually pure glucose. Low-GI meals are associated with a lower postprandial rise in glucose and insulin. A common international table of measured glycemic index values for specific foods has been compiled by Foster-Powell et al[32].

The *Glycemic load* is the product of its glycemic index and the grams of carbohydrate from a single serving of that food[33].

Li Jiao et al[34] prospectively examined the relationship between dietary glycemic index, carbohydrates, glycemic load, starch, and simple sugar and the risk of pancreatic cancer in the "NIH-AARP Diet and Health Study" large cohort. This study has by far the largest sample size in literature. A total of 1,151 exocrine pancreatic cancer cases were identified from 482,362 selected participants, including 280,542 men and 201,820 women. According to the cancer registry 71.4% were microscopically confirmed, 16.6% were diagnosed by cytology, 6.6% were diagnosed by radiology/imaging technique, 2.5% (n = 25) were diagnosed by other clinical approach, and 2.9% (n = 29) by unknown diagnosis method.

Their analysis was generated using quintiles of glycemic index, glycemic load, free fructose and glucose intake and BMI (cut point 30 kg/m^2), physical activity, and smoking status.

In conclusion, the Authors did not detect associations between glycemic index, carbohydrate intake, and glycemic load and the risk of pancreatic cancer. High free fructose and, less strongly, high free glucose intake were associated with increased risk of pancreatic cancer.

There were no statistically significant interactions between risk of pancreatic cancer and nutrient intakes by BMI, physical activity, and smoking status.

Reviewing the literature to date, epidemiologic studies on the relationship of total carbohydrate intake with the risk of pancreatic cancer have been fairly inconsistent. Six case-control studies have reported a positive association[35]; one case control study[36] and one cohort study of Finnish male smokers[37] have reported an inverse association. Six prospective cohort studies have investigated the association between glycemic index and glycemic load in relation to the risk of pancreatic cancer and consistently found no associations[38-43].

In the Nurses Health Study[38] glycemic load has been positively associated with the risk among sedentary and obese women but not among normal weight and active women.

Li Jiao et al findings[34] were consistent with other studies showing overall null associations of starch, sucrose[35,38,39,41], simple sugars[42], and total sugar[39,41] with risk of pancreatic cancer.

According to the Authors high fructose intake related risk, consistently with Multiethnic Cohort Study findings[41], was from fruit but not related to free fructose from soft drinks or other non-natural resources. They hypothesize a role of the uric acid but the metabolic function of the transient increase in uric acid after fruit consumption is unknown.

Heinen et al[42] examined the association between pancreatic cancer risk and dietary GL and GI, and total carbohydrates, mono and disaccharide intakes, in men and women within the Netherlands Cohort Study (NLCS) on diet and cancer. Their case selection resulted in a final sub-cohort of 4438 subjects and 408 exocrine pancreatic cancer cases. No significant association was found when examining the association between GL, GI, carbohydrate, mono- and disaccharide intake, and the risk of pancreatic cancer in the total population. In additional analyses, the Authors stratified by both BMI and physical activity level to test whether the risk estimates were more pronounced for overweight and inactive individuals: they observed no associations in the total pancreatic cancer case group.

Moreover, they observed no associations between increased intake of some high-GI foods (eg, added sugar, soft drinks, sweet sandwich spreads, and sweets) and pancreatic cancer risk. Very few studies have examined these relations[44,45], and they reported no associations for jam, marmalade and sweets[44] and positive associations for soft drinks[44,37]. The Multiethnic Cohort Study showed null association with soft drinks[41].

Eight studies have examined the role of simple (monosaccharide and disaccharide) sugars[37,48,49], refined sugars[47], or sucrose[37,39,40,46]. Just two of these studies found an increased risk of pancreatic cancer[47,49].

Even if most cohort studies in the literature do not support the hypothesis that high glycemic index or glycemic load diets increase pancreatic cancer risk, the possibility that carbohydrates may contribute to the pancreatic cancer risk among individuals who had different states of homeostasis (BMI, lifestyle, smoke) needs further investigation.

Dietary Fatty Acids and Pancreatic Cancer

Consumption of fat overall and fat from animal products has been associated with an increase of pancreas cancer risk in some epidemiological ecological studies[50-52], case control studies[53-55], prospective studies[37,56-57], but not in others[46,48,58-66].

The relation between fat intake and pancreas carcinogenesis may be related to the function of enzymes such as lipases. An increase of pancreatic enzyme secretion mediated by cholecystokinin may lead to hypertrophy and hyperplasia with susceptibility to other environmental mutagens. Moreover, saturated fat is related with insulin resistance in several studies[50].

Thiébaut et al[50] recently analyzed the association between intakes of fat and pancreatic cancer risk in a large cohort of US men and women, the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study. After a meticulous selection their wide analytic cohort consisted of 525473 individuals (308736 men and 216 737 women).

Intakes of total fat and fat subtypes (saturated, monounsaturated, and polyunsaturated fatty acids), cholesterol, and individual fatty acids were considered to better understand which peculiarity of fat may be relevant in pancreatic cancer etiology.

Food sources of total, saturated, and monounsaturated fat, in particular red meat (beef, processed meat, red meat dishes, and sauces) and dairy products (milk, cream, yogurt, cheese, butter, ice cream, and cream soup) were further examined. Together with poultry, fish and eggs, these two groups contributed to the animal source food group, as opposed to the vegetable food group.

Variables associated with an increased risk of pancreatic cancer were included: smoking history, BMI and self reported history of diabetes. During up to 7.2 years of follow-up 865 men and 472 women were diagnosed with incident exocrine pancreatic cancer, reflecting incidence rates of 45.0 and 34.5 cases per 100 000 person-years, respectively[50] Men in the highest quintile of fat consumption (as a percentage of total energy intake) had a 53% higher incidence of pancreatic cancer than men in the lowest quintile (53.5 vs. 35.0 cases per 100000 person-years), and women in the highest quintile demonstrated a 23% higher incidence of pancreatic cancer than women in the lowest quintile (37.5 vs. 30.5 cases per 100 000 person-years). After multivariable

analysis, pancreatic cancer risk was directly related to the intakes of total fat and major fat subtypes with the exception of polyunsaturated fat and from-vegetable-sources monounsaturated fat. Compared with those in the lowest quintile, men and women in the highest quintile of percent energy from fat had increased risks of pancreatic cancer associated with *total fat consumption* (46.8 vs. 33.2 cases per 100 000 person-years, HR = 1.23, 95% CI = 1.03 to 1.46; *p* trend = 0.03), with *saturated fat consumption* (51.5 vs. 33.1 cases per 100 000 person-years, HR = 1.36, 95% CI = 1.14 to 1.62; *p* trend < .001), and with *monounsaturated fat consumption* (46.2 vs. 32.9 cases per 100 000 person-years, HR = 1.22, 95% CI = 1.02 to 1.46; *p* trend = .05). If sources of fat are considered, the positive association of total, saturated, and monounsaturated fat with pancreatic cancer was mostly determined by animal foods, especially red meat and dairy products, and was not determined by vegetable food sources[50].

No apparent modification was determined by BMI, self-reported diabetes, or smoking history.

To date few prospective studies have examined associations between dietary fat and pancreatic cancer, and their findings have been inconsistent mainly due to the small number of patients diagnosed with pancreatic cancer.

One cohort study in Finland[37] provided suggestive evidence of a positive association of exocrine pancreatic cancer with total and saturated fat but not with other fat components (monounsaturated).

Similar analyses in the Nurses Health Study women cohort (178 pancreatic cancer cases over 18 years of follow-up)[64] and the Multiethnic Cohort Study (482 incident pancreatic cancers occurred in 190545 cohort members during 7 years of follow-up)[57] showed no association for overall fat intake and pancreatic cancer. However, in the MCS cohort, when sources of fat were examined, total fat and saturated fat from red meat and processed meat appeared to be positively related to pancreatic cancer: fat from dairy products conversely appeared to be unrelated[57].

The literature shows a larger number of case control studies inheriting relation between dietary fat and pancreatic cancer. A positive association was found only in four[53-55] of 12 studies[46,48,60-67]. However, case-control studies are more prone to survival biases, selection biases, reporting biases. Thiébaut et al[50] have provided important data from the prospective National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study. This cohort study is a relevant addition because the large base population leads to a large number of pancreatic cancer cases available for analysis. However, the evidence that animal fats or meat are important per se or are instead related to other dietary and lifestyle preferences is still lacking. The mechanism underlying pancreatic tumorigenesis needs further investigation.

Meat and Meat-Mutagen Intake and Pancreatic Cancer Risk

Carcinogens present in meats include heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), and N-nitroso compounds (NOC).

Formation of heterocyclic amines and polycyclic hydrocarbons appears to be related to meat-cooking methods, temperature, and level of doneness. Well-done grilled/barbecued contain high concentrations of these compounds; conversely stewed and microwaved meats do not[68,69].

N-nitroso compounds may be isolated in preserved, cured and smoked meat. Moreover endogenous N-nitroso compounds formation may occur from the reaction of nitrosating agents (nitrite), with amines or amides catalyzed by gastrointestinal bacteria. Endogenous NOC formation appears to be dose dependently related to red meat intake[70]. Even dietary fat and iron, both found in meat, may also be relevant to pancreatic carcinogenesis[37,57,70].

Stolzenberg-Solomon et al[68] performed a complex analysis on the largest cohort available to date: 537,302 individuals were selected among people recruited for the NIH American Association of Retired Persons (NIH-AARP) Diet and Health Study, to investigate the association between meat intake, meat-cooking methods, doneness, as well as meat-derived heterocyclic amine, polycyclic aromatic hydrocarbons, meat-derived mutagenic activity index and pancreatic cancer risk.

Six months after the NIH AARP baseline 124 item-food frequency questionnaire was administrated, baseline respondents received a second food frequency questionnaire that included a meat-cooking module[71] that 332,913 subjects completed.

The meat-cooking module queried consumption of hamburgers, bacon, chicken and steak.

Respondents were asked for usual cooking method (pan-fried; grilled or barbecued; oven-broiled; other such as sautéed, baked, or microwaved), and level of doneness on the outside and inside[36].

The CHARRED database[72] was used to estimate daily intake of meat-mutagens, including the HCAs: DiMeIQx, 2-amino-3, 8-dimethylimidazo [4,5-f] quinoxaline (MeIQx), PhIP, B(a)P, and an overall meat-mutagenic activity index[69].

The CHARRED database was developed using 120 categories of meat samples prepared by different cooking methods, varying doneness levels and their composites analyzed for HCAs, B(a)P, and overall mutagenic activity[73,75].

Eight hundred and thirty-six incident pancreatic cancer cases were identified, with 459 cases having complete meat-cooking module data.

Baseline meat and the meat module meat mutagens were categorized into quintiles. Cooking methods were categorized into tertiles due to the small intake range.

As results, high total meat intake was associated with a 26% (95% CI, 1.02-1.56; *p* trend = 0.004) increased pancreatic cancer risk for men and women combined in adjusted models. Compared with the lowest quintile, the highest quintiles of total, red, and high-temperature cooked meats showed significant 41%, 42%, and 52% increased pancreatic cancer risk in men, respectively, with trends across quintiles (*p* trends < 0.01), but not in women.

Men with the highest intake compared with those with the lowest intake of meat that was grilled/barbecued and oven broiled had significant 48% and 47% increased pancreatic cancer risk, respectively. No associations were observed for pan-fried or sauteèed, baked, or microwaved meat among men or any of the meat-cooking methods among the women.

Sex discrepancies could be explained with most women in this cohort consuming less meat and meat-related mutagens at levels below which associations may be evident. Even iron loss during menstruation could play a role. Higher free iron serum levels and percent transferring saturation were significantly associated with pancreatic cancer.

Among men, meat-mutagenic activity intake calculated using CHARRED database was significantly associated with pancreatic cancer, with the second to fifth quintiles having 1.8 to 2.3 fold risks compared with the lowest quintile.

DiMeIQx in both sexes and PhIP among men showed patterns of association with pancreatic cancer, in particular the highest DiMeIQx quintile showed positive associations for both sexes and a significant 29% correlation.

There were no significant interactions of any of the meat variables and pancreatic cancer by smoking status.

Reviewing the literature, of the 10 cohort studies that have been examined consumption of various meats in association with exocrine pancreatic cancer[56,64,76-83], five showed significant or borderline significant positive associations for total or red meat, with risks ranging from 1.4 to 3.0[57,77-79].

The Multiethnic Cohort Study, (482 cases of pancreatic cancer), reported significant 45% and 68% increased risks in the highest compared with the lowest intake of red and processed meat, respectively[57].

Meat-cooking methods and pancreatic cancer risk has been evaluated in one cohort study that showed no associations[37] and eight case-control studies[47,67,84-90], five of which reported greater pancreatic cancer risk for fried or grilled/barbecued meats, with odds ratios ranging from 2.2 to 16.7[82-84, 87].

A recent study[91] (population-based case-control study – 193 cases) showed a significant 2-fold pancreatic cancer risk with higher consumption of grilled/barbecued red meat: the highest quintiles of meat-derived PhIP, DiMeIQx, B (a) P, and mutagenic activity intake were significantly associated with risks ranging from 1.8 to 2.4.

One more study[90] (large hospital-based case control with 626 cases) showed an overall significant 52% increased pancreatic cancer risk for the highest compared with the lowest DiMeiQx intake quintile (*p* trend = 0.02). These studies show patterns of risk between the meat-related mutagens and pancreatic cancer, similar to the associations observed in the NIH-AARP Diet and Health Study for DiMeiQx in both sexes and PhIP among men: the positive risk is perceivable only in the highest quintile of intake[90,91].

We may argue that usually cooking related meat mutagens are consumed at very low concentrations and small quantities, where a sort biological threshold is hypothesizable: only at high intake we may observe an association with cancer[91-93]. Overall meat-derived mutagenic activity, based on the integration of all classes of meat-related mutagens may be a more comprehensive exposure measurement.

NOCs found in processed meat are carcinogens in animals and suspected to be carcinogenic in humans[94,95]. To date their role is still unclear;

most cohort studies[37,64,78,79,94] do not find any positive association with increased risk of pancreas cancer as Multiethnic Cohort Study conversely do[57]. Since 1970 the amount of nitrite found in meat has been reduced by more than 80% because of restrictive rules[95]. These preventive measures may have contributed to the lack of a positive association between processed meat and pancreatic cancer. In conclusion, most of the literature support the hypothesis that meat intake, particularly red meat, meat that is cooked at high temperatures, meat-associated HCAs, DiMeiQx, and PhIP, and overall mutagenic activity may play a role in exocrine pancreatic cancer development. Further research is needed to confirm our results, particularly pertaining to meat-related mutagens and pancreatic cancer risk in other populations with extended follow-up.

Alcohol Use and Risk of Pancreatic Cancer

Alcohol use has been implicated in the etiology of cancers of the mouth, pharynx and larynx, esophagus, breast, liver, and colorectal[7,9].

Acetaldehyde, oxidative stress, and cytokines are known to mediate the effect of alcohol in the development of both chronic and acute pancreatitis. In addition, various predisposing factors such as genetic mutations, intestinal infections, and dietary factors have been advocated in susceptibility of the pancreas to alcohol-induced tissue injury. Alpha-hydroxyethyl radicals as well as 4-hydroxynonenal, an index of lipid peroxidation, have been detected in pancreatic secretion after chronic ethanol exposure. Furthermore, chronic ethanol has been shown to induce Cytochrome P2E1 in the pancreas, which can result in the generation of reactive oxygen species (ROS)[96-99].

Chronic alcohol consumption may further exacerbate oxidative stress by reducing the levels of reduced glutathione (GSH) in the pancreas. Acetaldehyde has been shown to be mutagenic and carcinogenic in many *in vitro* and *in vivo* studies. It can be produced in the pancreas through oxidative metabolism of alcohol, catalyzed by alcohol dehydrogenase (ADH) as well as CYP2E1. Increased acetaldehyde production in pancreas during heavy alcohol ingestion may increase the risk of pancreatic cancer. The mechanism of action of these factors in pancreatitis and pancreatic cancer development requires additional study[100-101].

Even the epidemiologic evidence for the role of alcohol use in the etiology of pancreatic cancer is still unclear.

Li Jao et al[102] recently selected among NIH-AARP (NIH American Association of Retired Persons) Diet and Health Study a final analytical cohort consisted of 470,681 AARP members, including 280,084 men and 190,597 women.

Servings of alcohol use per day were computed for total beverages and for each type of alcoholic beverage. One serving (1 drink) was defined as 12 fluid ounces of regular beer (12.96 g of alcohol), 5 fluid ounces of wine (13.72 g of alcohol), or 1.5 ounces of 80 proof distilled spirits liquor (13.93 g of alcohol)[103].

Participants were distinguished in ever smokers (at least 100 cigarettes over the life) and never smokers. Ever smokers reported whether they currently smoked, when they had stopped smoking and their daily smoking dose.

During the average follow-up time of 7.3 years, we identified 748 cases of pancreatic cancer in men and 401 cases in women. The age standardized incidence rate per 100,000 person-years was 40.2 (95% CI: 35.9, 44.4) among non-drinkers, 32.6 (95% CI: 30.0, 35.1) among light drinkers, 29.9 (95% CI: 25.4, 34.4) among moderate drinkers, and 46.4 (95% CI: 37.7, 55.5) among heavy drinkers.

Compared with light drinkers, those who consumed 6 or more drinks per day had a relative risk of 1.55 (95% CI: 1.13, 2.13; Ptrend ¼ 0.004) and 3 or more drinks per day had a relative risk of 1.45 (95% CI: 1.17, 1.80; Ptrend ¼ 0.002)

The study did not detect a significant increased risk with heavy alcohol use in women. Beer or wine use was not associated with the risk: the positive association surprisingly was mostly related to heavy liquor use[104]

Heavy liquor use has been associated with pancreatic cancer in 3 studies[81,105-106]. Volatile nitrosamines and polycyclic aromatic hydrocarbons are found in liquor and beer. Because nitrosamines are known pancreatic carcinogens in hamsters, the higher risk of pancreatic cancer may be explained by nitrosamines in liquor with heavy use[104-106].

Alternatively, the positive association may be due to residual confounding by factors such as smoking and lifestyle factors. To minimize the residual confounding by smoking, the Authors attempted to examine the association among never smokers and found that heavy total alcohol or liquor use showed a slightly non-statistically significant increased risk of developing pancreatic cancer in never smokers[102].

At least 38 analytical epidemiologic studies[76,108], 13 prospective cohort studies[105,111-119], have examined the association between alcohol use and incidence and/or mortality of pancreatic cancer. Many studies did not find any association[109]. Five case control studies[36,119-120] and 3 cohort studies[105,112,115] have shown an increased risk of pancreatic cancer in heavy alcohol drinkers. Five studies have shown statistically significant relative risk ranging from 1.7 to 3.7 after adjustment for smoking[112,115,120,121,123] because people who drink also tend to smoke and cigarette smoking is a risk factor for pancreatic cancer.

Six have shown an increased risk with beer and liquor[102,103,112,117-119], and 4 have shown a reduced risk with white wine[87,124-126]. Several studies that have investigated alcohol use in never smokers showed inconsistent findings[87,105,106,117].

The lack of associations between alcohol use and pancreatic cancer risk in the existing studies may reflect methodological difficulties, including small sample size, reverse causation, and selection, recall, and proxy reporting biases, as well as a narrow range of alcohol consumption in the study populations.

Although we could not completely exclude residual confounding by cigarette smoking, the significant positive association between heavy alcohol use and pancreatic cancer in longtime former smokers might suggest a potential etiologic role of alcohol use in pancreatic cancer development. Moderate alcohol use appears not to be a risk factor for pancreatic cancer.

Fruit, Vegetables and Pancreatic Cancer

It has been hypothesized that vegetable consumption offers protective effects against several cancers. Various constituents of these foods have been proposed as sources of possible beneficial effects, including dietary fiber, folic acid, selenium, and phytochemicals such as carotenoids, flavonoids, and isoflavones[126]. Several investigators have studied the associations of vegetable intake with pancreatic cancer and have suggested that vegetable intake may reduce risk[128-129]. However, the findings have been inconsistent so far, rendering further investigations necessary before firm conclusions can be drawn.

Nothlings et al[130] studied the relation between vegetable intake and pancreatic cancer risk within the Multiethnic Cohort Study. The Authors analyzed data from 183, 522 participants after an average of 8.3 years of follow-up.

The Food Frequency questionnaire inquired about the consumption of over 180 food items, including more than 20 individual vegetable items as well as mixed dishes containing vegetables. Moreover, it inquired about the amount of each food and usual frequency.

After an average of 8.3 years of follow-up, 529 pancreatic cancer cases were identified.

According the Authors, after adjustment for confounding variables, in their analysis no statistically significant association between total vegetable intake or vegetable subgroups and pancreatic cancer risk was detected. Only current smokers, who were at increased risk of pancreatic cancer (relative risk ¼ 1.78, 95% confidence interval: 1.40, 2.27), had a decreased risk with higher intake of dark green vegetables (for comparison of extreme quartiles, relative risk ¼ 0.50, 95% confidence interval: 0.27, 0.92; p-trend ¼ 0.029).

In stratified analyses by BMI, inverse associations with total vegetables, light green vegetables, and legumes were significant in overweight/obese persons (BMI 30 kg/m^2).

In conclusion, the Authors found no evidence for an inverse association between vegetable intake and pancreatic cancer overall, but inverse associations in high-risk persons suggest the need for further investigation.

Vrieling et al[131] recently examined the associations of fruits and vegetables intake and pancreatic cancer risk within the *European Prospective Investigation into Cancer and Nutrition (EPIC)*. The EPIC study is the second largest cohort study investigating the association between fruit and vegetable consumption and pancreatic cancer risk thus far. EPIC is comprised of over 520,000 subjects recruited from 10 European countries. 555 exocrine pancreatic cancer cases after an average follow-up of 8.9 years were selected. According to their analysis, total fruit and vegetable consumption was not significantly associated with risk of pancreatic cancer (HR 5 0.92; 95% CI 0.68-1.25 comparing highest with lowest quartile). Also, no significant associations between total vegetable and total fruit consumption and no significant associations between subgroups of vegetables and fruits and pancreatic cancer risk were observed.

Reviewing the literature, at least 10 other prospective studies have investigated vegetable intake as a risk factor for pancreatic cancer[34,76,78,129-132]. The widest sample size, 3751 persons died of pancreatic cancer in a US cohort of 483,109 men and 619,199 during 14 years of fol-

low-up, was examined by Coughlin et al[81]: no association between vegetable intake and pancreas risk was detected. Only three prospective studies found a statistically significant inverse association, one with intake of raw vegetables[132], one with intake of cabbage[135], and one with intake of beans, lentils, and peas[56].

Case-control studies of vegetable intake and pancreatic cancer risk conducted so far have been much more inconsistent cause the are often necessarily relied on proxy interviews, which, in addition to possible recall bias in dietary reporting is a major limitation.

Various constituents of vegetables have been proposed to have anticancer effects like dietary fiber[127], the isothiocyanates in cruciferous vegetables, the lutein, an antioxidant contained in green leafy vegetables. The dietary role of folate in DNA methylation[124] has been studied by other researchers. Isothiocyanates, a group of molecules that are released from glucosinolates in the plant through enzymatic reactions that occur when plant cells are destroyed[136,137] have been studied hypothesizing a chemopreventive effect for pancreatic cancer and other cancers[136,138]. Phytoestrogens, especially isoflavones, are characteristic compounds of legumes. Isoflavones have been linked to cancer via their estrogenic properties, being able to bind to estrogen receptors[134] Protease inhibitors, saponins, phytosterols, and inositol hexaphosphate are further components of legumes which have been shown to have anticancer effects in animals or *in vitro*[137,140].

In conclusion, results from cohort prospective studies to date published in the literature show no evidence of an inverse association between vegetable intake and pancreatic cancer overall. However they suggest that vegetables may have a role against the disease in persons at higher risk, namely current smokers and overweight or obese persons. These findings need further evaluation.

Conclusions

Although large prospective cohort studies with questionnaire based analyses will continue to have much to offer in defining predisposing factors for difficult diseases, such as pancreatic cancer, unfortunately dietary questionnaires do not reflect the bioavailability of the nutrients from various foods, the level of absorption from the digestive tract, or individual differences in metabolism.

Greater use of participant-derived biological samples, banked plasma, germline DNA, and tumor tissue samples may help to the understanding of pancreatic cancer pathogenesis.

As already said, pancreatic cancer is a particularly devastating disease since the incidence/lethality proportion approaches 90% within 12 months following diagnosis. Therefore, understanding the etiology and identifying the risk factors are essential for the primary prevention of this deadly disease.

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