Review

Nutrition and Pancreatic Cancer

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Abstract. *Background: Pancreatic cancer is the fourth leading cause of cancer death in men and women. Prognosis is poor with a 5-year survival rate of less than 5%. As there is no effective screening modality, the best way to reduce morbidity and mortality due to pancreatic cancer is by effective primary prevention. Aim: To evaluate the role of dietary components in pancreatic cancer. Materials and Methods: Bibliographical searches were performed in PubMed using the terms "pancreatic cancer", together with "nutrition", "diet", "dietary factors", "lifestyle", "smoking", "alcohol" and "epidemiology". Results: Fruits (particularly citrus) and vegetable consumption may be beneficial. The consumption of whole grains has been shown to reduce pancreatic cancer risk and fortification of whole grains with folate may confer further protection. Red meat, cooked at high temperatures, should be avoided, and replaced with poultry or fish. Total fat should be reduced. The use of curcumin and other flavonoids should be encouraged in the diet. There is no evidence for benefit from vitamin D supplementation. There may be benefit for dietary folate. Smoking and high Body Mass Index have both been inversely associated with pancreatic cancer risk. Conclusion: The lack of randomized trials and the presence of confounding factors including smoking status, physical activity, distance of habitat from the equator, obesity, and diabetes may often result in inconclusive results. There is evidence to encourage the use of whole grain in the staple diet and supplementation within the diet of folate, curcumin and other flavanoids. Carefully designed randomized trials are required to further elucidate these important matters.*

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Pancreatic cancer is the fourth leading cause of cancer-related death in men and women (1). Epidemiological studies show incidence of pancreatic cancer to be lowest to native Japanese and highest in New Zealand Maoris and female native Hawaiians (2). Prognosis is poor with 1-year survival rate of 25% and a 5-year survival rate of less than 5% (3). Resection remains the only way of providing a potential cure but unfortunately, more than 80% of patients will have distant metastases at the time of diagnosis (4). As there is no effective screening modality, the best way to reduce morbidity and mortality from pancreatic cancer is by effective primary prevention. Several modifiable and non-modifiable risk factors have been identified such as age, sex, family history, history of chronic pancreatitis, diabetes, insulin resistance, obesity and cigarette smoking (3, 5-8). The role of diet in pancreatic carcinogenesis has also been extensively studied.

Materials and Methods

A PubMed search was performed for publications from 1985 through 2013, using the following key words, including both medical subject heading (MeSH) terms and free language words/phrases: "pancreatic cancer", "nutrition", "diet", "dietary factors", "lifestyle", "smoking", "alcohol" and "epidemiology".

Articles that described and compared the impact of various dietary factors on risk of pancreatic cancer were first screened according to abstracts and titles and the selected articles were assessed for eligibility as full-text articles. No language restriction was applied. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports. Reference lists from all available review articles, primary studies and proceedings of major meetings were also considered. The quality and strength level of the results were considered.

Results

As expected, a large number of results were returned for each of our search parameters. The parameters included were pancreatic cancer with nutrition, diet, dietary factors,

lifestyle, smoking, alcohol, epidemiology, and the result hits were 17,880, 22,720, 10,400, 3,000, 19,600, 25,520 and 166,320 respectively. The respective hits after filtering for year range, human studies and article type were 13,920, 12,100, 7,680, 2,600, 16,060, 17,840 and 148,640. The numbers were significantly less after we manually screened for full text articles and for documents, which were specific for the scope of this systematic review, Articles considered in this review were also qualified based on their evidence level. In more detail, we considered 110 articles for "Fruit and vegetables", 88 articles for "Whole grain", 160 articles for "Meat", 79 articles for "Fish", 91 articles for "Fat", 70 articles for "Refined Sugar", 105 articles for "Alcohol", 40 articles for "Coffee", 203 articles for "Polyphenols" (including tea and curcumin), 98 articles for "Vitamin D", 56 articles for "Folic acid" (and folate), 101 articles for "Other Micronutrients", 8 articles for " Gut Microbiota", 71 articles for "Smoking" , 43 articles for "Obesity and Physical Activity" and 40 articles for "Menstrual and Reproductive Factors".

Fruit and vegetables. Epidemiological studies have shown that consumption of fruit and vegetable is inversely-proportional to the risk of developing pancreatic cancer (9). This inverse association was also confirmed in case-control studies (10) where significant benefits were shown for consumption of fruit and vegetables such as citrus fruit, melon, berries, dark green vegetables, tomatoes, beans, peas, deep yellow vegetables, fibre and whole grain (11). Fruits, especially citrus fruits, are rich in flavonoids such as hesperidin, rutin and diosmin. Flavonoids have been shown to have antitumour, anti-proliferative and pro-apoptotic properties (12, 13). Citrus fruits are also rich in carotenoids such as beta-carotene and lutein, and these compounds may also decrease the risk of cancer (14). Citrus limonoids such as limonin and nomilin are compounds found in citrus fruits and they were found to possess anti-oxidant and anticancer properties (15-17).

Large prospective studies explored the effect of fruit and vegetables in different populations. The Japan Collaborative Cohort Study showed a 50% decrease in risk of pancreatic cancer in men who consumed high amounts of fruit. No other significant association was shown (18). The Swedish Mammography Cohort and the Cohort of Swedish Men study (19), the Iowa Women's Health Study (IWHS) (20), the Hawaii-Los Angeles multi-ethnic Cohort Study (21) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohort of over 520,000 individuals (22), concluded that higher consumption of fruit and vegetables was not associated with reduced risk of pancreatic cancer, but all studies are affected by confounding factors.

Conclusion: Citrus fruits may be helpful in reducing the risk of pancreatic cancer.

Whole grains. Case-control studies have provided evidence that consumption of whole grains and high-fibre foods may reduce the risk of pancreatic cancer and that refined grains were not associated with risk (23, 24). A meta-analysis of four studies confirmed an inverse association between whole grains and pancreatic cancer (25). In certain countries, additional benefits from whole grains were observed following fortification with folate. Xanthohumol found in oats has been shown to have antitumour properties in experimental models (26).

Conclusion: Consumption of whole grains has been shown to reduce pancreatic cancer risk and fortification of whole grain with folate may confer further protection (see folate section).

Meat. The findings of individual prospective studies are inconsistent but a recent meta-analysis showed a positive association between consumption of processed meat with pancreatic cancer. The same study showed that consumption of red meat is positively associated with pancreatic cancer risk only in men (26). This could be explained by the observation that men consume more fried, grilled, or barbecued meat than women (28) or according to Stolzenberg-Solomon *et al*., this association might be secondary to the fact that there are higher iron stores in men than in women (27). The IWHS and the Japan collaborative cohort studies did not observe an overall association between meat intake and pancreatic cancer risk (18, 28). Rohrmann and co-workers examined meat consumption in relation to pancreatic cancer in the EPIC study, a large European multi-center cohort study (29). In contrast to previous studies, they did not find consistent evidence for an association between meat consumption and the risk of pancreatic cancer, but instead described a positive association of red meat consumption with pancreatic cancer risk in women. Increased risk was found to be associated with the consumption of lamb, veal and game (10). In a recent meta-analysis, Larsson and Wolk reported that every 50 g of processed meat consumed per day is linked to a 19% increase in risk of pancreatic cancer (27).

Consumption of poultry appears to contribute less than red meat to the risk for pancreatic cancer (27, 30, 31) and one study even showed risk reduction (32). However, Rohrmann *et al*. found a positive association of poultry consumption with pancreatic cancer in linear models (29).

Epidemiological studies looked at the association of pancreatic cancer with intake of heterocyclic amines (HCA) in well-cooked red meat and chicken. In two studies, a direct association was demonstrated between HCAs and pancreatic cancer (33, 34) and Anderson *et al*., in their large cohort study of 33,000 individuals, demonstrated this association in men only (33).

Conclusion: Some studies showed that processed red meat or meat cooked at very high temperatures by methods such

as frying, broiling or barbequeing should be limited in order to reduce the risk of pancreatic cancer.

Fish. Seven cohort studies examined fish consumption in relation to incidence or mortality of pancreatic cancer and they all failed to show statistically significant associations between fish consumption and pancreatic cancer risk (31, 32, 35).

The possible protective role of fish against pancreatic cancer might be supported by the hypothesis that long-chain (n-3) polyunsaturated fatty acids (LC-PUFAs) abundant in fish, could be beneficial against pancreatic oncogenicity because of the anti-inflammatory properties of these nutrients, given the fact that chronic inflammation may play a role in pancreatic carcinogenesis (36). In a recent meta-analysis, which included nine prospective cohort and 10 case-control studies, no inverse association of fish or LC-PUFA consumption with risk of pancreatic cancer was found (37) and this was in line with other published studies (29, 32, 38).

Fish preparation methods may alter the relationship between fish intake and pancreatic cancer by changing the lipid profile and by generating new chemicals depending on the type of cooking method (39). Deep-frying reduces the amount of LC-PUFA in fish and generates several chemicals that may contribute to carcinogenesis and to increased pancreatic cancer risk (40). According to the meta-analysis by Qin and co-workers only non-fried fish but not total fish intake was inversely-associated with pancreatic cancer risk (37). A more recent prospective cohort study, highlighted the possible benefits for primary prevention of LC-PUFAs against pancreatic cancer (41). Moreover, higher intake of non-fried fish or shellfish, was associated with lower incidence of pancreatic cancer (41). The caution regarding shellfish also arises from the fact that they may potentially contain chemicals believed to be carcinogenic on the basis of both animal experiments and human studies (42, 43), and a case-control study showed a weak positive association between shellfish intake and the incidence of pancreatic cancer (10). This association was not shown in a recent cohort study by He *et al*. (41).

Conclusion: Consumption of non-fried fish might reduce the risk of pancreatic cancer.

Fat. As soon as lipids enter the duodenum, cholecystokinin is released, which induces secretion of pancreatic enzymes. Over long periods, this may lead to pancreatic hypertrophy and acinar hyperplasia and, consequently, pancreatic neoplasia (36, 44). Other suggested mechanisms, which may lead to pancreatic cancer, include bile acid secretion (45) and insulin resistance from saturated fats (40, 46).

Most case-control studies show a positive dietary association of consumption of saturated (42, 43, 47, 48) monounsaturated (42, 47) fatty acids and PUFAs (48) with pancreatic cancer. In contrast to this, Nkondjock *et al*. suggest that substituting PUFAs with saturated or monounsaturated fatty acids may reduce pancreatic cancer risk (43). Several cohort studies have shown a positive association between pancreatic cancer and total fat consumption (31), saturated fatty acids such as butter and cream (49), and monounsaturated fatty acids (50). Prospective studies, including the Nurses' Health cohort Study (NHS) (30), showed no such relationship. Thiebaut *et al*. examined the data from a cohort of more than half a million inidviduals showing a positive relationship between saturated and monounsaturated fatty acids and pancreatic cancer (50).

Conclusion: Intake of total fat, as well saturated and unsaturated fatty acids, may be related to pancreatic cancer.

Refined sugar. The association of readily absorbable sugars with the risk of developing pancreatic cancer has been examined through soft drink consumption. Intake of sugar-sweetened soft drinks appears to increase pancreatic cancer risk in some studies (38, 51, 52) but not in others (53). Other studies show this association to be true among women-only (54). A pooled analysis of 14 cohort studies showed a modest positive association for risk of pancreatic cancer for intakes of carbonated sugary soft drinks (55). Hyperinsulinaemia (56), metabolic syndrome (57) and diabetes (58-60) have all been associated with pancreatic cancer risk. Interestingly, metformin as a treatment for diabetes, appears to reduce pancreatic cancer risk (61, 62). In their recent prospective study, Wolpin and collegues investigated the relationship between markers of glycemia, peripheral insulin resistance, and impaired β-cell function in relation to pancreatic cancer risk by measuring circulating pre-diagnostic glycaeted haemoglobin (HbA1c), insulin, proinsulin, and proinsulin to insulin ratio among male and female participants from five large, american cohort studies with plasma samples collected prior to cancer diagnosis. Circulating markers of peripheral insulin resistance, rather than hyperglycemia or pancreatic β-cell dysfunction, were found to be independently associated with pancreatic cancer risk. These findings highlight the associations between obesity, type II diabetes mellitus, and pancreatic cancer risk and might suggest the correction of insulin resistance as a preventive strategy (63).

Conclusion: There is no direct link between consumption of refined sugar and pancreatic cancer, however hyperinsulinaemia, obesity, metabolic syndrome and diabetes have all been positively linked to pancreatic cancer risk.

Alcohol. Alcohol has been found to be an independent risk factor for pancreatic cancer (64), but may be associated with only heavy alcohol consumption (65, 66). This was also confirmed in large meta-analysis of 14 cohort studies for women-only who consumed more than 30 g of alcohol per day (67). However, a study of the EPIC cohort showed no

association between alcohol consumption and the risk of developing pancreatic cancer (68). There appears to be a strong confounding factor of smoking in most statistical analyses.

Conclusion: Alcohol consumption appears to be associated with a small fraction of all pancreatic cancers, usually in people who consume more units. That risk may be increased in patients with alcohol-induced chronic pancreatitis. Smoking is a strong confounding factor.

Coffee. Studies from the early 1980s suggested that there may be an association between consumption of coffee and development of pancreatic cancer. However, more recent meta-analyses showed none (55, 69) or inverse (70, 71) association between coffee intake and pancreatic cancer risk. Analysis of the data from the EPIC cohort showed no association between total and decaffeinated coffee and risk of pancreatic cancer (72).

Conclusion: There is probably no association between coffee and pancreatic cancer.

Polyphenols. Polyphenols are a class of chemicals known for their numerous benefits, especially their antioxidant effect (73-75), inhibition of cellular proliferation (76), induction of cell-cycle arrest (77), interaction with apoptotic pathways and anti-angiogenic and anti-metastatic effects (78). They are divided into five classes: flavonoids phenolic acids, ligans, stillbenes and others. The most important dietary sources of polyphenols are fruits, vegetables, seeds, and beverages such as fruit juices, green tea, coffee, cocoa drinks, red wine, and beer.

Green tea: Green tea is rich in flavonols; a type of flavonoid. Examples include catechin and epicatechin. These compounds have been found to posses anti-proliferative properties and induce apoptosis in pancreatic cancer cells both *in vitro* and *in vivo* (79-82). Case-control studies showed no causal association between tea and pancreatic cancer (83, 84). Two Japanese cohort studies found no protective or harmful relationship between green tea consumption and pancreatic cancer (85, 86). A recent analysis of 14 cohort studies showed no association between tea intake and pancreatic cancer risk (55). In the present study, the authors were unable to examine the association between types of tea (*i.e.* green versus black) and risk of pancreatic cancer, as few studies had measured these exposures. In the few studies that have examined these associations, most studies reported no association with green tea. A more recent study conducted within the EPIC cohort showed no association between tea consumption and pancreatic cancer risk (72). Overall tea consumption appears to be safe in moderation, although available studies did not show any protective role against pancreatic cancer. Interestingly, one recent study conducted in China showed that regular green tea drinking was associated with 32% reduction of pancreatic cancer risk in women compared to those who did not drink tea regularly. Increased consumption and longer duration of tea drinking were both associated with reduced pancreatic cancer risk in women, whereas among regular tea drinkers, lower temperature of tea was associated with reduced risk of pancreatic cancer in both men and women, independent of amount or duration of tea drinking (87).

Conclusion: There does not appear to be any impact of total or green tea consumption on pancreatic cancer.

Isoflavones. Isoflavones are a group of compounds belonging to the family of flavonoids. Examples include genistein and genistin. Foods such as soybeans are very rich in genistein, which has been found to inhibit cancer cell growth and induce apoptosis (88, 89). *In vitro* studies showed a potential role for genistein in reducing pancreatic cancer risk; Xia *et al*. found that genistein could function as a non-toxic activator of a microRNA that can suppress the proliferation of pancreatic cancer cells (90). These properties have been extensively explored in combination with chemotherapeutic drugs; genistein is considered to potentiate the effect of agents such as gemcitabine, cisplatin and erlotinib (91-93). El-Rayes *et al*. conducted a phase II study to determine the effects of adding isoflavone to a regimen of gemcitabine and erlotinib on survival in patients with advanced pancreatic cancer. They enrolled 20 patients treated with two cycles of chemotherapy and isoflavone, but the addition of soy isoflavones to gemcitabine and erlotinib did not appear to increase the survival of patients with advanced pancreatic cancer (94).

Curcumin: This polyphenol is a curcuminoid found in turmeric spice and has anti-oxidant, anti-inflammatory and anti-tumour properties (95, 96). It has been studied in *in vitro*, *in vivo* and phase I-III clinical trials. Just like genistein, curcumin has been used alone (97, 98) and in combination with chemotherapeutic agents such as gemcitabine in localized, advance unresectable pancreatic cancer (99, 100) or for patients with gemcitabine-resistant disease (101). Human clinical trials indicated no dose-limiting toxicity when curcumin was administered at doses up to 10 g per day. The bioavailability of curcumin ingested in foods may be increased as a result of cooking or dissolution in oil (102). A recent study investigated the combinatorial effect of dietary compounds, garcinol and curcumin, on human pancreatic cancer cells (BxPC-3 and Panc-1) and demonstrated a synergistic effect between curcumin and garcinol (103).

According to available evidence, the use of curcumin should be encouraged in the diet; further studies are needed to elucidate the underlying mechanisms of combinatorial approach using curcumin in pancreatic cancer.

Conclusion: Curcumin demonstrated anti-tumour properties and benefits in pancreatic cancer.

Folic acid/folate (vitamin B9). This is one of the water-soluble vitamins found in fruits, dark green vegetables and dried beans. Humans are not able to synthesize this vitamin, hence it must come from dietary sources. Folic acid is the synthetic form of folate and has higher bioavailability because it is non-conjugated and hence more stable. Folic acid is used in supplements and added to fortified foods. Several mechanisms have been suggested for its role as a preventer of carcinogenesis though molecular processes such as DNA synthesis, repair and methylation (104, 105). A recent study suggested that folate receptors may be involved in the molecular process of systemic metastasis of pancreatic cancer (106). Epidemiological studies suggest that increased intake of folate from food, may be associated with a reduced risk of pancreatic cancer (104). Many studies examined the relationship between pancreatic cancer and total, diet-derived, supplemented and serum folate. The Swedish Mammography Cohort and the Cohort of Swedish Men study showed that total folate was inversely-associated with risk of pancreatic cancer (107). A study of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort showed an inverse relationship in women only (108). Total folate intake was not associated with the risk of pancreatic cancer in either men or women in the NHS, Health Professionals Follow-up Study (HPFS) and Netherlands cohort study (109, 110).

Regarding folate supplementation, the HPFS, NHS, PLCO and Swedish Mammography Cohort and the Cohort of Swedish Men found no association between supplemented folate and pancreatic cancer (107, 108, 110).

Prospective nested case-control studies showed inconclusive results for serum folate levels. Stolzenberg-Solomon *et al*. suggested that maintaining an adequate folate status may reduce the risk of pancreatic cancer (111) whereas Schernhammer *et al*. reported no significant reduction in the risk of pancreatic cancer (112). A nested case-control study within the EPIC cohort recorded a U-shaped association between plasma folate and pancreatic cancer risk (113).

Conclusion: Increased intake of folate from food sources may be associated with a reduced risk of pancreatic cancer.

Vitamin D and calcium. Vitamin D is one of the fat-soluble vitamins and more than 90% is synthesized endogenously from skin exposure to ultraviolet sunlight. The remaining comes from the diet as pro-vitamin cholecalciferol (D3), which is found naturally in oily saltwater fish, egg yolk and liver, as well as from plant-derived pro-vitamin ergocalciferol (D2) found in foods such as mushrooms. Food fortification may provide an extra source of vitamin D. There are two major pro-vitamins, ergocalciferol and cholecalciferol. The active form of vitamin D is 1,25- dihydroxyvitamin D_3 (calcitriol), which is formed by hydroxylating the pro-vitamins in the liver and kidneys. The use of calcitriol in experimental studies has been shown to induce differentiation and inhibition of tumour cell proliferation of various types of cancer cells, however, its use is limited due to development of toxic hypercalcaemia. For this reason, calcitriol analogues are instead usually used (114).

In vitro and *in vivo* studies showed that normal and malignant pancreatic ductal cells express the 1α-hydroxylase enzyme (115). Vitamin D and its analogues can induce apoptosis (116, 117) and inhibit cell growth (115, 117) and cell proliferation (115, 116).

Similar to findings from studies examining the aetiology of colorectal cancer, show that sunlight exposure is associated with reduced risk of pancreatic cancer (118). Ecological studies have shown an inverse association between North-South of the globe and the incidence risk of pancreatic cancer (119-121), as well as greater mortality with increasing distance from the equator (122).

Studies have shown truly conflicting results on the association of vitamin D with pancreatic cancer.

A case-control study showed that dietary intake of vitamin D was associated with an increased risk of pancreatic cancer in men (123). Prospective cohort studies examined associations between dietary intake of vitamin D and calcium and subsequent risk for pancreatic cancer. Higher intakes of vitamin D (more than 600 IU per day) was associated with lower risk of pancreatic cancer (124, 125). An inverse relationship was also demonstrated in other prospective studies (126). In a Finnish cohort, male smokers with higher 25-hydroxyvitamin D3 concentrations had a 3-fold increased risk of pancreatic cancer. Seasonal variations were detected in the result sub-analysis (127). Analysis of the data from the PLCO cohort showed a weaker association between hydroxyvitamin D3 concentrations and pancreatic cancer but the increased risk among participants with low residential UVB exposure was similar (128). A pooled nested case-control study of participants from 8 cohorts showed that high serum levels of 25-hydroxyvitamin D3 were associated with a statistically significant 2-fold increase in the overall pancreatic cancer risk (129). Liu *et al*. examined, more recently, the results of 9 studies in a meta-analysis and reported that dietary vitamin D or circulating concentrations of 25-hydroxyvitamin D are not associated with the risk of pancreatic cancer (130). A phase II trial showed increased time-to-progression when oral calcitriol with docetaxel were given to patients with locally advanced or metastatic pancreatic cancer (131).

Conclusion: There is no recommendation (unless in cases of vitamin D deficiency) for additional vitamin D supplementation in patients with pancreatic cancer.

Other micronutrients. Antioxidants might protect against pancreatic carcinogenesis since they have been reported to reduce oxidative DNA damage and genetic mutations (132).

The recent Vitamins and Lifestyle (VITAL) study investigated the association between some known antioxidants agents (β-carotene, lutein plus zeaxanthine, lycopene, vitamin C, vitamin E, selenium, and zinc) and risk of pancreatic cancer, and no strong evidence of an association with the intake of the studied antioxidants was observed, other than with selenium (133).

A recent study of the EPIC cohort in the United Kingdom indicated that high intake of selenium was associated with a reduced risk of pancreatic cancer (134) and these findings have been confirmed by two further studies which have described an inverse association between biomarkers of selenium and pancreatic cancer (135, 136).

Inverse or no association have been observed with high total intake of vitamins C and E (47, 137). The combination of vitamin C with gemcitabine and erlotinib in patients with metastatic pancreatic cancer was evaluated in a phase I trial, with good observed response to treatment (138). A prospective nested case-control study examining the relationship between vitamin B12 and B6 showed that there might be an inverse relation between circulating levels and pancreatic cancer risk (139). On the contrary, Gong *et al*. report possible increased pancreatic cancer risk with dietary intake of vitamin B12 (140).

There are prospective studies supporting a protective effect of dietary magnesium against type 2 diabetes, including a recent meta-analysis (141). The explanation of this association is that magnesium intake has been reported to improve insulin sensitivity and reduce insulin resistance (142, 143). On the other hand, there is evidence that a high intake of haeme-iron increases the risk of diabetes (144). Iron itself may lead to insulin resistance through oxidative stress, but haeme-iron seems to be more deleterious because it is more easily absorbed than iron (145). In the HPFS, magnesium supplement among overweight men was associated with a 33% reduced risk of pancreatic cancer (146), whereas no association between iron intake and pancreatic cancer risk was found in an exploratory analysis in the United States (30) and in the Netherlands Cohort study (38). Review in the EPIC cohort of total iron and haeme-iron and the risk of pancreatic cancer showed no association during the follow-up period (147).

Lead nickel, cadmium and arsenic have all been positively associated with risk of pancreatic cancer (148).

Conclusion: Selenium supplementation may be beneficial in reducing the risk of pancreatic cancer. Magnesium supplementation might be considered in obese patients at risk of type-2 diabetes mellitus.

Gut microbiota. There is some evidence to suggest the use of probiotics to reduce post surgical complications in patients who have pancreatic surgery (149), but no studies looking at the impact of probiotics on pancreatic cancer risk are available in the literature. We could not identify studies on prebiotics.

Smoking. It has been estimated that more than one in five cases of pancreatic cancer are caused by smoking (150). Smoking has been directly associated with pancreatic carcinogenesis (151) and indirectly as it is an independent risk factor for developing chronic pancreatitis which may predispose to pancreatic cancer (152). Smoking has also been associated with earlier onset of this malignancy (153, 154). A case-report study has estimated that tobacco may be responsible for up to one thirds of all pancreatic cancers (64). The EPIC cohort data revealed that both active cigarette smoking as well as exposure to environmental tobacco smoke is associated with increased risk of pancreatic cancer, and this risk is reduced to the levels of non-smokers five years after quitting smoking (155).

Conclusion: Smoking is associated with the development of pancreatic cancer.

Obesity and physical activity. Physical activity appears to reduce the risk of pancreatic cancer, especially among those who are overweight (156). A systematic review of 28 studies identified a reduction in pancreatic cancer risk with higher levels of total and occupational activity (157). In a systematic review, Aune *et al*., showed that both general and abdominal fatness increases pancreatic cancer risk (158). In a cohort of 720,000 adolescent men risk of pancreatic cancer was higher for individuals with higher body mass index (159).

Conclusion: Reduced physical activity and high body mass index are associated with increased pancreatic cancer risk. Individuals should aim to maintain a healthy body mass index and adequate levels of physical activity.

Menstrual and reproductive factors. Incidence of pancreatic cancer is 30-50% higher in men than women and thus it has been hypothesized that hormonal factors related to oestrogen exposure may be protective against pancreatic cancer (160). Duell and co-workers conducted a prospective cohort analysis of menstrual and reproductive factors and exogenous hormone use in relation to pancreatic cancer risk in the EPIC cohort and none of the menstrual and reproductive factors, with the possible exception of an early age of menarche, were associated with susceptibility to pancreatic cancer (161).

Conclusion: There is no evidence that oestrogen exposure is protective against pancreatic cancer.

Conclusion

There is an abundance of evidence in the literature on the role of nutrition in pancreatic carcinogenesis. Often the evidence is inconclusive due to confounding factors, such as smoking status, physical activity, distance of habitat from the equator, obesity, ABO blood group and diabetes. The lack of large randomized control trials makes it harder to establish causative associations for various nutrient types. In the current review, we set out to identify nutritional factors that might play a role in

Table I. *Summary of current evidence on the relationship between dietary factors and risk of pancreatic cancer.*

1.	Citrus fruits are helpful in reducing the risk of pancreatic cancer.
2.	Consumption of whole grains may reduce pancreatic cancer risk and fortification of whole grains with folate may confer further protection.
3.	Processed red meat or meat cooked at very high temperatures by methods such as frying, broiling or barbequing should be limited to reduce the risk of pancreatic cancer.
4.	Consumption of non-fried fish may reduce the risk of pancreatic cancer.
5.	Intake of total fat and saturated and unsaturated fatty acids may be related to increased risk of pancreatic cancer.
6.	Hyperinsulinaemia, obesity, metabolic syndrome and diabetes have all been linked positively to pancreatic cancer risk, although there is no direct link between refined sugar intake and pancreatic cancer.
7.	Alcohol consumption is associated with a small fraction of all pancreatic cancer, usually in people who consume more units.
8.	There is no association between coffee and pancreatic cancer.
9.	There is no impact of total and green tea on pancreatic cancer.
10.	Curcumin demonstrated antitumour properties and benefit in pancreatic cancer.
11.	Increased intake of folate from food sources may be associated with a reduced risk of pancreatic cancer.
12.	Additional vitamin D supplementation should not be recommended in patients with pancreatic cancer, unless in cases of vitamin D deficiency.
13.	Selenium supplementation may be beneficial in reducing the risk of pancreatic cancer; magnesium supplementation might be considered in obese patients at risk of type-2 diabetes mellitus.
14.	Smoking is associated with the increased risk of pancreatic cancer.
15.	Reduced physical activity and high body mass index are associated with increased pancreatic cancer risk.
16.	There is no evidence that oestrogen exposure is protective against pancreatic cancer.
17.	There are no data on impact of probiotics and prebiotics on pancreatic cancer.

the development of pancreatic cancer (Table I). Fruit (particularly citrus) and vegetables may be beneficial. The consumption of whole grains has been shown to reduce pancreatic cancer risk. Fortification of whole grains with folate may confer further protection as increased intake of folate from food sources, but not from supplements, may be associated with reduced risk of pancreatic cancer. Red meat consumption should be avoided, especially when cooked at high temperatures, and it should be replaced with poultry or fish whenever possible. The use of polypohenols such as curcumin and flavonoids should be encouraged in the diet. There is no evidence for vitamin D supplementation. Alcohol consumption appears to be responsible only for a small fraction of all pancreatic cancers, especially in people who consume more units. Smoking can cause pancreatic cancer both directly and indirectly. Reduced physical activity and high body mass index have both been negatively-associated with pancreatic cancer risk.

Further studies are needed to better clarify the interaction between dietary factors and pancreatic cancer. The results of therapy for pancreatic cancer are very poor and thus there is also an urgent need to understand the possible positive impact of nutrients *e.g.* curcumin in combination with other therapies. This also highlights the need for the development of novel agents that can influence the survival rates and quality of life for the patients. Randomized trials for supplements are recommended but difficult to design and perform because of confounding factors.

Conflicts of Interest

None.

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