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Systematic Review

A Systematic Review of Environmental Risk Factors for Pancreatic Cancer

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ABSTRACT

Background :
More than 250,000 people die annually of pancreatic cancer, worldwide. The highest incidence and mortality rates of pancreatic cancer are reported in developed countries. In developing countries the rate have been stabilizing over the past two decades but in countries which rates have been low for decades is now increasing. Recognizing pancreatic cancer's risk factors and its prevention are important roles in reducing pancreatic cancer mortality. Risk factors for pancreatic cancer are not well recognized. The aim of the study is to review the environmental risk factors of pancreas cancer.

Materials and Methods:
We performed a systematic review of the published literature to identify all studies that provided environmental risk factors in association with pancreatic cancer .we conducted MEDLINE search limited to last 5 years up to June 2011, for all relevant case –control, meta analysis, systematic review and cohort studies. Citations were limited to those published in the English language. Review and comment articles have been excluded.

Results:
Sixty six independent studies met the predefined inclusion criteria. Seven studies out of 15 found positive association between cigarette smoking and pancreatic cancer.Five articles out of 10 reviewed articles found high alcohol intake as a risk factor for pancreas cancer and the other 5 articles found dose related association with pancreas cancer. Coffee: according to 2 reviewed studies coffee not only does not have a substantial impact on pancreatic cancer risk but also coffee drinking has been associated with a reduced risk of pancreatic cancer in men. Frequent intakes of red meat and well-cooked meatand Vitamin D deficiency have positive association with pancreatic cancer risk.

Conclusion:
Cigarette smoking is the most consistent risk factor for pancreas cancer in relevant studies about pancreas cancer risk factors.

Keywords: Pancreas cancer; Neoplasm; Risk factor
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BACKGROUND

Worldwide, more than 250,000 people die annually of pancreatic cancer with the highest incidence and mortality rates in developed countries. Pancreatic cancer is the fourth leading cause of cancer death in the United States and the sixth in Europe. Pancreatic cancer is the eighth most frequent cause of cancer death and the 13th most common cancerworldwide (1). In the Middle Eastand Asia, pancreatic cancer is not among the top ten cancers, however there is a possibility of underreported findings. Diagnostic modali-

ties, equipment, experience in determining the exact diagnosis of pancreas cancer (PC), in addition to obtaining tumor tissue are expensive and not available in many towns of developing countries.

the high fatality rate of pancreas cancer makes the incidence rates of pancreatic cancer equal to its mortality rates (1). Due to the lack of effective screening diagnostics, most patients present with metastatic or advanced disease, which are inoperable. Pancreatic cancer has one of the highest mortality rates of all cancers, with a median survival of three to six months, due to the lack ofeffective therapeutic treatment options(2). Treatment has not improved significantly during the past few decades and is still ineffective in prolonging survival(2). Therefore, recognizing pancreatic cancer‘s risk factors and its prevention are important roles in reducing mortality worldwide.

Environmental factors seem to play a major role in the etiology of pancreatic cancer as rates and time trends vary in different countries. In countries with high pancreatic cancer rates, the rates have been stabilizing over the past two decades whereas in countries where rates have been relatively low for four decades, such as in Japan, they continue to increase(3).

Pancreatic cancer risk factors are not well-known. Studies on this cancer have methodological problems, thus the risk factor findings have been inconsistent.

The aim of the study is to review the environmental risk factors of pancreas cancer.

MATERIALS AND METHODS

We performed a systematic review of the published literature to identify all studies that provided environmental risk factors in association with pancreatic cancer. We conducted a MEDLINE search limited to the previous five years (until June, 2011) for all relevant case–control, meta analyses, systematic reviews and cohort studies. The following medical subject headings (MeSH) or keywords were used: pancreatic cancer, pancreatic tumor, pancreatic neoplasm and risk factor. Citations were limited to English language publications. Reviewand comment articles were excluded. We only included the human studies. Excluded were genetic risk factors.

Study selection

Two reviewers separately assessed studies for inclusion using “priori-defined criteria”. To assess for potential association, case control, cohort and meta-analysis, studies were selected for inclusion.

Data extraction and quality assessment

A standardized data extraction tool was used to extract study data. Obtained data from each study included study design, inclusion and exclusion criteria, methodological quality criteria, study population, and data related to the primary outcomes.

Study characteristics

There were 66 independent studies that met the predefined inclusion criteria. The numbers of studies to relevant risk factors are as following: Smoking; 15, Alcohol; 10, Coffee; 2,Vitamin D ;11, medication;5, Diet ;17,Folate ;3, Fe-Mg ;1, Physical Activity ;5, Water;2,Vitamin E ;1,Methionine ,Vitamin B6;3 .

RESULTS

Smoking

We reviewed 15 articles regarding smoking (active and passive) and pancreatic cancer (4-18), of which ten were cohort, four were case-control, one meta-analysisand one was a systematic review.

Out of the 15 studies, 8 have found a positive association between active cigarette smoking and risk of pancreatic cancer(4-11). Among these 8 studies a prospective cohort study with 465,910 participants(8), a case-control study from Italy with326 cases and 652 control(7) and hospital based case-control with 808 patients(11) have been reviewed. Regarding passive smoking, twocase-control studies and one cohort did not support any role for passive smoking in the etiology of pancreatic cancer. The cohort study was done in Netherland with a population of 120,852 men and women has found no association between passive smoking exposure and pancreatic cancer risk, particularly among women(6).Three studies regarding environmental tobacco smoke (ETS) and maternal smoking found positive association between pancreas cancer and ETS and maternal smoking. Two prospective cohort studies,one with 465,910 partcipantsand the other study was a prospective study from USA examined 86,673 women,both of these studies have found that maternal smoking and exposure to ETSto be positively associated with pancreas cancer(8,12) another prospective study done in UK reviewed 8,372 cancer cases among 112,430 never smoker population, hassuggested that childhood environmental tobacco smokeexposure is a major risk factor for pancreatic cancer (13).A prospective cohort study from Japan studied 30,826 inhabitants, has proposed that smoking increases the mortality rate among female Japanese pancreatic cancer patients(14).According to

one prospective study done in US with 29,239 confirmed adenocarcinoma cases of pancreas cancer, the age at diagnosis of pancreas cancer for smokers is significantly younger compared with non-smokers(15).

Alcohol

Ten articles (7,8,14,16,19-24) (8 cohort studies; 1 meta-analysis; and 1 case-control) were included in this systematic review.

Of these, five articles have been found high alcohol intaketo be a risk factor for pancreas cancer(7,8,19-21). One study was a pooled analysis of fourteen cohort studies undertaken in the US, their study population consisted of 862,664 individuals from which 2187 incidental pancreatic cancer cases were identified. In this study a minimal positive association has been observed between pancreatic cancer risk and alcohol intake. According totwo other studies, no significant association was observed among different alcoholic drinks such as wine, beer, and spirits, as well as the amount of alcohol consumed and pancreatic cancer(22,23). On the other hand, one meta-analysis which included 33 case-control and cohort studies has suggested that the amount of drink may change the result. The study provided strong evidence to confirm no role for moderate drinking in pancreatic cancer, whereas heavy alcohol consumption may increase the risk(24).according to one prospective study from US with 1,030,465 population and 6847 pancreatic cancer death among has found drinking liquor, three or more drinks per day, increased pancreatic cancer mortality rate without any dependency on smoking but this association has not been reported for beer or wine(20).Regarding the age at diagnosis, either a history of past or current alcohol consumption both have been found to be associated with a younger age at diagnosis(19).

Coffee

We reviewed two studies regarding coffee intake and pancreatic cancer. One study was a meta-analysis of cohort studies performed in China. This meta-analysis included 14 studies and 671,080 individuals (1496 cancer events), compared the individuals who drank 1cup/day withthe population who did not drank or seldom drank coffee daily. The other study was a large population-based cohort study from Japan (JPHC study) in which 102,137 participants. Both of these studies supported the idea that not only green tea or coffee consumption did not have a substantial impact on pancreatic cancer risk but also a reduced risk of pancreatic cancer by coffee drinking has been reported among men who drank at least three cups of coffee per day (25,26).

Water

We reviewed 2 case-control studies regarding water hardness and nitrate. A case-control study from Taiwan suggested that magnesium (Mg+2) intake modified the relationship between risk of pancreaticcancer and total trihalomethane (TTHM) levels in public water supplies, whereas calcium (Ca+2) levels in drinkingwater did notmodify the effect on TTHM and risk regarding of developing pancreaticcancer(27).Regarding nitrate exposure from water we reviewed a case-control done in Taiwan. The study found no statistically significant association between the levels of nitrate in drinking water and increased risk of pancreaticcancer(28).

Medication

We included five studies that investigated the association between medications and pancreatic cancer (3 case-controls; 2 meta-analyses)(29-33). Two out of five studies observed no association between statins and the risk of pancreatic cancer. Statins did not affect the risk of pancreatic cancer, either by dose, duration or type of statin (simvastatin vs. atorvastatin) (29,30).A nested case-control study from US suggested a reduction in risk using statins that depended on dose or the duration of taking the medicine. In this study, 163,467 patients out of 483,733 were on statins. Of these, 475 had a primary diagnosis of pancreatic cancer. In 67% of these patients (adjusted OR: 0.33) a risk reduction by statin usage for more than six months has been observed(31).

In two studies, the effect of acetylsalicylic acid/ Nonsteroidal anti-inflammatory drugs (ASA/ NSAIDs) on the risk of pancreatic cancer showed no association between pancreas cancer(32,33) however there have been some evidences of reduced pancreatic cancer risk with long-term use (five years or more) of lower doses of NSAIDs (OR: 0.70)(32).

Diet

There were 17 articles haveb been included regarding correlation between diet and risk of pancreatic cancer (15,34-49). We reviewed this topic under 3 subtitle as following:

Meat

We reviewed four studies (1 cohort, 3 case-con-

trols) on meat and pancreatic cancer(34-37). All four studies have found positive correlation between red meat intake and meat cooked at high-temperatures with pancreatic cancer. In addition, frequent meat consumption may increase the risk of pancreatic cancer up to two-foldalso a significantassociation between risk of pancreas cancer and meat cooked by boiling, stewing, broiling, and roasting has been found (37).

Vegtable

we reviewedd 6 studies 4 case-control and 2 cohort studies regarding vegetable and pancreas cancer. Four of these six studies(15,36,38-41) have suggested that more vegetable consumption has an inverse effect on pancreatic cancer risk. One of these five studies was a case-control study from Canada with 179 pancreas cancer case and 239 control this study has also found vegetable consumption reduces the risk of pancreas cancer(15).Only one case-control study from Italy with 326 cases and 652 controls, has found no significant association between vegtable consumption and risk of pancreas cancer(36).

Sugar and Soft Drinks

Nine studies have been reviewed(34,42-49). Three studies support that sugar consumption increases the risk of pancreas cancer and 4 studies have found no association between pancreas cancer and sugar consumption. The role of dietary glycemic load(GL),glycemic index(GI)and consumption of added on pancreas cancer risk was the topic of two large cohort studies from US with total population of 640000. Their results showed no adverse effect added sugar on the risk of pancreas cancer(34,42) whereas The results of one prospective study from Sweden which has 77,797 population has showed that higher sugar intake is associated with higher pancreas cancer risk(44).

Two studies found no significant association between juice and soft drink consumption with pancreatic cancer risk(48,49) and one study found a significant association between low-calorie soft drinks and increased risk only among men. Among the three sugars (lactose, fructose, and sucrose), only lactose has been found to be associated with pancreatic cancer risk(48).

Vitamin E

According to one cohort study from USA serum concentration of alpha-tocopherol (C29H50O2) which is a form of vitamin E an inverse association with the risk of pancreatic cancerhas been shown even itsprotective role on pancreatic cancer in smoker male patients has been observed(50).

Flavonol,Methionine,Vitamin B6

Under this topic 3 articles have been reviewed(51-53). According to one multiethnic cohort study from USA which had 183,518 participants, intake of flavonols reduces pancreatic cancer risk and additionally protective effect for current smokers has been shown(50). One of the two studies which focused on intake of methionine, found a significant inverse association between pancreatic cancer, the higher methionine intake reduces the risk of pancreas cancer risk(51). According to the second study's results, a population based case-control study from USA, no association was found between intake of vitamin B6 or methionine and pancreatic cancer risk(52).

Folate

There were three studies we reviewed regarding this topic. Two of these thress studies found that folate and B12 intake decreased pancreatic cancer risk(53,54).One study, has found no protective role of total dietary folate or individual folate vitamins on the risk for pancreatic cancer(52).

Iron/magnesium supplements

The cohort study we reviewed about this topic was a prospective study from UK with 851,476 population, 20 years of follow up , 300 pancreatic cancer cases have been documented among this population. The study was done among men population. According to this study no significant association has been found between iron or magnesium supplement use and decreasing pancreatic cancer risk. Whereas in subjects with a body mass index of ≥25 kg/m2 a statistically significant inverse relationship only between magnesium intake and pancreatic cancer risk has been found but the same association between Iron and over weight pancreas cancer cases has not been proven(55).

Vitamin D

Eleven articles (9 cohorts, 2 case-controls) have been included in our systematic review study(56-65). Of these, seven showed a significantpositive association between high circulating 25(OH)D concentration(≥100 nmol/L) which is an indicator of vitamin D derived from diet and sun with pancreatic cancer risk. Annual residential solar UBV (Ultraviolet B ir-

radiance) exposure caused an increase in pancreatic cancer with significant mortality(56-58).Whereas another study from the US examined UVB (Ultraviolet B) irradiation and worldwide incidence rates of pancreatic cancer. Incidence rates have been noted to be greater at higher altitudes whereas ultraviolet B radiation was independently inversely associated with the pancreatic cancer incidence in men (p<0.01) and women (p=0.02)(59). According to a cohort study done in Japan which was reviewed regarding global solar radiation and mortality rate of pancreas cancer, number of deaths and demographic data from 1998 to 2002 have been used for the calculation of SMR(standardized mortality ratio).Increased daily maximum temperature or amount of global solar radiation has been found to be significantly related to decreased SMRs for pancreatic cancer(60).

According to only one study in men, dietary vitamin D intake levels is related to pancreatic cancer risk (highest intake ≥450 IU/day vs. lowest intake <150 IU/day; OR = 2.6)(61).Regarding Vitamin D seven studies support Vitamin D decreases risk of pancreas cancer and one study supports Vitamin D intake increases the risk. Three studies found that UBV increases the rate and one study found an inverse association, the rate of pancreas cancer has been found higher in higher altitude.

Physical activity

Five articles have been reviewed(10,66-69). In four, no significant association has been found between physical activity and pancreatic cancer(10,66-67). Only one study has found a decreased risk of pancreatic cancer which was suggestively related to increased physical activity(69).

CONCLUSION

About 55% of known pancreatic cancer patients have inappropriate nutritional habits and about 35% of this group has a history of tobacco use.These are consistent findings but regarding other risks,more date are required.

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