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Cancer

Risk factors for pancreatic cancer: a summary review of meta-analytical studies

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Abstract

Background: The aetiology of pancreatic cancer (PC) has been extensively studied and is the subject of numerous meta-analyses and pooled analyses. We have summarized results from these pooled and meta-analytical studies to estimate the fraction of PCs attributable to each of the identified risk factors.

Methods: Using a comprehensive strategy, we retrieved 117 meta-analytical or pooled reports dealing with the association between specific risk factors and PC risk. We combined estimates of relative risk and estimates of exposure to calculate the fraction of PCs caused or prevented by a particular exposure.

Results: Tobacco smoking ('strong' evidence) and *Helicobacter pylori* infection ('moderate' evidence) are the major risk factors associated with PC, with respective estimated population attributable fractions of 11–32% and 4–25%. The major protective factors are history of allergy ('strong' evidence) and increasing fruit or folate intake ('moderate' evidence), with respective population preventable fractions of 3–7% and 0–12%.

Conclusions: We summarized results of 117 meta-analytical or pooled data reports dealing with 37 aetiological exposures, to obtain robust information about the suspected causes of PC. By combining these estimates with their prevalences in the population, we calculated population attributable or population preventable fractions. About two-thirds of the major risk factors associated with PC are potentially modifiable, affording a unique opportunity for preventing one of our deadliest cancers.

Key words: Pancreas cancer, risk factors, meta-analysis, pooled analysis, population attributable fraction, review

Key Messages

- This report, by summarizing 117 meta-analytical or pooled studies representing thousands of patients, provides robust estimates of causative or preventive risk factors for pancreatic cancer.
- It identifies areas where future research is likely to be rewarding.
- It confirms that nearly two-thirds of the known causes of this deadly cancer are potentially avoidable.

Introduction

Because of its poor prognosis, pancreatic cancer (PC) is one of the four or five most common causes of cancer mortality in developed countries and is emerging as a growing health problem in less developed countries.[1] The incidence of PC varies greatly across regions and populations, suggesting roles for genetic factors, lifestyles and environmental factors. Since PC is strongly age-dependent, increasing longevity will lead to an increase of the global burden of PC in coming decades.[2]

Each year, more than 500 new articles are published on the epidemiology of PC, with many reports focusing on aetiology. Often these studies are small, limiting the ability to identify moderate associations or to study infrequent risk factors. Recently, meta-analysis has become a popular way to combine individual studies, allowing researchers to identify patterns and to study sources of heterogeneity.

Meta-analytical procedures are, however problematic if the individual studies use different analytical methods or define variables differently. To overcome these difficulties, investigators can pool original data from several studies and then analyse the combined dataset. Such pooled analyses theoretically provide more reliable summary risk estimates than meta-analyses, since the pooled data standardize individual variables allowing for better control of potential confounding.

Until recently, most epidemiological reviews were based on a comprehensive assessment of original published reports, allowing only large or significant associations to be trusted. Additional information from meta-analyses and from pooled analyses changed that situation; today, almost every possible aetiological factor for PC has been the subject of one or more meta-analyses or pooled analyses. The aim of this review was to retrieve, review and summarize results from pooled analyses and meta-analyses in order to estimate the fraction of PCs attributable to many different risk factors.

Methods

We performed a comprehensive review of the literature using PubMed, Google Scholar and ISI Web of Knowledge (Science Citation Index Expanded). We searched for meta-analytical studies on the association between specific risk factors and PC risk or multiple cancer sites, published up to 31 October 2014.

Search terms included: *(Pancreatic cancer [MeSH])* AND *(Meta-analysis* OR *Pooled-analysis* OR *Review)* AND *(Risk factor[MeSH])*. We then repeated the search, substituting (*Risk factor[MESH])* with specific risk factors such as: *tobacco*, *alcohol*, *height*, *weight*, *diet*, *aspirin*, *etc.* We checked titles and abstracts and retrieved pertinent information from the full text of relevant studies. We also reviewed additional articles listed in the bibliography of retrieved publications.

For each single exposure, we averaged the risk estimates reported in all available meta-analyses and pooled analyses; we could not apply a pooling technique since results from the same studies were often included in more than one meta-analysis. From the study reports or from external sources of information such as the *Global Burden of Disease* report,[3] we estimated the range of the population fraction exposed to these risk factors in representative regions. We also assessed qualitatively the strength of evidence of the various associations: qualifying as 'strong', evidence based on more than one meta-report, confirmed in cohort studies or by a pooled analysis; qualifying as 'moderate', evidence based on either more than one meta-report or on a single meta-report of cohort studies; and qualifying 'poor', evidence based on a single meta-analysis not exclusively based on results from cohort studies or in case of discordant results.

For dichotomous exposure (such as tobacco smoking), we calculated the population attributable fraction ($PAF = Pe(RRe\text{-}1) / [1 + Pe(RRe\text{-}1)]$), i.e. the fraction of PCs attributable to exposure.[4] In case of protective factors (such as allergy), we calculated the population preventable fraction ($PPF = Pe(1\text{-}RRe)$), i.e. the fraction of PCs that could be avoided if it was possible to expose everyone to this protective factor.[4] For continuous variables (such as red meat intake or fruit intake), we calculated the potential impact fraction ($PIF = (Pe–P^*)(RRe\text{-}1) / [1 + Pe(RRe\text{-}1)]$), i.e. the fraction of PCs attributable (or preventable), shifting exposure from one quintile to the next quintile.[5]

Results

The overall study results are summarized in Table 1, with individual results from the 86 published meta-analyses and 31 pooled analyses available in Supplementary Tables 1a–h (available as Supplementary data at *IJE* online).

Tobacco

Tobacco (Supplementary Table 1a) is the most well-established risk factor for PC. In a comprehensive meta-analysis of 47 case-control and 35 cohort studies, Iodice *et al.*[6] calculated the respective summary risk estimates for current and former smokers to be 1.7 and 1.2. A previous pooled analysis of 30 cohort studies from the Asia-Pacific region,[7] a subsequent pooled analysis of data from three Japanese cohorts,[8] a nested case-control study from eight cohort studies,[9] a meta-analysis of three case-control and four cohort studies conducted in Japan[10] and a pooled analysis of individual data from 12 case-control studies[11] confirmed these results, with summary relative risk (SRR) between 1.6 and 2.2 for current smokers and between 1.1 and 1.2 for former smokers. In a recent meta-analysis based on 42 observational studies, Zou *et al.*[12] reported a non-linear dose–response association for smoking intensity. The strength of evidence is 'strong' and justified by the numerous reports showing a positive association, the consistency of findings in those based on case-control and cohort studies, and the further confirmation of the association in pooled analyses of individual data.

Risk estimates for other forms of tobacco exposure are available. For example, PC risk was elevated for persons who only smoke cigars (SRR = 1.6), but not for exclusive pipe smokers (SRR = 1.1).[13] Although smokeless tobacco, including snuff and chewing tobacco, and environmental tobacco smoke exposure have been associated with increased PC risk in some studies, results from meta-analyses are either discordant or negative.[14–17]

Alcohol

In the past, consuming alcohol was not considered an important risk factor for PC (Supplementary Table 1a). However, recent studies based on persons who consume relatively large amounts of alcohol provide evidence that moderate or heavy drinking can increase the risk for this tumour. Results from meta-analyses and pooled analyses consistently show that daily consumption of ≥30 g of alcohol, or the equivalent of >3 glasses of any alcoholic beverage per day, is associated with a 20% increased risk of PC.[18–21] The evidence is 'strong'.

Coffee and tea

Neither tea nor coffee consumption seem to be associated with PC risk (Supplementary Table 1a) despite the results from a meta-analysis of 14 cohort studies that pointed to an inverse association with regular coffee drinking and the results from another meta-analysis that indicated an inverse association with tea consumption only in China.[22–26] However the protective effects of coffee or tea against PC was not found in a large study based on pooled data from 14 different cohort studies.[25]

Other environmental exposures

Summary risk estimates for the principal jobs and occupational exposures associated with PC are presented in Supplementary Table 1b. Four meta-analyses summarized results from almost 100 studies published on the topic.[27–30] The strength of evidence is however 'poor', as pooled risk estimates rely on a very limited number of exposed cases in each single study. Exposure to chlorinated hydrocarbon solvents and related compounds are major occupational risk factor for PC, with SRRs ranging from 1.4 to 2.2.[29,30] Metal plating workers, and in particular those exposed to nickel, are associated with a 2-fold increased risk of PC; formaldehyde exposure causes a modestly increased risk (SRR = 1.1) of PC.[27] Two other meta-analyses based on risk estimates from, respectively, 13 and 4 independent studies, found no association between occupational exposure to diesel exhaust or methylene chloride and PC.[31,32]

Two pooled analyses and a single meta-analysis studied the association between circulating 25-hydroxyvitamin D [25(OH)D] level and PC risk. The first pooled analysis found no association with lower 25(OH)D status but a 2-fold increased risk for those with a high concentration (≥100 nmol/l),[33] whereas the second pooled analysis demonstrated a 30% risk reduction associated with high 25(OH)D levels.[34] In the single meta-analysis based on nine studies, the authors found no association with either increased dietary vitamin D or circulating concentrations of 25(OH)D.[35] Overall, the strength of association between circulating vitamin D and PC is 'poor'.

Anthropometric measures and physical Activity

Tall or obese people are known to have an increased risk for several cancers (Supplementary Table 1c). A pooled analysis of 14 cohort studies,[36] a meta-analysis of 10

Table 1. Summary of the associations between risk factors and pancreatic cancer reported in published 86 meta- and 34 pooled-analyses

Degree of association	Risk factors	Number of published meta/ pooled-analyses[a]	Number of reports showing			Strength of association (or lack of association)				
			Inverse association	Null association	Positive association	Grade[b]	Association confirmed in several reports	Association confirmed in cohort studies	Association confirmed in pooled analyses	*Note*
High risk (RR ≥2.0)	History of chronic pancreatitis	1/1	–	–	2	++	Yes		Yes	
	History of idiopathic thrombosis	1/0	–	–	1	0	No			
Moderate risk (RR 1.5-1.9)	Tobacco smoking	3/5	–	–	8	++	Yes	Yes	Yes	
	Diabetes mellitus	7/7	–	–	14	++	Yes	Yes	Yes	
	Use of antidiabetic drugs other than metformin	4/1	–	1	4	++	Yes	Yes	Yes	
	Family history	1/1	–	–	2	++	Yes	Yes	Yes	
	Metabolic syndrome	2/0	–	–	2	0	No			The 2 reports are very similar
Low risk (RR 1.1-1.4)	Obesity (high body mass index)	5/5	–	2	8	++	Yes	Yes	Yes	No association in Asians, stronger in women
	Hepatitis B virus infection	5/0	–	1	4	++	Yes	Yes		
	Non-O blood group	2/1	–	–	3	++	Yes	Yes	Yes	
	Heavy alcohol intake	1/3	–	1	3	++	Yes	Yes	Yes	
	Tallness (height)	1/3	–	2	2	++	Yes		Yes	
	High waist-to-hip ratio	1/1	–	–	2	++	Yes		Yes	
	Helicobacter pylori infection	4/0	–	–	3	+	Yes			Heterogeneous definitions
	History of gastrectomy	1/1	–	–	2	++	Yes	Yes	Yes	
	History of cholecystectomy	1/0	–	–	1	+	No	Yes		
	High waist circumference	1/1	–	1	1	0	No		No	Only cohort studies included
	Hepatitis C virus infection	2/0	–	1	1	0	No			
	Red meat	2/0	–	1	1	0	No	No		
	Processed meat	1/0	–	–	1	0	No			
	Elevated sugars intake	1/0	–	–	1	0	No			
No association (RR = 1.0)	Aspirin / NSAIDS use	4/1	–	5	–	++	Yes	Yes	Short-term use	Possible association with long-term use
	Statins use	2/0	–	2	–	++	Yes	Yes		

(Continued)

Table 1. Continued

Degree of association	Risk factors	Number of published meta/pooled-analyses[a]	Number of reports showing			Strength of association (or lack of association)				
			Inverse association	Null association	Positive association	Grade[b]	Association confirmed in several reports	Association confirmed in cohort studies	Association confirmed in pooled analyses	*Note*
	Fish consumption	2/0	–	2	–	++	Yes	Yes		
	Soft drinks consumption	1/1	–	2	–	++	Yes		Yes	
	Coffee consumption	2/1	1	2	–	++	Yes	Yes	Yes	Discordant results
	Tea consumption	1/1	–	2	–	++	Yes	Yes	Yes	Possible association in China
	Smokeless tobacco use	3/0	–	2	1	+	Yes			
	Glycaemic index	5/0	–	5	–	+	Yes			
	Glycaemic load	5/0	–	5	–	+	Yes			
	Plasma 25(OH)D level	1/2	1	1	1	0				Discordant results
	Environmental tobacco smoke exposure	1/0	–	1	–	0	No			
Low to moderate protection (RR 0.5-0.9)	Allergy	1/1	2	–	–	++	Yes		Yes	
	Metformin use (for diabetics)	4/0	2	2	–	+	Yes			
	High adiponectin level	0/1	1	–	–	+	No		Yes	
	Intense occupational physical activity	2/0	2	–	–	+	Yes			
	High dietary folate intake	3/1	3	1	–	+	Yes	No	No	
	High fruit consumption	2/1	2	1	–	+	Yes	No	No	
	High vegetables consumption	1/1	1	1	–	0	No	No	No	

[a]Number of published meta-analyses and pooled analyses by 31 October 2014; study details are available in Supplementary Tables 1a–h, available as Supplementary data at *IJE* online.
[b]'Strong' evidence (++); 'moderate' evidence (+); 'poor' evidence (0).

cohort studies[37] and a pooled analysis of 121 prospective studies[38] demonstrated an association with PC which translates into a 7–8% increased risk per 5-cm increase in height, but no association was found in a pooled analysis of 30 cohorts from the Asia-Pacific region.[7] Similarly, five meta-analyses and five pooled analyses reviewed the association between body mass index (BMI) and PC.[7,36,39–46] Apart from those from the Asia-Pacific region,[7] overweight and obese people had, respectively, a 10% and a 20% increased risk of PC compared with people of normal weight ('strong' evidence). A five-unit increase in BMI was associated with approximately a 10% excess PC risk. Other anthropometric measures such as waist circumference or waist-to-hip ratio were associated with excess PC risk.[36,43] A nested case-control study using pooled data from five cohort studies also demonstrated a protective effect of adiponectin: adiponectin $\geq$4.4 μg/ml being associated with ~40% risk reduction.[47] Two meta-analyses reviewed the association between several forms of physical activity and PC risk.[48,49] Occupational physical activity emerged as a protective factor whereas no association was found with other forms of physical activity. The strength of the association is only 'moderate' because the findings were neither based on meta-analyses of cohort studies nor validated in pooled analyses.

Diet

Diet is a suspected aetiological factor for cancer in general and has been subject of thousands of epidemiological studies (Supplementary Table 1d). Two meta-analyses[50,51] and one pooled analysis of 14 cohort studies[52] summarized the association between fruit and vegetable intake and PC risk. Results from case-control studies are consistent with a protective role of fruits (particularly citrus fruits) and vegetables on PC risk, with risk reduction ranging from 30% to 40% for high vs low consumption. In contrast, results from cohort studies demonstrate no association between either fruit or vegetable intake and PC risk. Two meta-analyses summarized the association between meat and PC risk:[51,53] intake of red meat was associated with increased PC risk only in case-control studies. In cohort studies, however, increased consumption of processed meat (50 g/day) was responsible for a 20% increased risk of PC.[53] No association was observed with fish consumption in two meta-analyses.[51,54]

The association between dietary folate and PC risk has been subject of three meta-analyses[55–57] and a nested case-control study based on pooled data from 14 cohort studies.[58] Somewhat discordant results were reported, with risk reduction observed in the three meta-analyses and no association in the nested case-control study.

A meta-analysis[59] and a pooled analysis of 14 cohort studies[25] evaluated the association between soft drink consumption and PC risk. In both studies, consumption of $\geq$250 g/day was associated with a modestly increased risk (15–20%), but of borderline statistical significance.

Finally the association between glycaemic index, glycaemic load and PC risk has been extensively studied and summarized in five meta-analyses.[60–64] Whereas no association was found in any of the reports, high fructose intake appeared to be associated with PC in a meta-analysis based on data from 10 cohort studies but the potential association was only modest (20% excess risk for an increased consumption of 25 g of fructose/day).[63]

The strength of association is only 'moderate' or 'poor' for most dietary items, mainly due to the lack of confirmation of the associations in pooled analyses of data from cohort studies.

Past medical history

Many medical conditions have been associated with PC risk (Supplementary Table 1e). Diabetes (or impaired fasting blood glucose) has been the subject of the largest number of reviews. At least seven meta-analyses[65–71] and seven pooled analyses[7,72–77] have been performed recently. All studies are concordant ('strong' evidence), showing that long-term diabetes is associated with at $\geq$50% increased risk of PC; results are similar for individuals with metabolic syndrome, although based on few reports.[78,79]

A meta-analysis[80] and a pooled analysis of case-control studies[81] demonstrated an association between pancreatitis and PC, SRR = 2.7, for studies where the type of pancreatitis (acute or chronic) was ill-defined. For studies based on patients with established chronic pancreatitis, the SRR ranged from 5.0 for long-standing chronic pancreatitis, to $\geq$70 for hereditary or tropical pancreatitis.[80]

A history of cholecystectomy appears to be associated with a 23% increased risk of PC,[82] and gastrectomy appears to be associated with a 50% increased risk of PC, in results from case-control and cohort studies.[83,84] The association with gastrectomy is supported by three meta-analyses that reported an association of similar magnitude between *Helicobacter pylori* infection and PC risk.[85–87] Such association was however not confirmed in another recent meta-analysis.[88]

Although a formal meta-analysis was not performed, a systematic review revealed that an association between periodontal diseases and PC has been found in most studies performed on this topic.[89]

Unexplained thromboembolic events have also been associated with an increased risk of cancer, particularly cancer of the pancreas, but the strength of evidence is only

'poor'.[90] Conversely, based on evidence from one meta-analysis[91] and one pooled analysis,[92] there is 'strong' evidence that atopic allergy or hay fever reduces the risk of PC by 20–30%.

Finally, five meta-analyses summarized the association with hepatitis B virus (HBV) infection.[93–97] Most reviews reported a positive association, with relative risks ranging from 1.2 to 3.8 according to HBV carrier status. Results from two meta-analyses suggest a positive association (RR = 1.2) between *hepatitis C* virus infection and PC risk.[96,97]

Drugs

Many studies have assessed the possible effect of common drugs, such as aspirin, other non-steroidal anti-inflammatory drugs (NSAIDS), statins or antidiabetic drugs including metformin (Supplementary Table 1f). Unlike aspirin[98–102] or statins,[103,104] that are not or weakly associated with PC risk, metformin use appears to reduce PC risk among diabetics.[105–108] The most recent meta-analysis based on the largest number of studies however found that the protective association was observed only in observational studies (RR = 0.56), whereas results from two randomized controlled trials did not find a protective effect (RR = 0.93).[108] Association with other antidiabetic drugs was summarized in five meta-reports.[72,107,109–111] Recent use of insulin (RR = 3.18) or insulin glargine (RR = 1.63) was associated with an increased risk of PC, but the association could possibly be due to reverse causality.[110]

Hereditary and genetic factors

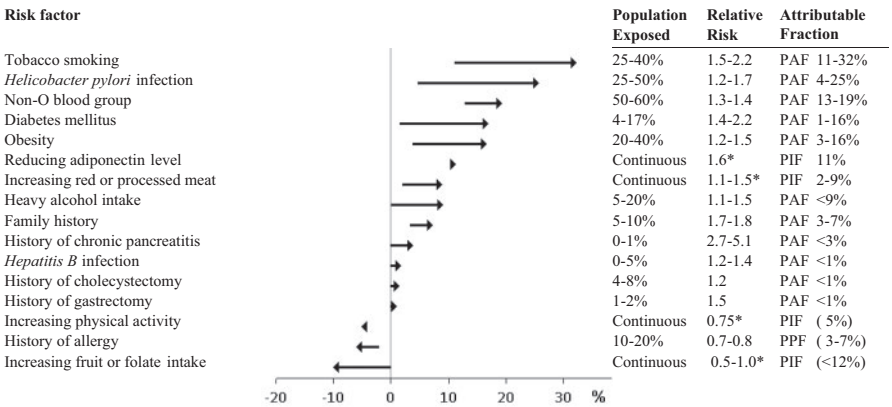
Several hereditary and genetic factors for PC have been identified and a few have been subject of meta- or pooled analysis (Supplementary Table 1g, h). A positive family history of PC has been associated with an 80% increased risk of developing the disease, both in a meta-analysis[112] and in a nested case-control study using pooled data from 10 cohort studies.[113]

The ABO blood group has recently re-emerged as an important susceptibility factor for PC. Two meta-analyses[114,115] and a pooled analysis[116] reported a 30–40% increased risk of PC among individuals having a non-O blood group. Whereas the evidence of the previous associations between family history and ABO blood group and PC risk is 'strong', most meta-analyses that examined genetic single nucleotide polymorphisms (SNPs) as possible susceptibility factors for PC are based on very limited number of underpowered original reports (Supplementary Table 1h).

Germ-line mutations (BRCA1, BRCA2, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1 and STK11) have been associated with an elevated PC risk, often as part of a familial cancer syndrome, but available risk estimates often rely on single studies. Several systematic reviews on the topic have been published but no meta-analysis or pooled analysis.[117–119]

Population attributable fraction

Figure 1 ranks the population attributable fraction for individual exposure variables, obtained by combining estimates of the proportion of the population exposed and of the relative risk for each exposure variable. The range of the population exposed that we used is indicative of representative regions (World, USA, Europe) or extrapolated from single study reports, and could be adjusted using finer country- or population-specific estimates if available. For



* for continuous variables the relative risk is expressed for the highest versus lowest quintile

Population attributable fraction (PAF) = $P_e (RR_e\text{-}1) / [1 + P_e (RR_e\text{-}1)]$
Population preventable fraction (PPF) = $P_e (1\text{-}RR_e)$
Potential impact fraction (PIF) = $(P_{e-}P^*) (RR_e\text{-}1) / [1 + P_e (RR_e\text{-}1)]$

Figure 1. Population attributable fraction of major risk factors for pancreatic cancer.

example, in the *WHO Global Health Risks* report:[3] current smoking prevalence for both sexes was estimated at 26% worldwide, 24% in the USA and 33% in Europe; similarly, the prevalence of obesity (BMI $\geq$30) was 12% worldwide, 33% in the USA and 24% in Europe; and the prevalence of diabetes was 11% worldwide, 10% in the USA and 12% in Europe. These estimates are comprised in the ranges proposed in Figure 1.

Tobacco smoking represents the commonest exposure, with nearly half of the general population being current or former smokers. Considering that the average increased risk for ever-smokers is 70%, we estimate that 11–32% of all PC might be attributable to tobacco smoking.

Another important causative factor is blood group: since about 56% of the general population carries a non-O blood group, the proportion of PC attributable to this inherited trait ranges from 13% to 19%.

Obesity is associated with about 30% increased risk in all studies, but the proportion of obese people varies considerably from one country to another. Therefore, we estimated that the proportion of PC attributable to obesity could range from 3% to 16%.

The global prevalence of *H. pylori* infection also varies widely; with an estimated prevalence ranging from 25% to 50% in Westernized countries, *H. pylori* could be responsible for 4% to 25% of all PC cases in these countries.

Because of their low prevalence in the general population, the remaining risk factors explain only a small fraction of all PC, even though some factors, such as a history of chronic pancreatitis, are associated with large elevated relative risks (Figure 1).

Discussion

This review summarizes results from hundreds of case-control and cohort studies focusing on the aetiology of PC. It provides an overview of well-established risk factors as well as rarer causes recently identified by meta- or pooled analyses. From an estimate of the proportion of the population exposed to each risk factor and the magnitude of the association, we were able to quantify the proportion of PC attributable to each individual risk factor. Although PC is often considered a poorly understood disease, identified risk factors for PC taken together could explain an appreciable proportion of all cases (Figure 2). Unlike lung or cervical cancers, which are attributable largely to a single risk factor, i.e. tobacco smoking or human papilloma virus, respectively, PC has a multifactorial aetiology. For most of the risk factors the associations are generally modest (with relative risks ranging between 1.2 and 1.8), making it difficult to identify a high-risk group that would benefit from screening.

Many of the identified risk factors are interrelated, indicative of several common underlying aetiological pathways and, possibly, specific carcinogenic pathways (Figure 2). Insulin resistance is related to many of the risk factors for PC including obesity, central adiposity, adiponectin level, hyperglycaemia, diabetes and metabolic syndrome, as well as dietary factors such as fructose intake or lifestyle factors such as reduced physical activity. All these factors can be combined into a specific aetiological pathway for PC.[120] Other factors such as tobacco, alcohol, pancreatitis, cholecystectomy, *H. pylori* and hepatitis virus infection are known triggers of inflammation, another established pathway leading to PC carcinogenesis.[121] Factors such as blood group or history of thrombosis could be broadly linked to haemostasis, another important process involved in PC.[122]

Several risk factors have been included in successive meta-analyses or pooled analyses, with generally concordant results. For example, all 14 meta-analyses investigating the association with diabetes mellitus indicated an increased risk of PC, with very little variation in the magnitude of the association across studies. Vitamin D studies are exceptional because the results are discordant. Occupational and other environmental exposures are greatly understudied possible aetiological factors in PC due to the difficult nature of conducting such studies.

We believe that for many risk factors for which the current evidence of an association with PC is 'strong', replicate meta-analyses are not warranted in the absence of strong new studies containing conflicting data. This is true for factors with a positive association (tobacco smoking, obesity, family history, blood group, heavy alcohol intake), no association (glycaemic index or glycaemic load, aspirin), or an inverse association (allergy). However, despite existing meta-analysis, the evidence of an association remains only 'moderate' or 'poor' for several risk factors such as dietary factors for which results from meta-analyses of case-control studies have not been confirmed in pooled-analyses of data from prospective cohort studies. Other specific risk factors requiring further investigation include: physical activity, metabolic syndrome, circulating vitamin D and *Helicobacter pylori* infection because of their high prevalence in the general population and because of a possible role for prevention. Lower priority should be given to the remaining factors for which level of evidence is poor (history of idiopathic thrombosis, cholecystectomy or gastrectomy, hepatitis C virus infection) because of their very low attributable fraction (<1%).

Our estimate of the fraction of PC attributable to tobacco, alcohol, blood group, obesity, physical inactivity, diabetes, meat and fruit intake, family history, infection and pancreatitis is comparable to that calculated by others in single studies (Supplementary Table 2).[7,46,81,112,113,116,123–140]

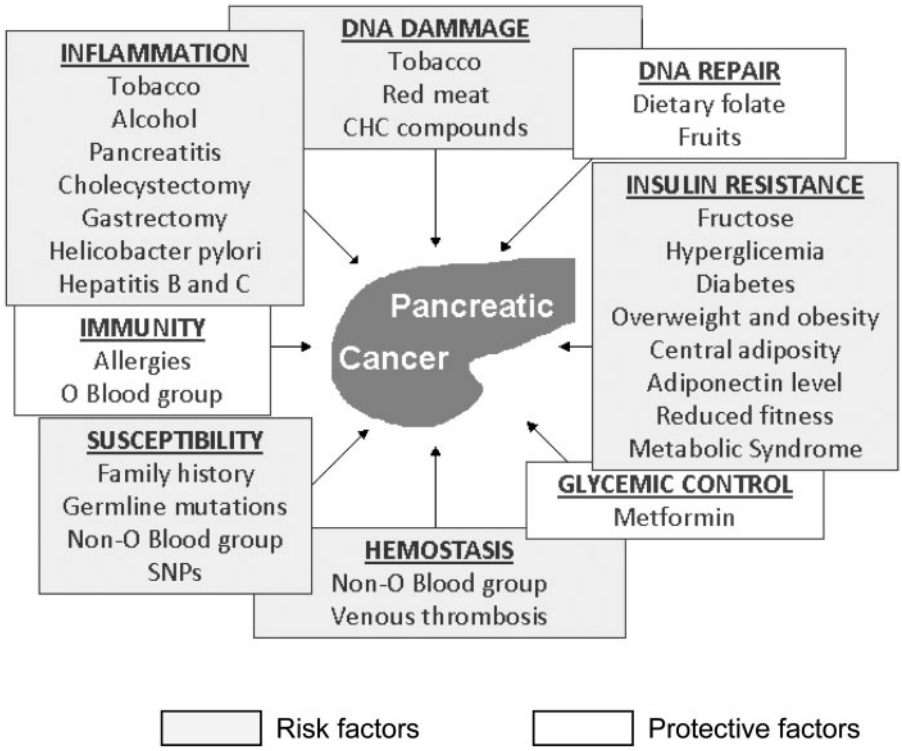


Figure 2. Aetiological factors and general pathways in pancreatic cancer.

Surprisingly, *H. pylori*, a common pathogen only recently suspected to be associated with PC, could be responsible alone for 10% to 20% of all PC cases, and even more among individuals with non-O blood type if the association between non-O blood type, *H. pylori* and PC is to be confirmed.[85] From this review, we could not estimate precisely the combined attributable fraction for all preventable risk factors (tobacco, alcohol, obesity, physical inactivity, diet), but we have evidence that one-third of PC burden could be prevented applying our current knowledge, in agreement with estimates from single reports.[129,130,140]

The description of the single meta-analytic studies included in our review was intentionally succinct. It may be seen as a limitation but was chosen to allow readers to easily appreciate the nature and the strength of evidence of the various associations considered. We acknowledge that our tabular data do not allow us to determinate with precision the overlap between related meta-analyses, but this overlap could be estimated from the number of studies and PC cases available for each risk factor in each single meta-report. Providing more information would require huge amounts of space and become difficult to manage.

Another limitation of our study is related to the calculation of the population attributable fraction for each single risk factor. The prevalence of these risk factors varies considerably worldwide. We considered a wide range of exposure, representative of the studied population, to give an overall idea of the burden of the major risk factor for PC, but it may not apply to populations with varying levels of exposure.

In conclusion, this study summarizes results of aetiological studies from 117 meta-analytic or pooled data reports covering 37 individual exposures, allowing for a comprehensive overview of the causes of PC and their relative importance in the population. For some tumours, such as lung and cervical cancer, a single cause explains all or nearly all cases; in contrast, for PC the number of known risk factors is surprisingly large and varied. About two-thirds of the major risk factors associated with PC are potentially modifiable, affording a unique opportunity for preventing one of our deadliest cancers.

Supplementary Data

Supplementary data are available at *IJE* online.

Conflict of interest: There are no competing financial interests in relation to this work.

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