Diabetes type II, other medical conditions and pancreatic cancer risk: a prospective study in The Netherlands

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Background: To date, only a few risk factors for pancreatic cancer have been established. We examined prospectively relations between several medical conditions and pancreatic cancer incidence.

Methods: In 1986, 120 852 participants completed a baseline questionnaire on cancer risk factors, including several self-reported physician diagnosed medical conditions. At baseline, a random subcohort of 5000 participants was selected using a case-cohort approach for analysis. After 16.3 years of follow-up, 448 pancreatic cancer cases (63% microscopically confirmed) were available for analysis.

Results: Diabetes mellitus type II and hepatitis were positively associated with pancreatic cancer risk (multivariable-adjusted hazard ratio: 1.79; 95% confidence interval: 1.12–2.87 and hazard ratio: 1.37; 95% confidence interval: 1.04–1.81, respectively). Furthermore, a positive trend in risk with increasing years of diagnosis of diabetes ($P = 0.004$) and of hepatitis ($P = 0.02$) was observed. However, an inverse association was observed between hypertension and pancreatic cancer risk, this was found among microscopically confirmed cases only (hazard ratio: 0.66; 95% confidence interval: 0.49–0.90), while years since diagnosis of hypertension significantly decreased cancer risk (P for trend $= 0.02$).

Conclusion: In this prospective study, a positive association was observed between self-reported physician diagnosed diabetes mellitus type II and hepatitis and pancreatic cancer risk, whereas an inverse association was observed with hypertension.

Cancer of the pancreas is a less common form of cancer, with approximately 170 000 new cases occurring annually worldwide, around 2.1% of all cancer cases (Ghadirian *et al*, 2003). Due to its poor prognosis, pancreatic cancer is one of the most fatal cancers worldwide (Jemal *et al*, 2009). To date, only a few consistent risk factors for pancreatic cancer have been identified, including smoking and obesity (Lee *et al*, 1996; Anderson *et al*, 2009). This study aims to provide further insight into possible associations between several medical conditions and pancreatic cancer, which remain under debate in the literature, specifically the duration of diabetes mellitus type II (DMII) and hypertension. To our knowledge, the effect of the hepatitis B virus (HBV) and hepatitis C virus (HCV) has not been studied yet in a European population.

Previous studies have investigated the association between several medical conditions and pancreatic cancer risk. Most studies of DM II observed positive associations (Lee *et al*, 1996; Silverman, 2001; Ghadirian *et al*, 2003; Huxley *et al*, 2005; Wang *et al*, 2006; Hassan *et al*, 2007; Luo *et al*, 2007; Jamal *et al*, 2009; Ogunleye *et al*, 2009; Stevens *et al*, 2009; Chodick *et al*, 2010; Ben *et al*, 2011; Lai *et al*, 2013). The effect of duration of DM II on the onset of pancreatic cancer is, however, still unclear with some studies observing a positive association with longer duration

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(Silverman, 2001; Ghadirian *et al*, 2003) and others showing an inverse association (La Vecchia *et al*, 1994; Huxley *et al*, 2005; Wang *et al*, 2006; Ben *et al*, 2011). For hypertension, Lindgren *et al*, reported a positive association with pancreatic cancer risk in women (Lindgren *et al*, 2005), whereas Batty *et al*, reported an inverse effect of diastolic blood pressure on pancreatic cancer risk (Batty *et al*, 2003); other studies reported no association (Grove *et al*, 1991; Batty *et al*, 2009; Inoue *et al*, 2009). Furthermore, some studies have reported elevated pancreatic cancer risks for infection with HBV or HCV (Berrington de Gonzalez *et al*, 2008; Hassan *et al*, 2008; Iloeje *et al*, 2010) and a recent meta-analysis supports that HBV infection is associated with pancreatic cancer (Luo *et al*, 2013). A study performed in an Asian population demonstrated that elevated levels of liver enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST) are both risk factor for pancreatic cancer (Berrington de Gonzalez *et al*, 2008). In the same study hepatitis B was associated with elevated levels of ALT and AST. Moreover, obesity, risk factors for pancreatic cancer, is associated with liver injury and elevated levels of ALT and AST levels too (Berrington de Gonzalez *et al*, 2006). Finally, a number of other studies have observed positive associations between pancreatic cancer risk and other medical conditions such as chronic pancreatitis (Ghadirian *et al*, 2003; Anderson *et al*, 2009; Apte *et al*, 2009; Greer and Whitcomb, 2009), cholecystectomy (Silverman, 2001; Ghadirian *et al*, 2003; Lin *et al*, 2012), and gastric ulcer (Bao *et al*, 2010).

The biological mechanism by which DM II may lead to pancreatic cancer relates to hyperinsulinemia. DM II is characterized by glucose intolerance caused by insulin resistance and/or relative insulin deficiency, which will finally result in hyperinsulinemia (Gapstur *et al*, 2000). Furthermore, *in vitro* research has revealed the presence of a dose-response relationship between elevated levels of insulin and the growth of pancreatic cancer cells (Gapstur *et al*, 2000). However, DM II can also be a result of pancreatic cancer; *in vitro* studies have suggested that blockage of insulin receptors, impaired insulin action and glucose transport were involved in pancreatic cancer induced insulin resistance (Ben *et al*, 2011). It has been established that HBV and HCV viruses travel through the bloodstream and can be deposited in non-liver tissue like the kidney or skin (Hassan *et al*, 2008). The fact that the liver and the pancreas share common blood vessels and ducts and the proximity of the liver and pancreas, make it plausible that pancreatic cancer risk is elevated for people with a HBV or HCV

infection (Hassan *et al*, 2008). Hepatitis B surface antigen (HBsAg) is an indicator of a current HBV infection; Different studies have shown that HBsAg positive subjects have an elevated risk of pancreatic cancer (Ben *et al*, 2012; Wang *et al*, 2012b). The possibility of a causal relation between cholecystectomy and pancreatic cancer is supported by an experimental study showing that cholecystectomy induces elevated levels of cholecystokinin, which is a known promoter of pancreatic cancer (Howatson and Carter, 1985). A relation between gallstones and chronic pancreatitis is suggested to be the underlying cause for pancreatic cancer (Hardt *et al*, 2001). Peptic ulcers might be a source of nitrosamines and therefore be involved in carcinogenesis (Bao *et al*, 2010). In addition, the role of cytokines, generated by inflammation, might play a role in carcinogenesis (Bao *et al*, 2010). Finally, in a recent meta-analysis performed by Trikudanathan *et al*. a positive relation between Helicobacter pylori infection, a known cause of peptic ulcers (Mhaskar *et al*, 2013), and pancreatic cancer was found (Trikudanathan *et al*, 2011).

In this large prospective cohort study, we investigated the associations between the medical conditions DM II, hypertension, cholecystectomy, gallstones, peptic ulcer, hepatitis and pancreatic cancer risk.

MATERIALS AND METHODS

Study population and cancer follow-up. The design of the Netherlands Cohort Study (NLCS) has been reported in detail elsewhere (van den Brandt *et al*, 1990a); for a schematic presentation see Figure 1. This large-scale prospective cohort study was initiated in 1986 and included 58 279 men and 62 573 women aged 55–69 years from 204 Dutch municipalities with computerized population registries. A self-administered questionnaire on potential risk factors for cancer was completed at baseline. For reasons of efficiency, the case-cohort approach was chosen (weighting of study subjects based on Prentice's method) (Prentice, 1986). A random subcohort ($n = 5000$) was selected immediately after identification of cohort members and followed biennially for migration and vital status to estimate the accumulated person-years of the whole cohort. The subcohort was selected as a simple random sample out of the total cohort at baseline ($n = 120\,852$), with a sampling fraction of 5000/120 852 (i.e., 0.04137). The entire
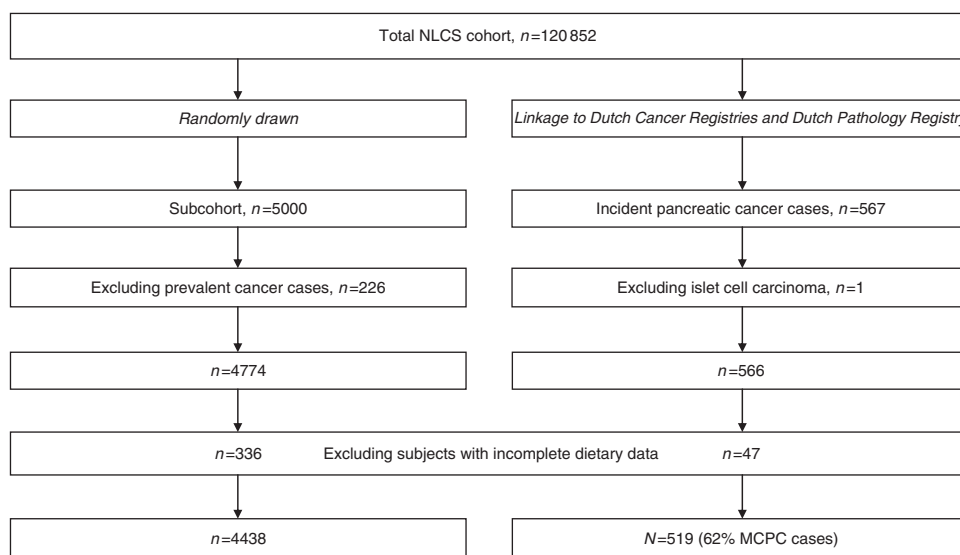

Figure 1. Schematic presentation of the Netherlands Cohort Study Design. Abbreviations: MCPC = microscopically confirmed pancreatic cancer; NLCS = Netherlands Cohort Study.

cohort is being monitored for cancer occurrence through annual record linkage with the Netherlands Cancer Registry and the nationwide pathology registry PALGA (van den Brandt et al, 1990b; Casparie et al, 2007). For the current analysis, 16.3 years of follow-up have been used. Only one subcohort member was lost to follow-up, and completeness of nationwide cancer follow-up was estimated to be greater than 96% (Goldbohm et al, 1994b). All subcohort members with prevalent cancer (other than skin cancer) at baseline were excluded ($n = 226$). Of the 567 incident cases of pancreatic cancer (ICD-O-3 code C25), persons with endocrine subtypes (islet-cell carcinoma; ICD-O-3 code C25.4; $n = 1$) were excluded. Furthermore, we excluded participants with incomplete or inconsistent dietary data (47 incident cases and 336 subcohort members). Details are given elsewhere (Goldbohm et al, 1994a). The institutional review boards of the TNO Nutrition and Food Research Institute (Zeist, The Netherlands) and Maastricht University (Maastricht, The Netherlands) have approved the Netherlands Cohort Study protocol.

Questionnaire. At baseline, all cohort members completed a mailed, self-administered questionnaire on dietary habits and other risk factors for cancer, including several medical conditions. Participants were asked to report whether a physician had ever diagnosed high blood pressure, diabetes (no subtypes), gallstones, cholecystectomy, hepatitis and/or jaundice or peptic ulcer and at what age. Furthermore, they were asked whether they ever had peptic ulcer surgery and at what age. The applicable age was recorded in 5-year age groups (from 'younger than 30 years', '30–34 years' to '65–69 years').

Statistical analysis. We used Cox proportional hazards model to calculate age-adjusted and multivariable-adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI). In our analyses we used the person-years of the subcohort to estimate the number of person-years of the full cohort and used these as the underlying time metric (van den Brandt et al, 1990a; Barlow et al, 1999). We estimated standard errors using the Huber-White sandwich estimator to account for the additional variance introduced by using the case-cohort approach (Lin and Wei, 1989). The proportional hazard assumption was tested using scaled Schoenfeld residuals and found to be justified (Schoenfeld, 1982).

We opted for two disease endpoints: microscopically confirmed pancreatic cancer (MCPC) cases ($n = 194$ for men; $n = 156$ for women) and all cases of pancreatic cancer (including both MCPC and non-microscopically confirmed pancreatic cancer (NMCPC) cases; $n = 298$ for men; $n = 268$ for women). The diagnosis of the NMCPC case group was made by the treating clinician and was based on clinical symptoms, physical examinations, and imaging results and recorded as discharge diagnosis. These cases were abstracted and recorded by a trained tumour registrar (van der Sanden et al, 1995).

To distinguish between subtypes of diabetes mellitus, the age of 30 years was used as a cut-off point; diabetes mellitus type I: diagnosed before age 30 years; DM II: diagnosed at age of $\geqslant 30$ years) as used in previous studies (Stevens et al, 2007). Due to low numbers, we did not analyse the possible association between diabetes mellitus type I and pancreatic cancer. Because diabetes can be both a cause and a sequel of pancreatic cancer, we excluded all cases who were diagnosed with DM II within five years prior to their diagnosis of pancreatic cancer ($n = 4$), as per (Silverman, 2001). All medical conditions used in the analyses were dichotomized, with participants not exposed to the concerning medical condition used as a reference group. Additionally, years since diagnosis of DM II, hypertension and hepatitis/jaundice, was evaluated. Years since diagnosis was calculated by subtracting the midpoint age of the age groups of diagnosis from the age at baseline. Years since diagnosis of DM II was categorized, based on previous research (Hassan et al, 2007), into two broad categories:

< 10 years and 10 years or more. Years since diagnosis of hepatitis/jaundice and hypertension were categorized based on the median values among subcohort members: 29 years and 8.5 years, respectively.

We used two methods to determine which variables finally entered the multivariable-adjusted models: (1) is the potential confounder predefined, i.e. been used in other models in literature describing the association between the exposure of interest and pancreatic cancer?; or (2) is the potential confounder associated with pancreatic cancer risk and with the exposure of interest and does the potential confounder change the risk estimate by at least 10%? In the final models, we made use of two different sets of confounders. For the exposure variable DM II we used a model that included: age at baseline (years), sex, current cigarette smoking (yes/no), cigarettes smoked (number/day), years of cigarette smoking (years), alcohol consumption (g/day), body mass index (BMI; $\mathrm{kg\,m}^{-2}$), socio-economic status (based on education: lower vocational, second & medium vocational and university and higher vocational), and family history of pancreatic cancer (yes/no) (model 1). In our analyses concerning the medical conditions hypertension, cholecystectomy, gallstones, peptic ulcer and hepatitis/jaundice, we included all confounders from model 1 plus the variable DM II (yes/no). This model will be referred to as model 2. To permit comparison, we restricted age-adjusted analyses to participants included in the multivariable-adjusted analyses, which left 3962 subcohort members (1944 men and 2018 women) and 448 incident cases of pancreatic cancer (63% microscopically confirmed). Trends were evaluated by fitting the median value for each level of the categorical exposure variable among the subcohort members as a continuous term. For all medical conditions, except DM II, we evaluated whether early symptoms of pancreatic cancer before diagnosis could have influenced the results by excluding early cases (diagnosed within 2 years after baseline) in additional analyses. Furthermore, we investigated the interaction between DM II (yes/no) and smoking status (never/ex/current smoking). Interaction on a multiplicative scale between sex and any of the medical conditions examined in the current study were tested for pancreatic cancer and were not found to be statistically significant (P for interaction > 0.05). Therefore, results for analyses on medical conditions are presented for both sexes combined. All analyses were performed using STATA statistical software package version 9. We considered a two-sided P-value of < 0.05 as statistically significant.

RESULTS

As Table 1 shows, the differences in most baseline characteristics between the pancreatic cancer cases and the subcohort, were small. A notable difference is that 6.0% of all pancreatic cancer cases were diagnosed with DM II compared to 3.3% in the subcohort. Also, there were more participants with a family history of pancreatic cancer among cases than among subcohort members, especially in women.

The age- and sex-adjusted and multivariable-adjusted associations between medical conditions and pancreatic cancer risk are shown in Table 2. For participants reporting to have ever been diagnosed with DM II, we observed a statistically significantly increased pancreatic cancer risk (multivariable-adjusted HR: 1.79; 95% CI: 1.12–2.87; Table 2). When the NMCPC cases were excluded in additional analyses, similar results were observed (Table 2). A statistically non-significantly reduced pancreatic cancer risk was observed in the group that reported to have ever been diagnosed with hypertension. When we restricted this analysis to MCPC cases, the point estimate decreased and became statistically significant (multivariable-adjusted HR: 0.66; 95%

Table 1. Description of the exposure variables and confounders, the Netherlands Cohort Study on diet and cancer, 1986-2003

	Men			Women		
Characteristic	Total pancreatic cancer cases	Microscopically confirmed pancreatic cancer cases	Subcohort	Total pancreatic cancer cases	Microscopically confirmed pancreatic cancer cases	Subcohort
Number	239	160	1.944	209	123	2.018
Age, mean (s.d.) (years)	62.0 (3.9)	61.6 (3.9)	61.2 (4.2)	62.2 (4.3)	61.3 (4.3)	61.4 (4.3)
History of DM II[a,b] (%)	15 (6.4%)	9 (5.7%)	61 (3.1%)	8 (3.8%)	6 (4.9%)	66 (3.3%)
Years since diagnosis of DM II[a,b] (%)						
<10 years	9 (60.0%)	5 (55.6%)	42 (68.9%)	4 (50.0%)	3 (50.0%)	45 (68.2%)
10–19 years	4 (26.7%)	2 (22.2%)	13 (21.3%)	3 (37.5%)	2 (33.3%)	18 (27.3%)
≥20 years	2 (13.3%)	2 (22.2%)	6 (9.8%)	1 (12.5%)	1 (16.7%)	3 (4.5%)
History of hypertension (%)	51 (21.3%)	27 (16.9%)	469 (24.1%)	64 (30.6%)	29 (23.6%)	584 (28.9%)
Years since diagnosis of hypertension (%)						
<8.5 years	28 (54.9%)	14 (51.9%)	246 (52.5%)	25 (39.7%)	15 (51.7%)	257 (44.9%)
≥8.5 years	23 (45.1%)	13 (48.2%)	223 (47.6%)	38 (60.3%)	14 (48.3%)	316 (55.2%)
History of hepatitis (%)	33 (13.8%)	22 (13.8%)	214 (11.0%)	37 (17.7%)	22 (17.9%)	287 (14.2%)
Years since diagnosis of hepatitis (%)						
<29 years	13 (39.4%)	10 (45.5%)	98 (46.0%)	11 (30.6%)	6 (27.3%)	129 (45.6%)
≥29 years	20 (60.6%)	12 (54.6%)	115 (54.0%)	25 (69.4%)	16 (72.7%)	154 (54.4%)
History of gallstones (%)	11 (4.6%)	5 (3.1%)	101 (5.2%)	34 (16.3%)	17 (13.8%)	282 (14.0%)
History of cholecystectomy (%)	8 (3.4%)	4 (2.5%)	87 (4.5%)	32 (15.3%)	16 (13.0%)	266 (13.2%)
History of peptic ulcer (%)	30 (12.6%)	21 (13.1%)	229 (11.8%)	9 (4.3%)	2 (1.6%)	94 (4.7%)
Current cigarette smoker (%)	101 (42.3%)	67 (41.9%)	660 (34.0%)	52 (24.9%)	32 (26.0%)	417 (20.7%)
Number of cigarettes smoked per day, mean (s.d.)[c]	16.9 (11.1)	16.6 (9.8)	17.2 (10.6)	11.3 (8.2)	10.7 (7.4)	11.6 (8.4)
Years of smoking, mean (s.d.; years)[c]	33.6 (11.9)	35.6 (12.0)	33.5 (11.7)	28.5 (12.2)	28.3 (11.9)	27.8 (12.4)
Ex cigarette smoker (%)	119 (49.8%)	82 (51.3%)	1018 (52.4%)	46 (22.0%)	28 (22.8%)	407 (20.2%)
Number of cigarettes smoked per day, mean (s.d.)[d]	15.6 (11.6)	15.5 (10.4)	14.8 (11.5)	5.3 (8.0)	5.2 (7.4)	4.7 (7.9)
Years of smoking, mean (s.d.; years)[d]	32.8 (14.9)	33.1 (14.7)	28.9 (15.8)	13.4 (16.5)	13.8 (16.4)	11.4 (15.8)
BMI, mean (s.d.; kg m^{-2})	25.3 (3.0)	22.5 (2.7)	24.9 (2.6)	25.5 (3.5)	25.9 (3.8)	25.1 (3.5)
Alcohol, mean (s.d.; g/day)	18.0 (18.0)	17.3 (18.1)	14.9 (16.9)	6.5 (10.3)	6.9 (10.0)	5.9 (9.6)
Level of education (%)						
Low	108 (45.2%)	72 (45.0%)	854 (43.9%)	174 (56.0%)	70 (56.9%)	1118 (55.4%)
Medium	82 (34.3%)	59 (36.9%)	706 (36.3%)	74 (35.4%)	43 (35.0%)	714 (35.4%)
High	49 (20.5%)	29 (18.1%)	384 (19.8%)	18 (8.6%)	11 (8.1%)	186 (9.2%)
Anti hypertensive medication (%)	39 (16.3%)	19 (11.9%)	381 (19.6%)	46 (22.0%)	19 (15.5%)	455 (22.6%)
Family history of pancreatic cancer (%)	5 (2.1%)	2 (1.3%)	16 (0.8%)	9 (4.3%)	3 (2.4%)	19 (0.9%)

Abbreviations: BMI = body mass index; DM II = diabetes mellitus type II; SD = standard deviation. Numbers of cases or subcohort members do not add up to the total number because of missing values on some observations of the main exposure variables.
[a]Only for persons who reported diabetes diagnosed at or above the age of 30 years.
[b]All cases excluded in whom a diagnosis of DM II was made within five years prior to pancreatic cancer diagnosis.
[c]Only for ever smokers.
[d]only for ex smokers.

CI: 0.49–0.90; Table 2). The sample size was too small to investigate the group that reported hypertension but no medication use or to study the risk of different types of antihypertensive medication, like diuretics and RAS blockers. Hepatitis/jaundice was positively associated with pancreatic cancer risk (HR: 1.37; 95% CI: 1.04–1.81; Table 2). This association became non-significant when we restricted the analyses to MCPC cases, although the risk estimate remained similar (Table 2). Null results were observed for the medical conditions cholecystectomy, gallstones and peptic ulcer (Table 2).

In Table 3, results for pancreatic cancer risk and years since diagnosis of DM II, hypertension and hepatitis/jaundice are presented. Statistically significantly increased risks and clear dose-response effects were observed for increasing number of years since diagnosis of DM II (P for trend = 0.04) and hepatitis/jaundice (P for trend = 0.02). The results observed for MCPC cases were similar (Table 3). For hypertension, years since diagnosis was not associated with pancreatic cancer risk among all cases (Table 3). However, when restricted to MCPC cases, years since diagnosis significantly decreased pancreatic cancer risk (Table 3).

Table 2. Age-adjusted and multivariable-adjusted hazard ratios for pancreatic cancer according to medical conditions

		All pancreatic cancer cases			Microscopically confirmed pancreatic cancer cases		
Exposure	Person-years at risk	Number of cases	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)	Number of cases	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)
DM II[b]							
No	55.273	421	1.00 (reference)	1.00 (reference)	265	1.00 (reference)	1.00 (reference)
Yes	1.624	23	1.75 (1.10–2.78)	1.79 (1.12–2.87)	15	1.90 (1.09–3.32)	1.87 (1.06–3.30)
Hypertension							
No	41.984	333	1.00 (reference)	1.00 (reference)[c]	227	1.00 (reference)	1.00 (reference)[c]
Yes	14.913	115	0.96 (0.77–1.21)	0.94 (0.75–1.19)	56	0.70 (0.52–0.95)	0.66 (0.49–0.90)
Cholecystectomy							
No	51.751	408	1.00 (reference)	1.00 (reference)[c]	263	1.00 (reference)	1.00 (reference)[c]
Yes	5.145	40	1.01 (0.71–1.43)	0.97 (0.68–1.38)	20	0.83 (0.52–1.33)	0.79 (0.49–1.26)
Gallstones							
No	51.358	403	1.00 (reference)	1.00 (reference)[c]	261	1.00 (reference)	1.00 (reference)[c]
Yes	5.539	45	1.06 (0.76–1.47)	1.00 (0.72–1.41)	22	0.85 (0.54–1.33)	0.78 (0.50–1.24)
Peptic ulcer							
No	52.405	409	1.00 (reference)	1.00 (reference)[c]	260	1.00 (reference)	1.00 (reference)[c]
Yes	4.491	39	1.02 (0.72–1.46)	0.95 (0.66–1.37)	23	0.94 (0.60–1.46)	0.87 (0.55–1.37)
Hepatitis							
No	49.607	378	1.00 (reference)	1.00 (reference)[c]	239	1.00 (reference)	1.00 (reference)[c]
Yes	7.289	70	1.32 (1.00–1.73)	1.37 (1.04–1.81)	44	1.30 (0.93–1.81)	1.35 (0.96–1.90)

Abbreviations: CI = confidence interval; DM II = diabetes mellitus type II; HR = hazard ratio.
[a]Adjusted for: age (years), sex, smoking (current cigarette smoker status: yes/no, number of cigarettes/day, years of cigarette smoking), body mass index (kg/m^2), level of education, (low/medium/high), alcohol (g/day), and family history of pancreatic cancer (yes/no).
[b]All cases excluded in whom a diagnosis of DM II was made within five years prior to pancreatic cancer diagnosis.
[c]Additionally adjusted for: DM II (yes/no).

Additional analyses with DMII and subsequently years since diagnosis of DMII as determinants in a model with all covariates included in model 1 completed with the medical conditions hypertension, cholecystectomy, gallstones and peptic ulcer yielded similar results (Results not shown).

When testing the multiplicative interaction between DM II and smoking, we observed a significant interaction between DM II and smoking (P for interaction = 0.03). Compared to a non-smoker without DM II, a current smoker diagnosed with DM II had almost a 5 times higher risk of pancreatic cancer (multivariable-adjusted HR: 4.79; 95% CI: 1.96–11.75). After excluding the first 2 years of follow-up, the results did not differ (data not shown).

DISCUSSION

In this study, we observed a significant positive association between both DM II and hepatitis/jaundice and pancreatic cancer risk. For hypertension, we observed an inverse association; however this was limited to MCPC cases. For cholecystectomy, peptic ulcer and gallstones, null results were observed. Furthermore, we observed a positive association between pancreatic cancer risk and time passed since diagnosis of DM II and of hepatitis/jaundice. Years since diagnosis of hypertension was inversely associated with pancreatic cancer risk, again, only for MCPC cases. The finding of a positive association between years since diagnosis of DM II and pancreatic cancer risk should be interpreted with some caution, however, as

the number of cases in the group diagnosed with DM II for 10 years or more was limited to 10.

So far, the majority of reported risk estimates for DM II correspond to our findings (La Vecchia et al, 1994; Gullo et al, 1996; Silverman, 2001; Ghadirian et al, 2003; Huxley et al, 2005; Ansary Moghaddam et al, 2006; Wang et al, 2006; Hassan et al, 2007; Jamal et al, 2009; Ogunleye et al, 2009; Stevens et al, 2009). A recent meta-analysis, including 35 cohort studies, observed a pooled relative risk (RR) of 1.94 (95% CI: 1.66–2.27; Ben et al, 2011). Furthermore, this study showed an inverse association between the years since diagnosis of diabetes mellitus and pancreatic cancer risk. However, reverse causality was not taken into account in this meta-analysis because the highest risk was found among patients diagnosed within less than 1 year. In a meta-analysis performed by Ghadirian et al, a pooled RR of 2.6 (95% CI: 1.6–4.1; based on nine cohort studies) was observed (Ghadirian et al, 2003). In this meta-analysis, studies were only included that had excluded cases in which a diagnosis of diabetes mellitus was made within one year prior to the diagnosis of pancreatic cancer.

Regarding studies investigating the role of hypertension in the onset of pancreatic cancer, most reported null results (Grove et al, 1991; Lindgren et al, 2005; Ansary Moghaddam et al, 2006; Batty et al, 2009). To our best knowledge only one study reported a significantly protective effect of hypertension (Batty et al, 2003). Batty et al, attributed their observed inverse association to chance or residual confounding (Batty et al, 2003). Similarly, we cannot rule out these possibilities in our study. In contrast with the current

Table 3. Age-adjusted and multivariable-adjusted hazard ratios for pancreatic cancer according to years since diagnosis DM II[a], hypertension and hepatitis

Years since diagnosis	Person-years at risk[c]	All pancreatic cancer cases			Microscopically confirmed pancreatic cancer cases		
		Number of cases[c]	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)	Number of cases[c]	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
DM II							
No DM II	55.273	421	1.00 (reference)	1.00 (reference)	265	1.00 (reference)	1.00 (reference)
Diagnosed since <10 years	1,110	13	1.46 (0.80–2.68)	1.45 (0.78–2.70)	8	1.50 (0.71–3.17)	1.41 (0.66–3.02)
Diagnosed since ⩾10 years	514	10	2.35 (1.16–4.72)	2.56 (1.26–5.18)	7	2.75 (1.23–6.15)	2.97 (1.31–6.74)
P for linear trend			0.008	0.004		0.008	0.006
Hypertension							
No Hypertension	41.984	333	1.00 (reference)	1.00 (reference)[d]	227	1.00 (reference)	1.00 (reference)[d]
Diagnosed since <8.5 years	7.126	53	0.94 (0.69–1.28)	0.92 (0.68–1.26)	29	0.76 (0.51–1.13)	0.72 (0.48–1.08)
Diagnosed since ⩾8.5 years	7.629	61	0.99 (0.74–1.32)	0.97 (0.72–1.31)	27	0.67 (0.44–1.01)	0.62 (0.41–0.95)
P for linear trend			0.91	0.79		0.04	0.02
Hepatitis							
No Hepatitis	49.607	378	1.00 (reference)	1.00 (reference)[d]	239	1.00 (reference)	1.00 (reference)[d]
Diagnosed since <29 years	3.442	24	1.11 (0.71–1.73)	1.15 (0.74–1.80)	16	1.05 (0.61–1.79)	1.10 (0.65–1.89)
Diagnosed since ⩾29 years	3.773	45	1.45 (1.03–2.04)	1.51 (1.07–2.13)	28	1.52 (1.00–2.32)	1.57 (1.02–2.41)
P for linear trend			0.04	0.02		0.09	0.06

Abbreviations: CI = confidence interval; DM II = diabetes mellitus type II; HR = hazard ratio.
[a]All cases excluded in whom a diagnosis of DM II was made within five years prior to pancreatic cancer diagnosis.
[b]Adjusted for: age (years), sex, smoking (current cigarette smoker status: yes/no, number of cigarettes/day, years of cigarette smoking), body mass index (kg/m^2), level of education, alcohol (g/day), and family history of pancreatic cancer (yes/no).
[c]Numbers of cases and person-years do not add up to the total number because of missing values on some observations of the main exposure variables.
[d]Additionally adjusted for: DM II (yes/no).

study, all of the abovementioned studies had biomarkers at their disposal, although only Batty *et al*, adjusted their models for antihypertensive medication. Several studies discuss the potential role of antihypertensive medication in preventing pancreatic cancer. In addition to acting in an antihypertensive capacity, renin-angiotensin system (RAS) blockers (AT1R blockers or ACE inhibitors) may yield protective effects against pancreatic cancer (Nakai *et al*, 2010). Experimental data from studies using cell and animal models of pancreatic cancer suggest that the RAS regulates tumour growth, angiogenesis, and metastasis; and a convergence of such findings suggests that pharmacological RAS blockade could have therapeutic potential in the management of pancreatic cancer (Lau and Leung, 2011). In the current study we did not analyze the group who reported the use of RAS blockers or the group who reported hypertension and no antihypertensive medication use, due to their low numbers.

Our findings regarding hepatitis should be interpreted with caution, as the variable 'hepatitis' included the condition 'jaundice', which is not only a symptom of hepatitis but can also be a symptom of a variety of other diseases like inflammation of the bile ducts, gallstones, nonalcoholic steatohepatitis, and pancreatic cancer. However, findings were similar when excluding the first 2 years of follow-up. Furthermore, we observed an increased risk and a clear dose-response effect for increasing number of years since diagnosis of hepatitis/jaundice. Therefore, we conclude that jaundice as an early symptom of pancreatic cancer probably did not influence our results. Secondly, we were unable to differentiate between different subtypes of hepatitis in our dataset while most other studies had blood sample at their disposal and could therefore distinguish between different subtypes (Berrington de Gonzalez *et al*, 2008; Hassan *et al*, 2008; Iloeje *et al*, 2010; Wang *et al*, 2012a). In a cohort study, Uchenna *et al*, measured HBsAg at

baseline and observed that chronic carriers of HBsAg had a almost twofold increased pancreatic cancer risk (RR = 1.95; 95% CI: 1.01–3.78; Iloeje *et al*, 2010). Two case-control studies observed significantly increased pancreatic cancer risks as well for chronic carriers of HBsAg (Hassan *et al*, 2008; Wang *et al*, 2012a), whereas one of these studies failed to observe an association with hepatitis C (Odds Ratio = 0.9; 95% CI: 0.3–2.8; Hassan *et al*, 2008). These results indicate that without distinction in subtypes, hepatitis as a determinant may be less informative. In the Netherlands, hepatitis A virus infection is the most common form of hepatitis infection, followed by HBV and HCV (National Institute for Public Health and the Environment, 2011). In western countries, the prevalence of hepatitis B core antibody (HbcAb) and/or hepatitis B surface antibody (HbsAb) positivity is higher than prevalence of HBsAg (Ott *et al*, 2012). Further research in low HBV endemic countries, like USA or Northern Europe, on the basis of biomarkers, including the assessment of HBsAg-/HBcAb+/HBsAb- and HBsAg-/HBcAb+/HBsAb+ patterns may contribute to the understanding of the etiology of pancreatic cancer.

We observed effect modification by smoking on the relation between DM II and pancreatic cancer risk. This finding should be interpreted with some caution, due to the low number of cases in some of the subgroups. Probably due to low sample sizes in several studies, this subgroup analysis has been reported only once to our knowledge (Hassan *et al*, 2007). It is possible that in people who smoke and are diagnosed with DM II smoking-induced oxidative stress appears, which results in the production of free radicals and peroxides. These substances might increase susceptibility to chronic inflammation, DNA damage and pancreatic cancer (Hassan *et al*, 2007). More research is needed to investigate whether and how smoking modifies the relation between DM II and pancreatic cancer risk.

Our findings showed no relationship between the conditions cholecystectomy and gallstones and pancreatic cancer risk. In some case-control studies, positive associations were observed for cholecystectomy and gallstones (Lee *et al*, 1996; Silverman, 2001; Ghadirian *et al*, 2003; Ko *et al*, 2007), whereas other cohort studies and case-control studies reported null results (Gullo *et al*, 1996; Ye *et al*, 2001; Schernhammer *et al*, 2002; Bosetti *et al*, 2003; Hassan *et al*, 2007). We also did not observe an association between peptic ulcer and pancreatic cancer risk. However, some studies have identified an increased pancreatic cancer risk for gastric ulcer (Ghadirian *et al*, 2003; Bao *et al*, 2010) and peptic ulcer (Ghadirian *et al*, 2003; Bao *et al*, 2010).

Some limitations in the current study need to be discussed. First, a validity issue might occur because we made use of self-reported medical conditions. Most researchers have biomarkers available at baseline (Lee *et al*, 1996; Gapstur *et al*, 2000; Zendehdel *et al*, 2003; Batty *et al*, 2003, 2009; Berrington de Gonzalez *et al*, 2008; Hassan *et al*, 2008; Ogunleye *et al*, 2009). Molenaar *et al*, compared self-reported data and biomarkers on hypertension and diabetes, observing an overall sensitivity of 34.5% for hypertension and 58.9% for diabetes and a high overall specificity of 96.4% and 99.4%, respectively (Molenaar *et al*, 2007). Molenaar *et al*, therefore concluded that making use of self-reported data on diabetes and hypertension underestimates the prevalence of these two conditions (Molenaar *et al*, 2007). Non-differential measurement error in our self-reported data is therefore likely. However, a meta-analysis conducted by Huxley *et al*, demonstrated no risk differences between studies that made use of self-reported diabetes and studies that used medical records or the oral glucose test (Huxley *et al*, 2005). The self-reported condition hepatitis/jaundice might not only represent hepatitis A, B, or C, but also a variety of other diseases; therefore it would be best for future researchers to use biomarkers over self-reported physician diagnosed data. Secondly, by using the cut-off point of age at diagnosis of 30 years as a surrogate for DM II, we inevitably introduced some measurement error. However, a study performed by Berger *et al*, showed that the mean age of diagnosis of diabetes mellitus type I and type II in a Swedish population in the early nineties was 24.1 and 66.6 years, respectively (Berger *et al*, 1999). Therefore, using the age of 30 as a cut-off point seems justified. Furthermore, it is not clear whether the observed inverse association between self-reported hypertension and pancreatic cancer risk is caused by hypertension itself or by the use of antihypertensive medication. Residual confounding by unmeasured variables could well have influenced our results. Finally, it should be noted that because of the relatively large number of analyses performed, some of the statistical significant findings might have occurred due to chance. This study has a number of strengths, which includes the fact that we could further restrict the analyses to MCPC cases. Moreover, selection bias caused by differential follow-up is unlikely to have made a substantial contribution to the findings, since there was very little loss to follow-up (Goldbohm *et al*, 1994b). Other strengths include a large sample size and detailed information on potential risk factors for pancreatic cancer. Furthermore, the prospective design avoided recall bias and the need to use next-of-kin respondents.

In summary, we observed a positive association between self-reported physician diagnosed DM II and hepatitis/jaundice and pancreatic cancer risk, whereas an inverse association was observed for hypertension. No association was observed for cholecystectomy, peptic ulcer and gallstones.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Pieter Eijgenraam analyzed the data, and drafted and revised the paper. Mirjam M Heinen analyzed the data and revised the draft paper. Bas AJ Verhage and Leo J Schouten participated in the coordination of the study, and critically reviewed the draft paper. Yolande C Keulemans critically reviewed the draft paper. Piet A van den Brandt conceived the study, participated in its design and coordination, and critically reviewed the draft paper. All authors contributed to the interpretation of the data, and all authors approved the final draft of the paper.

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