Cancer Epidemiology 37 (2013) 133–139

Contents lists available at SciVerse ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Smoking and other risk factors for pancreatic cancer: A cohort study in men in Lithuania

Irena Kuzmickiene [a,*], Ruta Everatt [a], Dalia Virviciute [b], Abdonas Tamosiunas [b], Ricardas Radisauskas [b], Regina Reklaitiene [b], Egle Milinaviciene [b]

[a] Group of Epidemiology, Cancer Control and Prevention Center, Institute of Oncology, Vilnius University, P. Baublio 3B, LT-08406 Vilnius, Lithuania
[b] Laboratory of Population Studies, Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Sukileliu 17, LT-50009 Kaunas, Lithuania

ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form 27 September 2012
Accepted 3 October 2012
Available online 26 October 2012

Keywords:
Pancreatic cancer
Risk factors
Cohort study
Smoking
Alcohol consumption
Cholesterol

ABSTRACT

Background: Cancer of the pancreas is a relatively rare, but highly fatal cancer worldwide. Cigarette smoking has been recognized as an important risk factor, but the relation to other potential determinants is still inconsistent. We investigated the association between different lifestyle, biological and anthropometric factors and the risk of pancreatic cancer in a prospective population-based cohort study from Kaunas, Lithuania. *Methods*: Our study included 7132 urban men initially free from any diagnosed cancer, followed for up to 30 years. 77 incident cases of pancreatic cancer were identified. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI). *Results*: Compared to never smokers, current smokers had a significantly increased risk of pancreatic cancer, HR was 1.79 (95% CI 1.03–3.09) after adjustment for age, body mass index, education and alcohol consumption. Among smokers, a significant association with higher smoking intensity was shown ($\geq$20 cigarettes/day: HR = 2.60; 95% CI 1.42–4.76, P_{trend} = 0.046). We also observed a significantly increased risk for $\geq$30 pack-years of smoking (HR = 2.24; 95% CI 1.12–4.49, P_{trend} = 0.16) and for age at starting smoking $<$18 years (HR = 2.29; 95% CI 1.11–4.70, P_{trend} = 0.43) as compared to never smokers. Alcohol consumption, body mass index and total cholesterol level were not significantly associated with pancreatic cancer. *Conclusions*: Smoking significantly increases pancreatic cancer incidence and its high prevalence in Lithuania may partly explain high incidence of the disease. No convincing evidence was found that alcohol consumption, body mass index or serum cholesterol level were associated with pancreatic cancer risk, although the assessment was limited by the lack of statistical power.

1. Introduction

Pancreatic cancer is one of the most common fatal malignant tumours worldwide [1]. Despite the low incidence, it ranks 7th in a world listing of cancer mortality [1]. Mortality from pancreatic cancer has been steadily increasing in the early 2000s in the European Union overall and in certain countries of southern and central/eastern Europe [2]. The risk of developing pancreatic cancer for men is higher than for women. Lithuania and some central and eastern European countries now have the highest rates among men in the world. In 2007, the mortality rate from pancreatic cancer was 11.1 per 100,000 men in Lithuania and over 9.5 per 100,000 men in the Czech Republic, Hungary, Slovakia and Latvia [2]. The lowest rates are observed in Latin America and Hong Kong (below 5 per 100,000).

International variations in rates and time trends suggest that, besides age and genetic risk factors, environmental factors are likely to play a role in the aetiology of pancreatic cancer. The International Agency for Research on Cancer (IARC) Working Group of Experts concluded that there is sufficient evidence for a causal relationship between tobacco smoking and pancreatic cancer [3]. It was shown that the risk of pancreatic cancer increases with the daily number of cigarettes smoked, duration and pack-years of smoking [3–5]. However, the association between cigarette smoking and pancreatic cancer might vary between geographical areas because of the differences in tobacco consumption patterns across countries.

In the evaluation by the IARC in 2009, it was concluded that there was limited evidence for a causal association between consumption of alcoholic beverages and pancreatic cancer risk [6]. In recent studies, heavy alcohol consumption was associated with

* Corresponding author. Tel.: +370 5 219 0916.
E-mail addresses: irena.kuzmickiene@vuoi.lt (I. Kuzmickiene), ruta.everatt@vuoi.lt (R. Everatt), dalivirv@itc.kmu.lt (D. Virviciute), abdonas.tamosiunas@lsmuni.lt (A. Tamosiunas), ricardas.radisauskas@med.kmu.lt (R. Radisauskas), regina@lsmuni.lt (R. Reklaitiene), egle.milinaviciene@kmuk.lt (E. Milinaviciene).

1877-7821/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.canep.2012.10.001

a modest increase in risk, but the low-to-moderate levels of alcohol consumption are unlikely to have an effect on pancreatic cancer risk [3,7–9]. It has been hypothesized that total energy intake, obesity [10], metabolic syndrome including insulin resistance [11], elevated blood pressure [12] and low physical activity [13–15], may increase the risk of developing pancreatic cancer; however, these findings are not universal. Until now, the evidence of the relationship between socioeconomic status [16–18], cholesterol level [11,19], blood pressure [11,19,20], or height [13,21,22] and pancreatic cancer incidence has been limited and inconsistent. Despite a large number of epidemiological studies concerning the relation between lifestyle factors and risk of pancreatic cancer, most have been case–control investigations, which are more susceptible to systematic biases than prospective cohort studies. Prospective long-term studies for high risk Central and Eastern European populations are lacking [5].

In this study, we investigated the association between smoking, alcohol consumption, height, body mass index, education, total cholesterol level, blood pressure, and the risk of pancreatic cancer using data collected in two population-based cohort studies with up to 30 years of follow-up.

2. Materials and methods

2.1. Study population and cancer follow-up

Our study included two cohorts – the Kaunas–Rotterdam Intervention Study (KRIS) and Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS). The KRIS is a WHO-coordinated prospective cohort study where a random sample of men aged 45–59, living in the city of Kaunas (Lithuania) in 1972–1974 were recruited and invited to participate in the baseline survey (phase 1) and in the initial screening (i.e. physical examination) (phase 2). After the screening, two cohorts – one, consisting of men with mildly elevated cardiovascular risk factor levels and a second, consisting of men with highly elevated risk factor levels – were recruited for a one-year intervention trial using a double-blind method of assignment, treatment and evaluation (phase 3). In addition, a third cohort, consisting of the normal population, was recruited as a control group. More detailed information about the study has been published elsewhere [23,24]. Participants of baseline interview and initial screening (phases 1 and 2) were included in our present study. The MIHDPS was carried out in 1976–1980 among Kaunas men, aged 40–59. This was a prospective population-based study designed to investigate risk factors for cardiovascular diseases and other health related outcomes among the urban population of middle-aged men from Kaunas. In all, 8380 participants – 2447 KRIS and 5933 MIHDPS – were available for analysis. During the follow-up period, the vital status of the subjects was determined from the Lithuanian Residents' Register Service. In addition, dates and causes of death were confirmed from death certificates at the Archives Department under the government of the Republic of Lithuania. We excluded 81 (1.0%) participants with self-reported diabetes. We also excluded 469 (5.6%) duplicates and 698 (8.2%) participants with vital status unknown at the end of follow-up, death or diagnosis of cancer before the start of the follow-up. After the noted exclusions, 7132 subjects were included in the study.

Follow-up time started on 1 January 1978 or, to avoid the influence of subclinical disease, 3 years after the date of interview (whichever came later). We identified cases of pancreatic cancer from the Lithuanian Cancer Registry, which has population-based information available since 1978. In addition, deaths from pancreatic cancer were identified in the National and Regional Archives on Causes of Death to supplement the information on cancer incidence. For the present study, the pancreatic cancer codes were 157.0–157.9 of ICD-9 or C25.0 to C25.9 of ICD-10 (International Statistical Classification of Diseases, Injury and Causes of Death, 9th or 10th Revision). The Lithuanian Cancer Registry (LCR) covers the entire population of the Republic of Lithuania (3.05 million at the 2011 census) and is located at the Vilnius University Institute of Oncology. The main sources of data are compulsory notifications from primary, secondary and tertiary health care institutions in Lithuania. All physicians, all hospitals and diagnostic centres in the country must send a notification to LCR of all cancer cases that come to their attention. This information is complemented by death certificates stating cancer diagnosis, and by notifications from National Centre of Pathology. The LCR data for the periods 1988–1992, 1993–1997 and 1998–2002 have been included in 'Cancer Incidence in Five Continents' [25,26]. Data on microscopic confirmation of diagnosis among cases is limited to the period 1993–2008 because detailed and reliable information on histology is not available from the LCR for patients diagnosed before 1993. Of 44 pancreatic cancer cases, diagnosed during the period 1993–2008, 27 (61.4%) were microscopically confirmed: 20 (45.5%) based on histology and 7 (15.9%) based on cytology.

Person-years were calculated until the day when participants were diagnosed with cancer or died, or were lost to follow-up, or censored at 31 December 2008, whichever came first.

Ethical approval for this study was obtained from the Regional Biomedical Research Ethical Committee in Vilnius (No. 158200-02-280-65).

2.2. Assessment of exposure

Data were collected using a standard protocol and uniform methods of measurement. All participants underwent physical examination (total cholesterol level, blood pressure, height and weight). Cholesterol levels were measured in serum using an enzymatic (CHOD-PAP) method [27]. Weight (kg) and height (cm) were measured in light clothing and without shoes by using a bodymeter and stadiometer, respectively, by registered nursing staff. Height, total cholesterol level, and blood pressure were categorized into quartiles based on the distribution observed in our male cohort population. The first (lowest) quartile was used as the reference category. Based on the values for height and weight, body mass index (BMI) was computed as weight in kilograms divided by the squared value of height in metres (kg/m^2). BMI was categorized into 3 groups based on the World Health Organization obesity classification: <25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥ 30.0 kg/m^2. Underweight (≤ 18.5 kg/m^2) and normal (18.5–24.9 kg/m^2) were combined and used as the reference category, as less than 1% of the cohort were in the underweight category. An interview was used to collect information on demographic factors, medical history of diabetes mellitus, and smoking and drinking habits. Educational attainment was categorized into a common classification using four categories (primary, unfinished secondary, secondary and high school education). The highest educational level attained was used as a reference group. Participants were asked if they smoke cigarettes now, the answer choices were: yes, regularly; yes, occasionally; no. Similarly, they were asked if they ever smoked cigarettes. The number of cigarettes usually smoked per day and the age at starting and quitting smoking were recorded on an interview. We classified smoking status in three categories, where individuals who had never smoked cigarettes regularly or occasionally were considered never smokers, and those who reported previous or present regular or occasional smoking were classified as former or current smokers. We further classified current smokers into categories ≤ 10 cigarettes/day, 11–19 cigarettes/day and ≥ 20 cigarettes/day. The cumulative amount of cigarette smoking, measured as pack-years, was

calculated by multiplying the number of packs smoked per day by years of smoking. For alcohol consumption, participants were asked how frequently they consumed alcohol, the answer choices were: several times per year, once per month, once per week, several times per week, or daily. We grouped participants into four groups according to reported frequency of alcohol consumption (never or former, a few times per year, 1–4 times per month, 2–7 times per week). Furthermore, they were asked how much of each type of drink (beer, wine, and vodka) they drank per occasion. The response options were, for beer: no beer, <1 l, ≥1 l; for wine: no wine, <0.5 l, ≥0.5 l; for vodka: no vodka, <200 g, ≥200 g (MIHDPS study); or: no vodka, <100 g, ≥100 g (KRIS study). Alcohol intake was converted into the number of alcohol units, and then into grams of ethanol per week, by calculating the dose as the mid-point of each category. For upper open-ended categories, the lower limit was multiplied by 1.2 [28]. A unit was defined as 10 g of ethanol. Individuals were classified into five groups according to their amount of ethanol consumed from all beverages: non-drinkers, 0.1–9.9 g/week, 10.0–24.9 g/week, 25.0–99.9 g/week and ≥100 g/week. The cut-points were selected on the basis of cohort distribution and aiming to retain extreme categories and sufficient number of cases in sub-groups. In order to avoid potential reverse causation bias, we chose occasional drinkers, that is, those who consumed a few times per year or those who consumed 0.1–9.9 g/week, as the reference group.

2.3. Statistical analysis

The strength of association between risk factors and pancreatic cancer incidence was examined using the age-adjusted and multivariable-adjusted incidence hazard ratios (HR) and corresponding 95% confidence intervals (CI). Multivariate Cox proportional hazards models, stratified by study to control for differences in study-specific effects [29], were used to calculate HR, adjusted for potential confounders such as age (<50, 50–54, and ≥55), education level, BMI, cigarette smoking (never, former, ≤10 cigarettes/day, 11–19 cigarettes/day, and ≥20 cigarettes/day), alcohol consumption frequency. Risk estimates were derived using adjusted models excluding subjects who had missing data for any of the covariates. Tests for trend were computed by modelling each study variable as a continuous variable in the proportional hazards model. We tested for linear trend for smoking and alcohol after excluding never or former smokers and never or former drinkers (respectively). Additionally, standard deviation (SD) score for the ethanol intake (g/week) variable was calculated and the multivariable-adjusted HR associated with an increase in 1 SD was estimated. We assessed the proportional hazards assumptions by inspecting the log(−log) survival curves for the exposure and adjustment variables. We observed no violation of proportional hazards for any analysis. We also carried out two sensitivity analyses: (1) excluding the individuals with BMI ≤ 18.5 kg/m^2 to examine the risk of BMI and (2) excluding 39 participants who reported cigar or pipe smoking (for MIHDPS study – variable not available). Results from sensitivity analyses were similar to those reported here. All statistical analyses were performed using the Statistical Package SPSS 19. All p-values were based on two-sided tests and, if less than 0.05, considered statistically significant.

3. Results

Baseline characteristics of participants are described in Table 1. Among the 7132 men with mean follow-up time of 19.3 years, 77 incident cases of pancreatic cancer were diagnosed.

Table 1
Selected characteristics of the 7132 study participants.

Characteristic	
Age at entry, mean ± SD[a], years	52.6 ± 5.7
High school education (%)	1570 (22.0)
Height, mean ± SD, cm^2	174.4 ± 6.5
BMI[b], mean ± SD, kg/m^2	27.4 ± 3.7
Total cholesterol levels, mean ± SD, mmol/l	6.0 ± 1.1
Cigarette consumption	
Current smokers (%)	3173 (44.5)
≥30 packs-year[c] (%)	1066 (15.2)
Alcohol consumption	
Never or former (%)	560 (7.9)
2–7 times per week (%)	400 (5.6)
Sitting time at work ≥6 h/day (%)	1858 (26.1)
Follow-up, mean ± SD, years	19.3 ± 8.5
Age at pancreatic cancer diagnosis, mean ± SD, years	69.1 ± 10.7
Person-years	137187.1

[a] SD, standard deviation.
[b] BMI, body mass index.
[c] Pack-years are calculated for current and past smokers.

Table 2 shows the HRs of pancreatic cancer in relation to cigarette smoking status, number of cigarettes smoked per day, pack-years of smoking, and alcohol consumption frequency. After adjustment for age, BMI, education and alcohol consumption, the HR for current smokers was 1.79 (95% CI 1.03–3.09). For cigarette smokers, pancreatic cancer risk increased significantly with increasing smoking intensity. Men who smoked 20 cigarettes/day or more had a substantially higher risk of pancreatic cancer than never smokers (HR 2.60, 95% CI 1.42–4.76, P_{trend} = 0.046). Smokers who smoked ≥30 pack-years were at a twofold greater risk compared with never smokers (HR 2.24, 95% CI 1.12–4.49, P_{trend} = 0.16). It also appeared that a younger age at starting smoking was associated with a significantly increased risk of pancreatic cancer. HR among men who began to smoke before the age of 18 years was 2.29, 95% CI 1.11–4.70, P_{trend} = 0.43. No increased risk for developing pancreatic cancer among former smokers was observed (HR 0.71, 95% CI 0.34–1.44) and there was no association with time since quitting smoking (data not shown).

Frequent alcohol consumption showed a higher risk of pancreatic cancer; however, the estimate was not statistically significant. Compared to men who drank occasionally (a few times per year), the HR among men who consumed alcohol most frequently (2–7 times per week), was 1.79, 95% CI 0.64–5.00, P_{trend} = 0.56. In an analysis by ethanol intake, HR for the highest category (≥100.0 g/week of ethanol) relative to men who drank 0.1–9.9 g/week was 1.57, 95% CI 0.66–3.74. The HR per 1 SD (90 g/week) increase in ethanol intake was 1.09, 95% CI 0.89–1.32.

After adjustment for age, BMI, smoking, and alcohol consumption, decreased HR was found in men with the lowest education as compared with persons in the highest education group (HR 0.42, 95% CI 0.19–0.95) (Table 3). There was a suggestion that BMI was associated with cancer of the pancreas. Compared to non-overweight (BMI < 25.0 kg/m^2), the risk for obese men (BMI ≥ 30.0 kg/m^2) was 66% higher, although the estimate was not statistically significant. There were also positive non-significant associations between cholesterol levels and pancreatic cancer, HRs were 1.81, 95% CI 0.92–3.58 for the second quartile and 1.76, 95% CI 0.87–3.55 for the fourth quartile versus the lowest respectively. The risk was not statistically significantly increased in the third quartile.

There was no evidence of an association between height or blood pressure and pancreatic cancer (Table 3).

Table 2
Hazard ratios (95% CI) of pancreatic cancer according to cigarette smoking and alcohol consumption.

Variables	Age adjusted		Multivariable-adjusted	
	No. cases/No. subjects	HR (95% CI)	No. cases/No. subjects	HR (95% CI)
Smoking status[a]				
Never	22/2126	1 (reference)	21/2092	1 (reference)
Former	12/1700	0.68 (0.34–1.39)	12/1672	0.71 (0.34–1.44)
Current	43/3303	1.61 (0.96–2.70)	43/3232	1.79 (1.03–3.09)
Missing	0/3	–	1/136	–
No. of cigarettes/day[a,c]				
Never	22/2126	1 (reference)	21/2092	1 (reference)
Former	12/1700	0.68 (0.34–1.39)	12/1672	0.69 (0.34–1.41)
≤10	10/977	1.17 (0.56–2.48)	10/963	1.29 (0.60–2.77)
11–19	4/605	0.79 (0.27–2.29)	4/589	0.90 (0.31–2.67)
≥20	27/1591	2.32 (1.31–4.08)	27/1554	2.60 (1.42–4.76)
Missing	2/133	–	3/262	–
P_{trend}		0.046		0.046
Age at starting smoking (current smokers only)[a,c]				
Never	22/2126	1 (reference)	21/2092	1 (reference)
≥18 years	30/2316	1.57 (0.91–2.74)	30/2271	1.75 (0.98–3.13)
<18 years	13/890	1.98 (0.99–3.94)	13/869	2.29 (1.11–4.70)
Missing	0/100	–	1/228	–
P_{trend}		0.54		0.43
Cumulative amount of smoking (pack-years)[a,c]				
Never	22/2126	1 (reference)	21/2092	1 (reference)
Former	12/1700	0.68 (0.34–1.38)	12/1672	0.69 (0.34–1.41)
<10	5/446	1.29 (0.49–3.41)	5/437	1.37 (0.51–3.65)
10–19	8/823	1.20 (0.53–2.70)	8/811	1.35 (0.59–3.09)
20–29	12/838	1.81 (0.89–3.67)	12/821	2.02 (0.97–4.22)
≥30	16/1066	1.96 (1.02–3.79)	16/1037	2.24 (1.12–4.49)
Missing	2/133	–	3/262	–
P_{trend}		0.17		0.16
Alcohol consumption (frequency)[b,d]				
Never or former	8/560	1.74 (0.70–4.34)	8/545	1.85 (0.74–4.60)
A few times per year	11/1228	1 (reference)	11/1190	1 (reference)
1–4 times per month	51/4923	1.27 (0.66–2.44)	49/4751	1.09 (0.58–2.13)
2–7 times per week	6/400	2.10 (0.77–5.72)	6/384	1.79 (0.64–5.00)
Missing	1/21	–	3/262	–
P_{trend}		0.27		0.56
Ethanol intake[b,d]				
Non-drinkers	8/560	1.87 (0.75–4.64)	8/545	1.97 (0.79–4.90)
0.1–9.9 g/week	11/1313	1 (reference)	11/1274	1 (reference)
10.0–24.9 g/week	23/2468	1.16 (0.56–2.38)	22/2386	1.02 (0.49–2.14)
25.0–99.9 g/week	22/1855	1.60 (0.78–3.31)	22/1786	1.40 (0.67–2.95)
≥100.0 g/week	12/907	1.99 (0.88–4.54)	11/871	1.57 (0.66–3.74)
Missing	1/29		3/270	
Continuous, per 1 SD (90 g/week)		1.13 (0.94–1.35)		1.09 (0.89–1.32)

[a] In multivariable analysis, adjusted for age, education, alcohol consumption, body mass index.
[b] In multivariable analysis, adjusted for age, smoking status, education, body mass index.
[c] Test for trend was carried out after exclusion of never smokers and former smokers.
[d] Test for trend was carried out after exclusion of never drinkers and former drinkers.

4. Discussion

In this prospective analysis, a strong positive association was observed between cigarette smoking and the risk of pancreatic cancer among men. Compared with never smokers, the risk of pancreatic cancer was increased 1.8-fold for current smokers. We found that smoking ≥20 cigarettes/day is associated with 2.6-fold increased risk for pancreatic cancer. Our results also show a significant association with higher number of pack-years and younger age when beginning to smoke, although the trend was not statistically significant. Our estimations are in agreement with previous reports from a recent meta-analysis [4], large cohort study of European Prospective Investigation into Cancer and Nutrition (EPIC) [5] and International Pancreatic Cancer Cohort Consortium (PanScan) nested case–control study [30] where a 71–78% increases in the risk for current smokers were reported. No increased risk for former smokers compared with never smokers was observed in our analysis, in contrast to other reports, where the risk for former cigarette smokers remained elevated for a minimum 10 years after cessation [4,31,32]. The possible explanation for this result might be the long follow-up period in our study, however we cannot rule out the possibility that the result was a chance finding due to relatively small number of cases in former smokers. Although little is known on cigarette smoke-induced pancreatic carcinogenesis, studies show that nicotine and a number of carcinogens from tobacco smoke have the ability to reach the pancreatic gland via the bloodstream, where they can be metabolized into toxic substances and affect pancreatic cells [32].

Our result is suggestive of an elevated risk of pancreatic cancer among men with the highest alcohol consumption frequency and quantity. The results of the present analysis are in general agreement with reports from a recent collaborative-pooled analysis of 10 case–control studies within the International Pancreatic Cancer Case–Control Consortium (PanC4) where a modest positive association between heavy alcohol consumption and a risk of pancreatic cancer was observed (OR = 1.6, 95% CI 1.2–2.2 for ≥9 drinks per day) [9]. A small excess risk for pancreatic cancer was also reported in a pooled analysis of 14 cohort studies [33]. In the PanScan pooled analysis, no significant association between moderate to high levels of alcohol intake and the risk of

Table 3
Hazard ratios (95% CI) of pancreatic cancer according to education, anthropometric factors, biological measurements, and sitting time at work.

Variables	Age adjusted		Multivariable-adjusted	
	No. cases/No. subjects	HR (95% CI)	No. cases/No. subjects	HR (95% CI)
Education status[a]				
High school	20/1570	1 (reference)	18/1518	1 (reference)
Secondary	22/1858	1.01 (0.55–1.86)	22/1820	0.98 (0.52–1.85)
Unfinished secondary	26/1997	1.14 (0.64–2.04)	25/1942	1.04 (0.56–1.93)
Primary	9/1623	0.46 (0.21–1.03)	9/1590	0.42 (0.19–0.95)
Missing	0/84	–	3/262	–
P_{trend}		0.14		0.07
BMI (kg/m^2)[b]				
<25.0	20/1920	1 (reference)	20/1865	1 (reference)
25.0–29.9	37/3671	0.85 (0.50–1.47)	34/3546	0.96 (0.55–1.69)
≥30.0	20/1509	1.25 (0.67–2.33)	20/1459	1.66 (0.88–3.15)
Missing	0/32	–	3/262	–
P_{trend}		0.31		0.27
Height (cm)[c]				
<168.0	13/1605	1 (reference)	12/1544	1 (reference)
168.0–171.9	16/1569	1.30 (0.62–2.70)	15/1523	1.25 (0.58–2.69)
172.0–175.9	23/1839	1.52 (0.77–3.02)	23/1786	1.57 (0.77–3.17)
≥176.0	25/2091	1.48 (0.75–2.91)	24/2017	1.48 (0.72–3.00)
Missing	0/28	–	3/262	–
P_{trend}		0.24		0.25
Total cholesterol levels (mmol/l)[c]				
<5.20	13/1791	1 (reference)	13/1722	1 (reference)
5.20–5.89	24/1721	1.91 (0.97–3.75)	23/1657	1.81 (0.92–3.58)
5.90–6.62	16/1751	1.24 (0.60–2.57)	16/1695	1.22 (0.58–2.54)
≥6.63	22/1778	1.87 (0.94–3.72)	21/1714	1.76 (0.87–3.55)
Missing	0/91	–	4/344	–
P_{trend}		0.21		0.21
Systolic blood pressure (mmHg)[c]				
<123.0	22/1775	1 (reference)	21/1717	1 (reference)
123.0–133.9	20/1722	0.96 (0.52–1.76)	20/1651	0.95 (0.51–1.77)
134.0–146.9	21/1764	0.98 (0.54–1.79)	19/1700	0.86 (0.46–1.62)
≥147.0	14/1871	0.75 (0.38–1.47)	14/1802	0.66 (0.32–1.34)
Missing	0/0	–	3/262	–
P_{trend}		0.46		0.24
Diastolic blood pressure (mmHg)[c]				
<79.0	16/1609	1 (reference)	15/1560	1 (reference)
79.0–86.9	24/1949	1.24 (0.66–2.33)	23/1866	1.25 (0.65–2.40)
87.0–94.9	20/1843	1.15 (0.60–2.22)	20/1742	1.18 (0.60–2.35)
≥95.0	17/1759	1.13 (0.57–2.23)	16/1701	1.02 (0.49–2.31)
Missing	0/2	–	3/263	–
P_{trend}		0.82		0.97

[a] In multivariable analysis, adjusted for age, smoking status, alcohol consumption, body mass index.
[b] In multivariable analysis, adjusted for age, smoking status, alcohol consumption, education.
[c] In multivariable analysis, adjusted for age, smoking status, alcohol consumption, education, body mass index.

pancreatic cancer was observed (OR = 1.38, 95% CI 0.86–2.23, for 60 or more g/day versus <5 g/day) [34]. In our analysis, former and never drinkers had a somewhat elevated risk of pancreatic cancer. It may be that past heavy drinking or factors related to abstinence or quitting (e.g. chronic pancreatitis) could possibly influence this result. Besides ethanol, acetaldehyde, the metabolite of the alcohol, is a recognized carcinogen [3]. High levels of acetaldehyde have been detected in fruit-based liquor samples from Central European countries [35]. Heavy alcohol consumption may increase pancreatic cancer risk by potentiating the effects of other risk factors such as tobacco smoking, poor nutrition, and inflammatory pathways related to chronic pancreatitis, or it may have independent genetic and epigenetic effects [3,6,32].

We found that taller individuals had no significantly higher pancreatic cancer risk compared to shorter individuals. Our findings agree with most previous epidemiological studies that examined the association between height and cancer risk. Most studies have reported no statistically significant associations between height and pancreatic cancer [10,13,22,36]. In the EPIC study [37] evidence was found that increased height was associated with an increased risk (RR = 1.74, 95% CI 1.20–2.52) of developing pancreatic cancer. However, as the significant trend was due to a reduced risk in the lowest quartile, rather than a consistently increasing risk across quartiles, it remains unclear whether there is a real relationship between height and the risk of pancreatic cancer.

Obesity was shown to increase the risk of pancreatic cancer in several studies [13,14,36,37]. In a recent meta-analysis that examined an association between BMI and pancreatic cancer [38], a potential non-linear association was found with the highest increase in risk at BMI > 35 kg/m^2. Consistent with this report, our analysis showed the strongest risk among individuals in the highest category of BMI (≥30 kg/m^2). In contrast, other studies on obesity and pancreatic cancer have found no significant association among men [11,19], or excess body weight in early life rather than later onset excess body weight had a larger impact on risk [21].

Our data show that an increased level of serum cholesterol is a potential risk factor for pancreatic cancer, although the association was not statistically significant. This is in agreement with the recent Canadian population-based case–control study which reported that high dietary cholesterol was positively associated with an increased risk of pancreatic cancer and several other cancer sites in both men and women [39]. Unlike this study, a number of other studies did not find an association between cholesterol and pancreatic cancer for men [11,19,40].

In the current analysis, decreased HR was found in men with the lowest education level as compared with persons in the highest educational group. A similar result was found in a nested case–control study conducted among a large US cohort [16]. We can offer no explanation for this finding, except that in our study this risk estimate was based on small number of pancreatic cancers. Residual confounding by some unmeasured factors such as occupational exposure [41] or diet [16] may have contributed to the results. No association was found between the educational level attained and the risk of developing pancreatic cancer in the EPIC cohort [17] and a large prospective cohort study [40] in the UK.

The strengths of this study include its prospective design which minimizes recall and selection bias and up to 30 years length of follow-up. In the statistical analysis, we were able to control for a range of potential confounding variables, including smoking, alcohol consumption, educational level and BMI. A potential limitation of our study is the exposure assessment at a single point of time which could contribute to non-differential misclassification and attenuate risk estimates. We may have underestimated alcohol consumption among heavy drinkers who may have quit or reduced their alcohol intake before the initial alcohol assessment. There is potential for misclassification of disease due to relatively low rate of morphologic confirmation. This may have attenuated the effect estimates toward null [42]. In addition, because of the lack of data on cigar or pipe smoking for all cohort participants, in analyses this information was not taken into account. Including men exposed to cigar or pipe smoking in the reference group could have attenuated the associations between smoking and pancreatic cancer. Nonetheless, because cigarette smoking is the strongest risk factor and the number of participants smoking cigar or pipe was small, it is unlikely, that cigar or pipe smoking could have appreciably influenced results. When we conducted sensitivity analysis excluding cigar or pipe smokers, the results were essentially unchanged. The present study was also limited by the choice of covariates and the lack of statistical power due to the small sample size. We could not adjust our analyses for chronic pancreatitis, family history of pancreatic cancer and dietary characteristics, since information on these potential confounding factors is lacking. Furthermore, a relatively small number of pancreatic cancer cases precluded a stratified analysis by smoking and BMI.

In the Baltic countries, the prevalence of smoking among men is higher than in most other populations and it was increasing until recently [43]. High pancreatic cancer incidence rates among men in Lithuania and several other Eastern and Central European Countries [1,2] may be closely related to the high prevalence of tobacco smoking in the populations a few decades ago. Tobacco smoking is a preventable exposure; therefore its avoidance could substantially decrease the burden of pancreatic cancer.

In conclusion, our results confirm the findings of previous studies that cigarette smoking is causally related to pancreatic cancer. This prospective study provides some suggestions that, after accounting for potential confounding factors, alcohol consumption, body mass index and total cholesterol level may be associated with a risk of pancreatic cancer in men; however, these associations were not significant.

Conflicts of interest

None declared.

Acknowledgments

This study was supported by a grant (No. LIG-07/2010) from the Research Council of Lithuania. We would like to thank the staff of the Lithuanian Cancer Registry for making data available.

References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127(12):2893–917.
[2] Bosetti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Boffetta P. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog 2012;1(51):3.
[3] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. A review of human carcinogens personal habits and indoor combustions, vol. 100E. Lyon: IARC, 2012.
[4] Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis Langenbeck. Arch Surg 2008;393: 535–45.
[5] Vrieling A, Bueno-de-Mesquita HB, Boshuisen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;126:2394–403.
[6] International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate, vol. 96. Lyon, France: IARC, 2010.
[7] Rohrmann S, Linseisen J, Vrieling A, Boffetta P, Stolzenberg-Solomon RZ, Lowenfels AB, et al. Ethanol intake and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 2009;20(5):785–94.
[8] Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer 2010;126:1474–86.
[9] Lucenteforte E, La Vecchia C, Silverman D, Bagnardi V, Bellocco R, Rota M, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4). Ann Oncol 2012;23(2):374–82.
[10] Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer 2011;129(7):1708–17.
[11] Johansen D, Stocks T, Jonsson H, Lindkvist B, Björge T, Concin H, et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. Cancer Epidemiol Biomark Prev 2010;19(9):2307–17.
[12] Batty GD, Shipley MJ, Marmot MG, Davey Smith G. Blood pressure and site-specific cancer mortality: evidence from the original Whitehall study. Br J Cancer 2003;89:1243–7.
[13] Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. J Am Med Assoc 2001;286:921–9.
[14] Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Inaba Y, et al. Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. Int J Cancer 2007;120(12):2665–71.
[15] Zhang J, Dhakal IB, Gross MD, Lang NP, Kadlubar FF, Harnack LJ, et al. Physical activity, diet, and pancreatic cancer: a population-based, case–control study in Minnesota. Nutr Cancer 2009;61:457–65.
[16] de Martel C, Llosa AE, Friedman GD, Vogelman JH, Orentreich N, Stolzenberg-Solomon RZ, et al. Helicobacter pylori infection and development of pancreatic cancer. Cancer Epidemiol Biomark Prev 2008;17(5):1188–94.
[17] van Boeckel PG, Boshuizen HC, Siersema PD, Vrieling A, Kunst AE, Ye W, et al. No association between educational level and pancreatic cancer incidence in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol 2010;34(6):696–701.
[18] Weiderpass E, Pukkala E. Time trends in socioeconomic differences in incidence rates of cancers of gastro-intestinal tract in Finland. BMC Gastroenterol 2006;6:41.
[19] Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Cause Control 2002;13(5):417–26.
[20] Stocks T, Van Hemelrijck M, Manjer J, Bjørge T, Ulmer H, Hallmans G, et al. Blood pressure and risk of cancer incidence and mortality in the metabolic syndrome and cancer project. Hypertension 2012;59(4):802–10.
[21] Urayama KY, Holcatova I, Janout V, Foretova L, Fabianova E, Adamcakova Z, et al. Body mass index and body size in early adulthood and risk of pancreatic cancer in a central European multicenter case–control study. Int J Cancer 2011;129(12):2875–84.
[22] Eberle C, Paige M, Holly B. Anthropometric factors and pancreatic cancer in a population-based case–control study in the San Francisco Bay area. Cancer Cause Control 2005;16:1235–44.
[23] Glasunov IS, Dowd JE, Baubiniene A, Grabauskas V, Sturmans F, Schuurman JH. The Kaunas–Rotterdam Intervention Study. Amsterdam: Elsevier/North-Holland Biomedical Press, 1981.
[24] Bosma H, Appels A, Sturmans F, Grabauskas V, Gostautas A. Differences in mortality and coronary heart disease between Lithuania and the Netherlands: results from the WHO Kaunas–Rotterdam Intervention Study (KRIS). Int J Epidemiol 1994;23(1):12–9.
[25] Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents, vol. VIII. Lyon: International Agency for Research on Cancer, 2002
[26] Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al., eds. Cancer incidence in five continents, vol. IX. Lyon: International Agency for Research on Cancer, 2007.

[27] Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld W. Monotest cholesterol. Clin Chem 1983;29:1075.
[28] Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012;23: 28–36.
[29] Cox D. Regression models and life tables. J R Stat Soc 1972;34:187–220.
[30] Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403–13.
[31] Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case–Control Consortium (Panc4). Ann Oncol 2012;23(7): 1880–8.
[32] Duell EJ. Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. Mol Carcinog 2012;51(1): 40–52.
[33] Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomark Prev 2009;18(3):765–76.
[34] Michaud DS, Vrieling A, Jiao L, Mendelsohn JB, Steplowski E, Lynch SM, et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). Cancer Cause Control 2010;21(8): 1213–25.
[35] Boffetta P, Kaihovaara P, Rudnai P, Znaor A, Lissowska J, Swiatkowska B, et al. Acetaldehyde level in spirits from Central European countries. Eur J Cancer Prev 2011;20:526–9.
[36] Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med 2010;170(9):791–802.
[37] Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition cancer. Epidemiol Biomark Prev 2006;15(5):879–85.
[38] Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose–response meta-analysis of prospective studies. Ann Oncol 2012;23(4):843–52.
[39] Hu J, La Vecchia C, de Groh M, Negri E, Morrison H, Mery L, et al. Dietary cholesterol intake and cancer. Ann Oncol 2012;23(2):491–500.
[40] Batty GD, Kivimaki M, Morrison D, Huxley R, Smith GD, Clarke R, et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomark Prev 2009;18:673–5.
[41] Ojajarvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med 2000;57:316–24.
[42] Verhage BA, Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry and pancreatic cancer risk: an illustration of the importance of microscopic verification. Cancer Epidemiol Biomark Prev 2007;16:1449–54.
[43] Zatoński W, Przewoźniak K, Sulkowska U, West R, Wojtyła A. Tobacco smoking in countries of the European Union. Ann Agric Environ Med 2012;19(2): 181–92.