Lung Cancer 85 (2014) 361–365

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Body mass index, cholesterol level and risk of lung cancer in Lithuanian men

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ARTICLE INFO

Article history:
Received 7 April 2014
Received in revised form 9 July 2014
Accepted 11 July 2014

Keywords:
Body mass index
Total serum cholesterol
Lung cancer risk
Cohort studies
Lithuania

ABSTRACT

Objective: Our objective was to investigate the association between body mass index (BMI), total serum cholesterol (TSC) level and risk of lung cancer in a Lithuanian population-based cohort study.
Materials and methods: The study included 6729 men initially free from cancer. During the follow-up (1978–2008), 358 lung cancer cases were identified. Cox proportional hazards models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI).
Results: Following adjustment for age, smoking, alcohol consumption, and education, BMI 25–29.9 and ≥30.0 kg/m^2 hazard ratios (HR) were significantly associated with decreasing risk for lung cancer, HR = 0.73; 95% CI: 0.59, 0.91 and 0.62; 95% CI: 0.45, 0.87, respectively (p_{trend} = 0.001) compared to BMI <25 kg/m^2. Inverse association between BMI and lung cancer was observed among current smokers. We found no evidence that BMI was associated with decreased lung cancer risk in never smokers, although small sample size precluded meaningful analysis. Not significantly lower risk of lung cancer among participants in the 5th quintile compared with the 1st quintile of TSC concentrations was observed. HR per 1 mmol/l increase of TSC was 0.90; 95% CI: 0.82, 1.00. Findings suggest consistent effects of BMI and TSC when follow-up was 1993–2008.
Conclusion: Our results show an inverse dose-dependent association between lung cancer risk and BMI in Lithuanian men, especially among current smokers. The inverse association could not be attributed to preclinical cancer effect hypothesis. TSC level was not statistically significantly related to a lung cancer incidence.

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1. Introduction

Lung cancer rates in Lithuanian men remain among the highest in the world [1], and this is closely related to the high prevalence of tobacco smoking in this population [2,3].

Previous studies confirmed the substantial body mass index (BMI) gradients in lung cancer incidence and mortality in the United States, Canada, Europe, Asia, lower lung cancer risk was mostly observed in individuals with higher BMI [4–9]. It has been hypothesized that a true etiologic effect might explain the inverse association between BMI and lung cancer [8,10]. However, the clear understanding is precluded by the fact that the relationships are easily biased by weight loss due to pre-clinical lung cancer (reverse causality), and by smoking, which is a strong risk factor for lung cancer and is associated with lower BMI. In some studies it was shown that BMI was associated with decreased lung cancer risk in smokers but no association was found in never smokers [7,9,11]. In contrast, in a recent study inverse association between BMI and lung cancer was identical for never/lighter smokers and heavier smokers [8]. Thus, due to differences in classification of smoking status (e.g. when never and lighter smokers are considered as one group), lack of prospective cohort studies (case–control study design is more susceptible to systematic biases), relatively modest sample sizes and other possible problems (e.g. weight, documented shortly before diagnosis), the epidemiological evidence for the association of BMI with lung cancer remains inconclusive. Furthermore, there is little information on the relation of obesity to lung cancer among Eastern Europeans specifically [4].

An inverse association between cholesterol level and lung cancer was shown in several studies [12–14]. Other studies observed no clear relationship with cholesterol level or inverse association only in the first year [15,16]. The hypothesis that there is a direct causal link between low cholesterol and lung cancer has been suggested, although biological mechanisms that might play role in this

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http://dx.doi.org/10.1016/j.lungcan.2014.07.009
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relationship are not well understood [8,14]. It is possible, that low serum cholesterol may be caused by undetected lung cancer; the inverse relation may be caused by competing risks of death, particularly from coronary heart disease; and, also, the association may be confounded by such factors as serum retinol, vitamin E, and b-carotene [13]. Thus, observations on causal link between low cholesterol and lung cancer are controversial.

We investigated the associations between baseline BMI, total serum cholesterol (TSC) level and risk of lung cancer. In this article we also report findings by smoking status and from a second half of the follow-up period (1993–2008).

2. Material and methods

2.1. Data source

Our study, described in detail elsewhere [3,17], included two cohorts–the Kaunas-Rotterdam Intervention Study (KRIS) and Multifactorial ischemic heart disease prevention study (MIHDPS). Briefly, a random sample of men aged 45–59 (KRIS) or 40–59 (MIHDPS), living in the city of Kaunas (Lithuania) were recruited during the years 1972–1974 (KRIS) and 1976–1980 (MIHDPS). In all, 8380 participants were available for analysis. We excluded 1651 participants with death or cancer other than non-melanoma skin cancer before the start of follow-up ($n = 309$), unknown vital status ($n = 389$), duplicates ($n = 469$) and incomplete information on smoking, alcohol consumption, education level, BMI and TSC ($n = 484$). The number of participants in the current analysis was 6729.

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). During the follow-up period, cases of cancer were identified through the Lithuanian Cancer Registry, which has population-based information available since 1978. The site of the primary cancer and the date of the cancer diagnosis were obtained from the Cancer Registry. The vital status of the subjects and causes of death were determined from the Lithuanian Residents' Register Service and the National and Regional Archives on Causes of Death. For the present study, lung cancer codes C33–34 (162) were used (International Statistical Classification of Diseases, 10th (9th) Revision).

At baseline, all participants underwent physical examination (height, weight, TSC level, blood pressure) and were interviewed (smoking history, education and other factors) [18]. Weight (kg) and height (cm) were measured in light clothing and without shoes by using a bodymeter and stadiometer, respectively, by registered nursing staff. 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 meters (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 to 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. Cholesterol levels were measured in serum according to the modified "direct" manual method of Huang et al. [18,19]. TSC level was categorized into quintiles based on the distribution observed in our male cohort population. The first (lowest) quintile was used as the reference category. Each cohort member was asked about smoking status, age they began and stopped smoking, amount of cigarettes per day, and type of cigarettes usually smoked. Participants were classified as current, former or never smokers. A summary measure of lifetime smoking exposure (pack-years) was calculated and current smokers were classified into categories: <10 pack-years, 10–19 pack-years, 20–29 pack-years and ≥30 pack-years. Smokers were further grouped according to the type of cigarettes (filter, non-filter, papirosi). Participants were categorized into four groups according to educational level (primary, unfinished secondary, secondary, high school).

Study participants were followed from 1 January 1978 to 31 December 2008. 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.

2.2. Statistical analyses

Cox proportional hazards models were used to assess the association between BMI, serum cholesterol and the incidence of lung cancer. In the multivariable analysis, all models were stratified by study and adjusted for age (<50, 50–54, ≥55 years), alcohol consumption (non-drinker, a few times per year, 1–4 times per month, 2–7 times per week), educational level (primary, unfinished secondary, secondary, high school) and pack-years of smoking (never, former, <10, 10–19, 20–29, ≥30 pack-years). For the effect of BMI on lung cancer risk with adjustment for serum cholesterol, TSC level (quintiles) was included as a covariate in the Cox regression models. For the effect of serum cholesterol on risk with adjustment for BMI, a three-level BMI (<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2) was included as a covariate in the Cox regression models.

The TSC levels within the quintiles were: <5.02; 5.020–5.612; 5.613–6.156; 6.157–6.854 and >6.854 mmol/l. In analyses among current smokers cigarette type was included as confounding variable. For the linear trend test ordinal BMI and TSC variables were modeled as continuous in the proportional hazards model. Additionally, the multivariable-adjusted HRs associated with a TSC level increase in 1 mmol/l were estimated.

We assessed the proportional hazards assumptions by inspecting the log(−log) survival curves for the exposure and adjustment variables; no violation of proportional hazards was observed. Sensitivity analyses were performed by excluding cases within the first half of the follow-up period, and BMI < 18.5 kg/m^2 (data not shown). Associations were essentially unchanged. Subgroup analyses were employed to examine the effects of BMI and TSC among never smokers and current smokers separately.

All statistical analyses were performed using the Statistical Package SPSS 19 for Windows (IBM Corporation, Somers, NY, USA). All p-values were based on two-sided tests and, if less than 0.05, considered statistically significant.

The study protocol and data handling procedures were approved by the Regional Biomedical Research Ethical Committee in Vilnius (No. 158200-02-280-65).

3. Results

Descriptive characteristics of the study cohort by BMI at baseline are presented in Table 1. About 30% of participants were never smokers, 25% were former smokers, and 45% were current smokers. The mean age at entry was similar across the different groups of BMI. Compared with participants with BMI <25 kg/m^2 at baseline, participants with higher BMI (≥25 kg/m^2) were less likely to have primary education, to be smoker or heavy drinker of alcohol; and more likely to have high cholesterol level. Correlation between total cholesterol and BMI was weak ($r = 0.13$). During the follow-up period, we observed 358 cases of lung cancer.

After adjustment for age, decreased HRs were found in men with the BMI 25–29.9 kg/m^2 or ≥30 kg/m^2 as compared with persons with BMI <25 kg/m^2 (HR = 0.49, 95% CI: 0.39–0.61 and HR = 0.36, 95% CI: 0.26–0.50, respectively) (data not shown). Multivariable-adjusted hazard ratios (HRs) for lung cancer in relation to BMI are presented in Table 2. In comparison to BMI <25 kg/m^2, BMI 25–29.9 kg/m^2 or ≥30 kg/m^2 was associated with a decreased

Table 1
Descriptive statistics for the study population by body mass index.

	BMI (kg/m^2)		
	<25	25–29.9	≥30.0
No. of participants	1804	3468	1457
No. of lung cancer cases	149	165	44
Age (years)[a]	52.6 ± 5.8	52.5 ± 5.7	53.1 ± 5.7
Education (primary)[b]	25.8	21.5	23.1
Cigarette smoking status[b]			
Never	22.8	33.4	33.1
Former	14.1	26.4	33.3
Current	63.0	40.2	33.6
Smokers ≥30 pack-years[b]	23.7	12.7	10.1
Alcohol intake "a few times/week–daily"[b]	7.9	4.7	4.6
Total serum cholesterol, 5th quintile[b]	14.3	22.6	22.7

[a] mean ± SD.
[b] indicated in %.

risk of lung cancer, HR = 0.73; 95% CI: 0.59–0.91 and HR = 0.62; 95% CI: 0.45–0.87, respectively, $p_{trend} = 0.001$. Further adjustment for serum TSC slightly attenuated these associations, nevertheless, statistically significant dose-response trend was observed ($p_{trend} = 0.019$). The analysis showed significant inverse association between BMI and lung cancer among current smokers ($p_{trend} = 0.018$) and no association among never smokers.

We also calculated the HR estimates for BMI for the second half of the follow-up period (1993–2008) to better address reverse causality problem as well as to assess the long-term effect of BMI on lung cancer. A total of 184 lung cancer cases were identified among the 5094 men who were alive on 1 January 1993. In this lag time analysis the inverse association remained, but was not statistically significant: among men with BMI ≥ 30 kg/m^2 compared with BMI < 25 kg/m^2; HR = 0.70; 95% CI: 0.42–1.16, $p_{trend} = 0.243$ (Table 2).

Hazard ratios for lung cancer according to TSC level are presented in Table 3. In the multivariate adjusted model, the relative risk for developing lung cancer among men within the 5th quintile of TSC was 0.75, 95% CI: 0.53–1.05; $p_{trend} = 0.096$) compared to those within 1st quintile. HR per 1 mmol/l increase of TSC was 0.90, 95% CI: 0.82–1.00. The multivariate adjusted HR per 1 mmol/l increase of TSC was statistically significantly reduced among current smokers (HR = 0.88, 95% CI: 0.79–0.98), whereas among never smokers, HRs were not statistically significant, but were in the expected direction. The lag time analysis showed similar pattern, however the inverse association was not statistically significant.

4. Discussion

The present study supports existing evidence that BMI is associated with a decreased risk of lung cancer in a dose-response manner. These results are consistent with previous epidemiological studies and reviews [4–9], and provided additional information on the link between lung cancer and BMI.

Our data show that an increased BMI was associated with a reduced lung cancer risk among smokers, whereas there was no association among never smokers. A number of studies have assessed the relation of BMI to lung cancer risk within categories of smoking status. Several studies found an inverse association among current smokers and a weaker or no association among never smokers [6–11]. Leung et al. [5] demonstrated an inverse relationship between BMI and lung cancer deaths among both smokers and non-smokers.

Cholesterol level was significantly associated with lung cancer risk in several studies [12–14,20]. In contrast, a number of studies did not find an association between cholesterol and lung cancer [15,16]. Our results show that, men with higher TSC levels experienced lower lung cancer risk compared with men with lower TSC levels, in particular among smokers. Moreover, the data suggest that inverse relation for lung cancer was present among never smokers, although results were not statistically significant and should be interpreted with caution due to sparse numbers. Finally, the inverse relation persisted for lung cancer diagnosed more than a decade after cholesterol measurement, similar to Ahn et al. study [14].

Factors that might explain the decreased risk of lung cancer among men with high BMI include an impact of increased body fat on adduct levels, probably by affecting the distribution of the lipid soluble carcinogens [10] or the relationship between obesity and endogenous estrogens [21]. Adipose tissue is the primary site for estrogen synthesis and studies have found the positive association between BMI and estrogen levels [21]. According to Smith et al. [7], "estrogen compounds may outcompete carcinogenic aromatic hydrocarbons from cigarette smoke for estrogen receptors in lung tissue, thereby reducing exposure at the target tissues". Other possible explanations might be obesity's effects on distribution of ventilation within the lungs that may alter the exposure of different lung regions to tobacco smoke and, consequently cancer risk [22]. It could also be speculated that various factors associated with leanness, e.g. psychosocial, dietary characteristics or heavy physical activity levels (often from occupational, unhealthy activities) may be linked to low body mass and, consequently, increased risk of lung cancer. As previously mentioned, biological mechanisms that might account for a cholesterol–cancer relationship are not well understood. High-density lipoprotein cholesterol regulation of cell cycle entry via a mitogen-activated protein kinase–dependent pathway or apoptosis, modulation of cytokine production, and antioxidative function have been considered as biologically plausible [14].

Another explanation for the observed inverse association between BMI and the risk of lung cancer as well as cholesterol and risk of lung cancer might be "preclinical cancer effect" hypothesis, that weight loosing and cholesterol level reduction might be caused by undiagnosed preclinical lung carcinoma at study entry [8]. However, our data show, that the inverse relation, although, not statistically significant, persisted for lung cancer diagnosed more than a decade after BMI and TSC measurement, indicating that lower BMI and serum cholesterol may be causal factors and not markers of existing malignancy. It has also been suggested that competing risks could explain inverse association, i.e. patients with high cholesterol levels are more likely to be depleted from a cohort due to cardiovascular mortality before they are diagnosed with lung cancer [16]. In a study by Eichholzer et al. [13] this explanation was supported by the fact that association between TSC and lung cancer was only seen in older but not in younger study participants, possibly because the older age is a strong risk factor for both cardiovascular diseases and lung cancer. In our study, mean age at baseline was similar to that in Eichholzer et al. [13] study, however

Table 2
Hazard ratios (HR) and 95% confidence intervals (CI) of lung cancer according to body mass index.

BMI	Adjustment A[a]		Adjustment B[b]		Follow-up 1993-2008[b]		Never smokers[c]		Current smokers[d]	
	No. of cases/*N*	HR (95% CI)	No. of cases/*N*	HR (95% CI)	No. of cases/*N*	HR (95% CI)	No. of cases/*N*	HR (95% CI)	No. of cases/*N*	HR (95% CI)
<25	149/1804	1	149/1804	1	69/1296	1	3/412	1	141/1137	1
25–29.9	165/3468	0.73 (0.59–0.91)	165/3468	0.81 (0.65–1.02)	95/2744	0.97 (0.71–1.34)	13/1159	1.69 (0.47–6.04)	136/1393	0.82 (0.64–1.04)
≥30.0	44/1457	0.62 (0.45–0.87)	44/1457	0.69 (0.49–0.97)	20/1054	0.70 (0.42–1.16)	3/483	0.99 (0.20–5.00)	31/489	0.65 (0.44–0.97)
p_{trend}		0.001		0.019		0.243		0.989		0.018

[a] In multivariable analysis, adjusted for age, smoking (pack-years), alcohol consumption, education.
[b] In multivariable analysis, adjusted for age, smoking (pack-years), alcohol consumption, education, total serum cholesterol (quintiles).
[c] In multivariable analysis, adjusted for age, alcohol consumption, education, total serum cholesterol (quintiles).
[d] In multivariable analysis, adjusted for age, alcohol consumption, education, total serum cholesterol (quintiles), smoking (pack-years), type of cigarettes.

Table 3
Hazard ratios (HR) and 95% confidence intervals (CI) of lung cancer according to quintiles of total serum cholesterol level.

Cholesterol level	Total		Follow-up 1993–2008		Never smokers		Current smokers	
	No. of cases/*N*	HR[a] (95% CI)	No. of cases/*N*	HR[a] (95% CI)	No. of cases/*N*	HR[b] (95% CI)	No. of cases/*N*	HR[c] (95% CI)
Quintile 1	90/1337	1	43/1029	1	6/402	1	78/618	1
Quintile 2	77/1359	0.92 (0.68–1.25)	41/1053	0.99 (0.65–1.53)	3/463	0.41 (0.10–1.66)	69/588	0.96 (0.69–1.32)
Quintile 3	67/1299	0.83 (0.60–1.14)	38/995	0.95 (0.61–1.47)	5/394	0.74 (0.22–2.45)	56/581	0.81 (0.57–1.14)
Quintile 4	70/1362	0.87 (0.63–1.19)	33/1025	0.83 (0.52–1.31)	2/404	0.26 (0.05–1.33)	62/624	0.90 (0.64–1.26)
Quintile 5	54/1372	0.75 (0.53–1.05)	29/992	0.77 (0.48–1.24)	3/391	0.51 (0.13–2.09)	43/608	0.71 (0.48–1.03)
p_{trend}		0.096		0.163		0.261		0.082
Continuous (per 1 mmol/l)		0.90 (0.82–1.00)		0.89 (0.77–1.02)		0.80 (0.51–1.25)		0.88 (0.79–0.98)
P^d		0.043		0.087		0.319		0.021

[a] In multivariable analysis, adjusted for age, BMI, smoking (pack-years), alcohol consumption, education.
[b] In multivariable analysis, adjusted for age, BMI, alcohol consumption, education.
[c] In multivariable analysis, adjusted for age, BMI, smoking (pack-years), alcohol consumption, education, type of cigarettes.
[d] In multivariable analysis, when continuous TSC level increment per 1 mmol/l was considered.

the follow-up time was considerably longer. Therefore, competing risks as possible explanation of inverse cancer-cholesterol relationships in our study can not be ruled out. Nonetheless, it is unlikely, that this effect could have appreciably influenced results, as studies that have incorporated competing risk of death in life-table analyses of cancer death and cholesterol concentrations, have failed to find such an effect [13].

The main strength of this study was the prospective design, with data collected up to 30 years prior to the cancer diagnosis, thus minimizing the risk of recall bias and bias due to reverse causation. The available data allowed us to test for a number of potential confounding factors. After adjustment the relationship between BMI and lung cancer risk was attenuated but remained statistically significant. Further adjustment for TSC slightly attenuated the risk estimates for BMI and lung cancer, but the association remained inverse and statistically significant. Thus, TSC likely accounts for some of the decreased cancer risk among men with high BMI. That the risk remains statistically significantly decreased may reflect residual confounding due to smoking or factors such as alcohol, diet, physical activity, occupation, income and environmental exposure. Since most of these factors are measured with a certain degree of error, residual confounding cannot be completely ruled out, but this possible bias is unlikely to be important, given that the associations found were strong. Previous large studies have reported a lower risk of lung cancer, not totally explained by smoking, alcohol intake or diet, among those in the highest BMI or cholesterol level category [7,8,12]. The use of data at baseline was a weakness of the study, because during the long follow-up the BMI, levels of TSC or confounding factors (e.g. smoking habits) of study participants may have changed; thus, it is likely that misclassification might have occurred. A more comprehensive approach to represent smoking behavior in this study was taken using pack-years instead of smoking status or smoking duration or intensity only. In addition, we incorporated an aspect of smoking habit, which was available in this study, such as type of cigarettes smoked. No information on pathological confirmation of cancer was available for this study, thus there is a potential for misclassification of disease due to relatively low rate of pathological confirmation of lung cancer in Lithuania [23]. This may have attenuated the effect estimates toward null. Further limitations include lack of power, thus we cannot entirely rule out the possibility of chance findings. The sample size was reduced a lot after focusing on never smokers in our study, thus the error may have occurred. The modest sample size also limited our ability to perform a more detailed analysis of the data, e.g. interaction analysis between BMI, TSC and tobacco consumption.

5. Conclusion

Our results confirmed that BMI is inversely associated with lung cancer, in particular among men smokers in Lithuania. The association could not be explained by the preclinical cancer effect hypothesis. TSC was not statistically significantly related to a lung cancer incidence.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to thank the staff of the Lithuanian Cancer Registry and Lithuanian Residents' Register Service for making data available.

This study was supported by a grant (No. LIG-07/2010) from the Research Council of Lithuania.

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