A case-control study of lifestyle and lung cancer associations by histological types

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The objective of the study was to investigate the contribution of dietary factors and physical exercise to the variation in the risk of lung cancer and its major histological types among men and women in the Czech Republic, and reveal interactions between smoking and diet/physical exercise, if any. In a hospital based case-control study, data collected by in-person interviews from 1096 microscopically confirmed lung cancer cases (587 women, 509 men) and 2966 controls were analyzed using unconditional logistic regression stratified by appropriate factors. Among all nonsmoking women protective effects were observed for black tea (OR=0.69), among all smoking women for wine (OR=0.71), physical exercise (OR=0.64) and vitamin supplements (OR=0.71). Among all men, inverse associations were found in smokers between lung cancer risk and frequent intake of fruits (OR=0.69) or moderate intake of spirits (OR=0.64), and a direct association for fat foods (OR=1.68). Comparing the effects of diet/physical activity on lung cancer risk among nonsmokers versus smokers, interactions with smoking appeared for the intake of black tea and milk/dairy products among women, and for moderate intake of spirits in men. When the effects of diet/physical exercise on risk were analyzed by major cell types in women, the intake of wine and physical exercise were inversely associated with the risk of both adenocarcinoma and small cell cancer, the intakes of fruits and vitamin supplements were inversely associated with the risk of squamous cell cancer. In men, the intake of fat foods was directly associated with the risk of squamous cell cancer, while the frequent intake of apples was inversely associated with the risk of both squamous- and small cell cancers. In men an inverse association with the risk of squamous cell cancer was found for the intake of other fruits. These data suggest that diet/physical exercise may affect the risk of lung cancer and major cell types, and that interactions between some dietary items and smoking may occur. Lung cancer is a multifactorial disease, since smoking, its main determinant, and other environmental and lifestyle factors interact with one another and with genetic factors to cause the disease.

Key words: lung cancer; diet; physical activity; risk factors; interaction; epidemiology

Current knowledge of the mechanisms of cancer suggests that all cancers are both environmental and genetic, meaning that there are multiple causes that involve exposures originating outside the body as well as hereditary and genetic changes that converge to produce the disease [1]. Significant associations with smoking have been found for all major cell types of lung cancer. However, smoking seems to have the strongest effect on small- and squamous-cell cancers and the weakest on adenocarcinoma [2]. Therefore, it is not surprising that adenocarcinoma has always represented the majority of lung cancers among nonsmokers of both genders, and that adenocarcinoma is the least affected by increasing duration of smoking cessation [3]. The greater proportion of adenocarcinoma among nonsmokers in comparison to other cell types may suggest that factors other than smoking may be involved in the etiology of this cell type of lung cancer [4]. The variation in association between smoking and cell types of lung cancer may be related to increase in use of filter low tar cigarettes [5, 6], tumor location, prevalence of other factors such as genetic profile, occupational or other environmental exposures [2]. Evidence has been provided [7, 8] that exogenous and endogenous oestrogens may be involved

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Table 1. Distribution of cases and controls by age and cell types

Variables	**Women**					**Men**				
	Adenoca	*Squamous*	*Small*	*All cases*	*Controls*	*Adenoca*	*Squamous*	*Small*	*All cases*	*Controls*
Population	207	149	132	587	2178	101	249	81	509	788
Mean age	62.4	63.8	63.2	63.2	57.3	63.5	63.9	62.0	63.4	56.5
(SD)	10.4	9.4	9.4	10.0	12.4	8.9	8.0	8.1	8.3	9.7
Age (yrs)	%	%	%	%	%	%	%	%	%	%
25-34	1.0	0.0	0.0	0.5	3.7	0.0	0.0	0.0	0.0	0.0
35-44	3.9	2.7	3.0	3.1	10.5	2.0	0.0	1.2	0.6	11.7
45-54	16.9	16.1	18.2	17.5	29.8	15.8	13.7	16.0	15.1	32.1
55-64	33.8	29.5	30.3	30.0	26.9	40.6	40.2	48.1	41.3	35.8
65-74	31.9	39.6	34.8	36.3	19.3	26.7	34.9	25.9	31.4	15.5
75-84	12.6	12.1	13.6	12.3	9.1	14.9	11.2	8.6	11.6	4.9
85-89	0.0	0.0	0.0	0.3	0.7	0.0	0.0	0.0	0.0	0.0

in the development of lung cancer, particularly adenocarcinoma, in women, acting as lung tumor promoters through a receptor-mediated mechanism. Epidemiologic studies have indicated that dietary factors may also play a role in lung cancer etiology [9]. It is possible that the degree of risk produced by smoking and genetic susceptibility varies, depending on diet [10]. Examining dietary patterns rather than specific nutrients may have an advantage, in that many epidemiologic studies have provided evidence that dietary and lifestyle patterns, rather than individual constituents, play a role in cancer prevention [11].

To obtain more insight in the contribution of dietary factors and physical exercise to the variation in the risk of lung cancer and its major histological types among men and women in the Czech Republic, and reveal interactions between smoking and diet/physical exercise, if any, we conducted a case-control study. This report is based on 1096 cases of lung cancer (including 308 cases of adenocarcinoma, 398 squamous cell cancers, and 213 small cell cancers) and 2966 controls.

Participants and methods

Study population and data collection. In a hospital-based case-control study of lung cancer, conducted in a major Prague university hospital, cases were patients with newly diagnosed microscopically confirmed primary lung cancer. Controls were spouses, relatives, or friends of other patients of the hospital, with conditions unrelated to smoking. Both cases and controls had to be aged 25-89 years, and reside within the catchment area covering the north-eastern sectors of Prague and the adjacent Central Bohemia Region (10 administrative districts). The interviewers were trained extensively to standardize data collection and coding techniques and to minimize inter-interviewer variation. Before the interview, informed consent was obtained from all interviewed cases and controls. Personal interviews were completed with 587 female lung cancer cases (92% of those eligible) and 2178 female controls (response rate 81%) from April 1998 to August 2006. The same interviewers completed the face-to-face interviews with 509 male cases (93% of eligible) and 788 male controls (response rate 78%) from April 2002 to August 2006. The reasons for non-participation among 638/547 eligible female/male cases included patient´s inability to cooperate during interview as a result of severe physical or mental disability (4.9%/4.5%), refusal to be interviewed (1.0%/2.0%), or death shortly after admission (2.1%/0.5%). Nonresponse among 2689/1010 eligible female/male controls was due to 'no time for interview' (14.6%/16.9%), refusal to be interviewed (3.9%/5.1%), and a language barrier or mental incompetence (0.5%/0.0%).

Questionnaire and definitions. The questionnaire has been described previously elsewhere [12, 13]. In brief, the questionnaire included a basic structured section on demographic characteristics; place of residence; type of house, occupation and workplace; further, a complete smoking history. Subjects were defined as current smokers if they smoked, at the time of the survey, either daily or occasionally. A daily smoker was someone who smoked at least one cigarette a day for at least three months, i.e., a total of approximately 100 cigarettes and over. An occasional smoker was someone who smoked, but not every day. Never smokers either have never smoked at all or have smoked less than 100 cigarettes in their lifetime. Ex-smokers were people who were formerly smokers but currently have not smoked for at least six months. In ex-smokers, the time since quitting was recorded. In this report, we present results for two study groups of cases and controls: Group 1, called 'Nonsmokers', including never smokers + long-term ex-smokers (quitted 20 or more years ago); and Group 2, called 'Smokers', defined as current smokers + short-term ex-smokers (quitted less than 10 years ago) (Table 2). The questionnaire included sections on exposure to environmental tobacco smoke, physical exercise (hours per week); preexisting lung disease or cancer (diagnosed by a physician at least 2 years before interview); family history of cancer among first degree relatives (parents and siblings); and menstrual and pregnancy history.

Information on dietary habits was collected with 9 food items (red meat, poultry, fish, milk and dairy products, fat

Table 2. Smoking habits, study groups, and the risk of lung cancer, by gender and cell types

WOMEN

Variables	*Adenoca*		*Squamous cell*		*Small cell*		*All cases*	
	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])
Smoking habits								
Never smokers	69	1.00 Referent	30	1.00 Referent	10	1.00 Referent	140	1.00 Referent
Ex-smokers:								
quit≥20 yrs	12	1.79 (0.92-3.47)	3	1.13 (0.33-3.84)	6	6.07 (2.13-17.27)	23	1.72 (1.04-2.83)
10 to <20yrs	15	2.07 (1.12-3.81)	12	3.70 (1.79-7.62)	9	7.47 (2.92-19.13)	41	2.80 (1.85-4.29)
quit<10 yrs	44	4.90 (3.18-7.55)	37	11.44 (6.63-19.77)	32	25.51136 (12.05-54.00)	8.10	(5.94-11.05)
Current smokers	67	4.03 (2.72-5.97)	67	10.94 (6.65-17.99)	75	35.27247 (17.41-71.45)	7.72	(5.88-10.12)
Study groups								
Group 1 [c] 'Nonsmokers'	81	1.00 Referent	33	1.00 Referent	16	1.00 Referent	163	1.00 Referent
Group2 [d] 'Smokers'	111	4.22 (3.00-5.92)	104	10.43 (6.67-16.30)	107	21.74 (12.32-38.40)	383	7.46 (5.85-9.51)

MEN

Variables	*Adenoca*		*Squamous cell*		*Small cell*		*All cases*	
	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])	Cases	OR[a](95%CI[b])
Smoking habits								
Never smokers	7	1,00 Referent	3	1.00 Referent	4	1.00 Referent	18	1.00 Referent
Ex-smokers:								
quit≥20 yrs	14	3.56 (1.32-9.61)	17	9.42 (2.60-34.12)	3	1.34 (0.28-6.30)	48	4.52 (2.38-8.50)
10 to <20yrs	12	6.23 (2.20-17.58)	19	20.01 (5.49-72.89)	5	4.49 (1.11-18.14)	40	7.25 (3.68-14.27)
quit<10 yrs	12	6.61 (2.35-18.62)	54	74.96 (21.71-259.04)	18	15.03 (4.71-48.04)	95	19.11 (10.25-35.66)
Current smokers	56	13.01 (5.35-31.60)	156	87.71 (26.23-293.24)	51	17.18 (5.80-50.91)	308	27.19 (15.24-48.47)
Study groups								
Group 1 [c] 'Nonsmokers'	21	1,00 Referent	20	1.00 Referent	7	1.00 Referent	66	1.00 Referent
Group 2 [d] 'Smokers'	68	5.24 (2.89-9.51)	210	18.69 (10.60-32.96)	69	15.04 (6.42-35.23)	403	10.35 (7.08-15.12)

[a] OR, odds ratio, adjusted for age, residence and education

[b] CI, confidence interval

[c] Group 1 'Nonsmokers' = Never smokers + Ex-smokers, quitted 20 or more years ago.

[d] Group 2 'Smokers' = Ex-smokers, quitted <10 years ago + Current smokers.

foods, vegetables, apples, other fruits, vitamin supplements); 4 nonalcoholic beverage items (black tea, green tea, herbal tea, coffee), and three alcoholic beverage categories (beer, wine, and spirits). The subjects were asked to try to estimate the best fitting answer reflecting the usual consumption in most years within the 10-year period before interview. One of four frequency estimates of consumption was to be selected: 1. Never, 2. Monthly or less, 3. Weekly or less, but more than once per month, or 4. Daily or several times per week. After completion of the questionnaire, the trained interviewer took basic anthropometric measures, such as standing height and weight.

Statistical methods. Statistical analyses were done using the unconditional logistic regression adjusted for age (in 5-year categories), residence, and education, and, where appropriate, for pack-years of smoking, as well. All adjusting variables were entered in the logistic regression as multiplicative and categorical factors. Tests for linear trend in tables

Table 3. Diet/physical exercise and the risk of lung cancer, by gender and smoking history.

	WOMEN					MEN				
	Group 1 'Nonsmokers'		Group 2 'Smokers'		Interaction	Group 1 'Nonsmokers'		Group 2 'Smokers'		Interaction
Variables	OR[a]	95%CI[b]	OR[a]	95%CI[b]	P-value[g]	OR[a]	95%CI[b]	OR[a]	95%CI[b]	P-value[g]
Red meat [c]	1.29	0.91-1.84	1.19	0.89-1.59	P=0.724	1.47	0.72-2.98	0.79	0.53-1.18	P=0.128
Poultry [c]	0.85	0.60-1.21	1.06	0.78-1.43	P=0.341	0.97	0.37-2.53	1.16	0.75-1.80	P=0.737
Fish [d]	0.94	0.66-1.36	1.34	0.98-1.83	P=0.138	0.82	0.41-1.66	1.15	0.80-1..66	P=0.391
Milk/dairy products [c]	1.74	0.76-3.96	0.62	0.37-1.03	P=0.034	4.35	0.69-27.28	0.64	0.31-1.31	P=0.052
Fat foods [d]	1.00	0.70-1.41	0.88	0.66-1.19	P=0.576	1.43	0.66-3.11	1.68	1.02-2.75	P=0.726
Vegetables [c]	1.11	0.64-1.94	0.75	0.50-1.15	P=0.258	1.13	0.44-2.85	0.79	0.52-1.20	P=0.484
Apples[e]	0.93	0.61-1.41	0.77	0.56-1.04	P=0.469	0.54	0.29-1.09	0.77	0.54-1.10	P=0.375
Other fruits [c]	1.09	0.77-1.56	0.98	0.73-1.32	P=0.644	1.07	0.56-2.03	0.69	0.48-0.99	P=0.235
Vitamin supplements[e]	1.08	0.76-1.54	0.71	0.53-0.95	P= 0.067	0.68	0.35-1.33	0.74	0.52-1.07	P=0.824
Black tea[c]	0.69	0.49-0.98	1.24	0.93-1.66	P=0.009	1.51	0.77-2.94	1.00	0.70-1.41	P=0.276
Green tea[e]	0.88	0.61-1.27	1.09	0.80-1.49	P=0.373	1.08	0.56-2.08	0.93	0.63-1.38	P=0.696
Herbal tea [c]	1.13	0.78-1.62	1.10	0.82-1.47	P=0.908	0.73	0.37-1.41	1.04	0.71-1.51	P=0.357
Coffee[c]	0.86	0.59-1.26	0.76	0.48-1.20	P=0.678	0.91	0.43-1.92	1.07	0.61-1.86	P=0.728
Beer[e]	0.97	0.69-1.37	1.15	0.86-1.53	P=0.447	1.15	0.38-3.50	1.16	0.65-2.08	P=0.989
Wine[e]	0.84	0.57-1.22	0.71	0.52-0.96	P=0.491	0.96	0.47-1.98	1.05	0.73-1.51	P=0.824
Spirits[e]	0.78	0.45-1.34	0.78	0.54-1.14	P=1.000	1.37	0.71-2.65	0.64	0.44-0.93	P=0.044
Physical exercise >1h/week[f]	0.97	0.62-1.52	0.64	0.45-0.90	P=0.142	0.75	0.15-3.66	0.73	0.37-1.41	P=0.975

[a] OR, odds ratio, adjusted for age, residence, education and pack-years of smoking
[b] CI, confidence interval
[c] Daily or several times per week
[d] Weekly or less, but more than once per month / Daily or several times per week
[e] Monthly or less / Weekly or less / Daily or several times per week
[f] Physical exercise, sport, or walking, more than 1 hour per week.
[g] P-value for test of no interaction.

were performed in equidistant categorical levels (1,2,…).The comparison of relative risks (odds ratio, OR) between smokers and nonsmokers was based on the so called interaction in terms of the ratio of the relative risks. For statistical evaluation, the interaction was converted into $LR = \ln(OR_2/OR_1)$ with standard error $SE(LR) = \sqrt{[\, SE(\ln(OR_2))^2 + SE(\ln(OR_1))^2}$]. The statistical test of no interaction (LR=0) and the confidence intervals were based on z=LR/SE(LR) with approximate normal distribution.

Results

Among women, the most frequent cell type was adenocarcinoma (35.3%), among men, squamous cell cancer (48.9%) (Table 1).The mean age did not differ significantly between all female cases (63.2 years) and all male cases (63.4 years). For both genders, the mean age of patients with squamous cell cancer (63.8 years in women, 63.9 years in men) was higher than the age of patients with adenocarcinoma or small cell cancer. The variation in lung cancer risk by smoking habits and cell types is shown in Table 2. As expected for ex-smokers, an inverse trend can be noted in the risk with years since quitting. The risk for all cases in the study group 2 'smokers' was significantly higher (OR for women 7.46; for men 10.35) than in the study group 1 'nonsmokers'. Very high relative risks were observed for female patients with small cell cancers, and for male patients with squamous cell cancers.

Lung cancer risk estimates associated with food and beverage intake and physical exercise are shown in Table 3, by gender and smoking history. After adjustment for age, residence, education and pack-years of smoking, protective effects were observed among women 'nonsmokers' for black tea (OR=0.69, 95%CI 0.49-0.98); and among women 'smokers' for wine (OR=0.71, 95%CI 0.52-0.96), physical exercise (more than 1 hour per week; OR=0.64, 95%CI 0.45-0.90), and vitamin supplements (OR=0.71, 95%CI 0.53-0.95). Among smoking men, a direct association with the risk of lung cancer appeared for fat foods (OR=1.68, 95%CI 1.02-2.75), and an inverse association for daily or several times per week consuming fruit (OR= 0.69, 95%CI 0.48-0.99), and for moderate intake of spirits (OR=0.64, 95%CI 0.44-0.93). In women, interactions between smoking and dietary components were found for milk/dairy products (P=0.034) and black tea (P=0.009); and in men for spirits (P=0.044).

Table 4. Diet/physical exercise and the risk of lung cancer, by gender and cell type

	Women						Men					
	Adeno-carcinoma		Squamous cell		Small cell		Adeno-carcinoma		Squamous cell		Small cell	
Variables	OR[a]	95%CI[b]	OR[a]	95%CI[b]	OR[a]	95%CI[b]	OR[a]	95%CI[b]	OR[a]	95%CI[b]	OR[a]	95%CI[b]
Red meat [c]	0.99	0.62-1.57	1.64	0.85-3.16	1.72	0.84-3.51	1.13	0.29-4.45	1.99	0.51-7.84	0.77	0.20-2.96
Poultry [c]	1.16	0.94-1.60	1.03	0.70-1.51	0.70	0.47-1.04	2.07	0.99-4.30	0.84	0.54-1.33	1.35	0.67-2.70
Fish [d]	1.15	0.83-1.60	1.27	0.85-1.90	1.06	0.70-1.62	1.21	0.72-2.04	1.02	0.69-1.50	1.13	0.65-1.96
Milk/dairy products [c]	0.83	0.47-1.60	0.60	0.31-1.15	0.79	0.37-1.66	1.09	0.42-2.83	1.12	0.54-2.34	0.79	0.29-2.13
Fat foods [d]	0.85	0.63-1.16	0.83	0.57-1.20	1.02	0.68-1.52	1.41	0.76-2.60	2.25	1.34-3.38	1.96	0.92-4.19
Vegetables [c]	0.91	0.57-1.45	0.63	0.38-1.03	0.70	0.40-1.21	1.44	0.72-2.88	0.70	0.45-1.10	1.18	0.60-2.31
Apples[c]	1.00	0.70-1.41	0.80	0.54-1.18	0.69	0.46-1.03	1.18	0.71-1.96	0.67	0.46-0.98	0.51	0.30-0.87
Otherfruits [c]	1.27	0.93-1.74	0.63	0.44-0.92	0.98	0.66-1.46	0.90	0.55-1.46	0.62	0.42-0.92	0.94	0.55-1.61
Vitamin supplements [e]	0.87	0.64-1.19	0.68	0.47-0.99	0.74	0.49-1.10	0.84	0.52-1.37	0.80	0.55-1.18	0.66	0.39-1.13
Black tea[c]	0.98	0.72-1.33	1.32	0.91-1.91	0.94	0.63-1.41	1.17	0.72-1.90	1.27	0.87-1.85	0.93	0.56-1.57
Green tea[e]	1.04	0.76-1.43	0.95	0.64-1.41	0.84	0.55-1.28	1.12	0.67-1.88	0.76	0.50-1.16	0.94	0.53-1.64
Herbal tea [c]	1.02	0.75-1.40	0.95	0.66-1.39	1.09	0.73-1.63	0.96	0.59-1.58	0.81	0.54-1.21	0.94	0.55-1.60
Coffee[c]	0.93	0.62-1.38	0.80	0.49-1.30	0.90	0.52-1.55	1.58	0.74-3.36	0.98	0.57-1.66	0.93	0.45-1.92
Beer[e]	0.81	0.59-1.10	1.28	0.88-1.86	0.97	0.65-1.45	1.17	0.51-2.71	1.26	0.65-2.44	0.75	0.33-1.68
Wine[e]	0.68	0.49-0.94	0.95	0.65-1.40	0.56	0.36-0.86	0.79	0.48-1.29	1.00	0.68-1.48	0.82-	0.48-1.38
Spirits[e]	0.67	0.43-1.04	1.10	0.69-1.77	0.76	0.45-1.29	0.99	0.60-1.64	0.77	0.52-1.14	0.70	0.41-1.21
Physical exercise[f]	0.59	0.42-0.84	0.71	0.46-1.11	0.61	0.39-0.97	1.80	0.51-6.41	0.63	0.30-1.29	0.79-	0.27-2.26

[a] OR, odds ratio, adjusted for age, residence, education and pack-years of smoking
[b] CI, confidence interval
[c] Daily or several times per week
[d] Weekly or less, but more than once per month / Daily or several times per week
[e] Monthly or less / Weekly or less / Daily or several times per week
[f] Physical exercise, sport, or walking, more than 1 hour per week

In Table 4, variations in lung cancer risk in relation to diet and physical exercise are shown by gender and major cell types. Among women, the intake of wine and physical exercise were inversely associated with the risk of both adenocarcinoma and small cell cancer, the intake of fruits and vitamin supplements were inversely associated with the risk of squamous cell cancer. In men, the intake of fat foods was directly associated with the risk of squamous cell cancer, while the frequent intake of apples was inversely associated with the risk of both squamous- and small cell cancers, and an inverse association with the risk of squamous cell cancer was found for the intake of other fruits.

Similar, but more detailed analyses (by gender, cell types and smoking-specific categories) could not been conducted, as numbers of observations in groups were too small.

Discussion

In the absence of precise knowledge of the biological mechanisms involved in the onset of the disease, synergism (or antagonism) is often used as a synonym for statistical interaction, ie. departure from additivity of the response variables of interest [14]. Another view of interaction is more general and the test of interactions is in fact the test of homogeneity of effects in different categories of a modifying factor. In our analyses, we used this view of interaction as effect modification, more precisely as a difference in the effect of a factor on disease risks depending on the presence or absence of another factor. We have tested the differences in the effect of dietary components on the risk of lung cancer depending on the presence or absence of smoking. However, the variations in smoking habits may be associated with considerable food and nutrient intake differences between smokers and non-smokers. The analysis of data from the Second National Health and Nutrition Examination Survey showed that smokers were less likely to have consumed vegetables, fruit, low fat milk, and vitamin and mineral supplements than non-smokers. These data suggest that the high cancer risk associated with smoking is compounded by somewhat lower intake of nutrients and foods which are thought to be cancer protective [15]. The associations between dietary factors and lung cancer are likely to be very weak in comparison to smoking. Therefore, it may be difficult to discern whether the dietary factors have truly been disentangled from the effects of smoking [16].

In women 'smokers' of the present study, a statistically non-significant protective effect was observed for daily or several times per week intake of milk/dairy products (OR 0.62, 95% CI 0.37–1.03). In the German study of lung cancer in non-

smoking women, protective effects with high intakes of cheese, milk and other dairy products were observed, showing a statistically significant trend with consumption of cheese [17]. Information on the type of milk (whole or reduced fat) was not available in the German or our studies. In a case–control study of lung cancer in Buffalo, subjects reporting consumption of whole milk three or more times daily had a twofold increase in lung cancer risk compared with those who reported never drinking whole milk. The same frequency of intake of reduced-fat milk was associated with a significant protective effect [18]. In a population-based study of non-smoking subjects in New York State, consumption of greens, fresh fruits and cheese was associated with a significant dose-dependent reduction in risk for lung cancer, whereas consumption of whole milk was associated with a significant dose-dependent increase in the risk [19]. Dietary data collected in the 1987 National Health Interview Survey, and linked to the National Death Index, showed an inverse association for dairy products, a positive association with lung cancer mortality for red meat intake, and no significant association for the intake of fruit and vegetables [20].

There is a substantial evidence for the role of diet in cancer prevention, including an important role for vegetable and fruit consumption [9]. Over 200 studies have been published referring to lung cancer risk related to vegetables and fruits [20]. Smith-Warner et al.[21] analyzed data on fruit and vegetable consumption and lung cancer risk in 8 prospective studies with a total of 3,206 incident lung cancer cases having occurred among 430,281 women and men, followed up to 6-16 years across studies. The results suggested that elevated fruit and vegetable consumption was associated with a modest reduction in lung cancer risk, which was mostly attributable to fruit, not vegetable, intake. In a large prospective study, the European Prospective Investigation into Cancer and Nutrition, carried out in 10 European countries, a significant inverse association between fruit consumption and lung cancer was found, however, there was no association between vegetable consumption or vegetable subtypes and lung cancer risk [22]. In the Danish prospective cohort study 'Diet, Cancer and Health' Skuladottir et al. [23] found an inverse association between lung cancer risk and high intake of fruit, vegetables and total plant food. In a prospective study of 77 283 women in the Nurses' Health Study and 47 778 men in the Health Professionals' Follow-up Study higher fruit and vegetable intakes were associated with lower risks of lung cancer in women but not in men [24]. Among men participating in the present Czech case-control study, we found an inverse association between the risk of squamous- and small-cell cancers and frequent (daily or several times per week) intake of apples (Table 3). Among both women and men an inverse relationship between the risk of squamous-cell lung cancer and the intake of other fruits was observed. Recently, it has been stated [25] that the evidence that overall increases in fruit and vegetable consumption will reduce cancer incidence appreciably has become much weaker than believed earlier, although modest benefits for some specific cancers cannot be excluded.

Alcoholic beverages have been classified as carcinogenic to humans by the International Agency for Research on Cancer [26]. A causal association with alcohol consumption is suspected for cancer of the lung [27]. On the other hand, evidence is accumulating that drinking low to moderate amount of alcohol (1–2 drinks per day) might also have beneficial effects, mainly on cardiovascular disease, while data for cancer are still inconclusive [28]. In a meta-analysis of 16 cohort studies, the lowest relative risk of all-cause mortality was observed for men consuming 1–2 drinks per day, and for women consuming 0-1 drink per day [29]. Differential effects of specific alcoholic beverages have been hypothesized. The cancer preventive effect appears more pronounced with wine, and it is speculated that resveratrol, a natural component specifically present in red wine, may be the main component responsible for this effect [28]. In a pooled cohort study in Denmark, the risk of lung cancer in men decreased by consumption of over 13 drinks of wine per week (RR=0.44), while consumption of corresponding amounts of beer and spirits increased the risk [30]. In the present study, protective effects were observed in the group of female 2smokers' for intake of wine (OR=0.71, 95%CI 0.52–0.96); and in male 'smokers' for moderate intake of spirits (OR=0.64, 95%CI 0.44–0.93) (Table 3), however, residual confounding by smoking cannot be excluded. Among men interviewed in the present study, 34% admitted to have never drunk spirits. Among ever drinkers, 72% had a drink of spirits monthly or less. In two population-based case-control studies in Montreal [31] the consumption of spirits was found to be harmful for men, while for women drinking moderate amounts of spirits (1-6 drinks/week) a protective effect was noted (OR=0.4, 95%CI 0.3–0.6). In the Montreal study, protective effects for drinking moderate amounts of wine was noted in both men and women.

Epidemiological studies on cancer-preventive effects of tea produce inconsistent results, which could partly be attributed to the lack of a universal standard for tea preparations [32]. In a review of the epidemiological evidence, Blot et al. [33] quoted 3 case-control, and 4 cohort studies, however, in all of them except one no association was noted. In the present study, we found a significantly decreased risk of lung cancer for women 'nonsmokers' consuming black tea daily or several times per week (OR=0.69, 95%CI 0.49-0.98), while no significant association with the risk was observed among women 'smokers', resulting in the test of interaction P-value of 0.009 (Table 3).

In a review of scientific evidence on physical activity and cancer prevention, Friedenreich and Orenstein [34] identified 11 studies examining physical activity as a risk factor of lung cancer, of which 8 found a risk reduction. In the report of the IARC Working Group on the Evaluation of Cancer Preventive Strategies [35], 5 cohort studies and two case–control studies have been listed. In all of the cohort studies, a lower

risk of lung cancer was associated with physical activity. The largest studies were the Harvard Health Alumni Study [36]), and a population-based cohort study in Norway [37]. The Norwegian scientists measured both recreational and occupational activity, and found a 30% decreased risk when these activities were combined into a total activity variable for the male study subjects, but no comparable risk decrease was observed for females. In the present study, an inverse association was found between lung cancer risk and time (hours/week) devoted to physical exercise among smoking women (Table 3), while no significant decrease in the risk appeared among women non-smokers. Among men, the decrease in the risk was not statistically significant. Some recent research on physical activity and cancer yielded unlike results. Detailed information on recreational, household and occupational physical activity among 416,277 men and women living in 10 European countries were obtained from the European Prospective Investigation into Cancer and Nutrition (between 1992 and 2000). No consistent protective associations of physical activity with lung cancer risk were found [38].

Conclusions. The results indicate, in agreement with findings of previous epidemiological studies, that diet and physical exercise, may contribute to variation in lung cancer risk, and act as modifiers of the degree of risk produced by smoking and genetic susceptibility.

In the present study, elevations or decreases in lung cancer risk related to diet and physical activity were observed more frequently among subjects with squamous- and small-cell cancers than among those with adenocarcinoma.

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