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Dietary Habits and Lung Cancer Risk among Polish Women

Jadwiga Rachtan

From the Epidemiology Unit, Centre of Oncology, M. Skłodowska-Curie Memorial Institute, Cracow, Poland

Correspondence to: Jadwiga Rachtan, Epidemiology Unit, Centre of Oncology, M. Skłodowska-Curie Memorial Institute, Garncarska 11, 31–115 Cracow, Poland. Tel: +48 12 429 3753. Fax: +48 12 422 6680. E-mail: z5rachta@cyf-kr.edu.pl

Acta Oncologica Vol. 41, No. 4, pp. 389–394, 2002

The purpose of this case-control study was to examine the effect of usual diet, in relation to other risk factors, on the risk of different histologic types of lung cancer in women. A total of 242 women with histologically confirmed primary lung cancer and 352 healthy controls were enrolled in a study conducted in Cracow between 1991 and 1997. A multivariate analysis showed that frequent consumption of carrots (at least five times a week) significantly lowered the risk of lung cancer. The protective effects of carrots were statistically significant for squamous cell carcinoma, small cell carcinoma and adenocarcinoma. It was found that daily consumption of other vegetables had a significant protective effect against squamous cell carcinoma, and for all histologic types combined. Furthermore, a significantly reduced risk was observed in women who consumed margarine (at least three times a week). This effect was observed for all cell types. The results also suggest that frequent consumption of carrots and frequent consumption of margarine can have a protective influence against lung cancer irrespective of the number of cigarettes smoked and the amount of vodka drunk.

Received 1 November 2001
Accepted 18 April 2002

The role of diet in the aetiology of lung cancer remains unknown. The hypothesis that diet may have an influence on risk for lung cancer is based, among other things, on the observation that about 15–20% of lung cancer cases are not attributed to smoking (1, 2).

The results of epidemiological studies over the past decade have consistently shown that diets high in fruits and vegetables decrease lung cancer risk (3). Data from epidemiological studies also indicate that diets rich in cholesterol or fat increase the risk for lung cancer (4).

Cigarette smoking accounts for the majority of lung cancers in both sexes. The epidemiology of lung cancer appears to differ between men and women in that a lower proportion of cancers in women are attributable to cigarette smoking. Therefore, the role of other risk factors in the aetiology of female lung cancer should be considered. The present study was designed to assess the association of a variety of possible risk factors, such as diet, smoking, passive smoking, alcohol, occupational exposure, family cancer and non-malignant respiratory diseases, with different histologic types of lung cancer in women.

This paper reports the results of one part of the study, addressing the risk associated with dietary habits.

MATERIAL AND METHODS

The case subjects included 242 women with histologically confirmed diagnosis of primary lung cancer (ICD 9th Revision, code 162) who were admitted to the M. Skłodowska-Curie Memorial Institute in Cracow, Poland between 1 March 1991 and 31 December 1997. Cases were identified during their first visit to the hospital. Patients with suspected primary lung cancer were usually interviewed before the first medical examination. There were no refusals among subjects, but 9 were judged by the interviewer to be too ill to be interviewed. Cases were definitely included in the analysis of the present study after histologic confirmation.

The controls included 352 women who were the healthy relatives of cancer patients (without tobacco-related cancer) other than the studied patients. There were no refusals among controls. All lung cancer cases and controls were residents of the same area (Cracow region).

After obtaining oral consent, all subjects were interviewed by a trained interviewer in the hospital. Interviews were conducted using a structured questionnaire including information (among other items) on demographic characteristics, complete lifetime history of smoking, occupational exposure, residence, respiratory diseases, cancer in

 ISSN 0284-186X

first-degree relatives, as well as usual consumption of alcoholic beverages since the age of 25 and usual diet.

To assess dietary habits 5 years prior to the investigation, the subjects were asked to estimate their frequencies of intake of 16 food items, including meat, fish, processed meat, liver products, eggs, milk, cheese, cheese spread, butter, margarine, carrots, tomatoes, lettuce, spinach and other vegetables and fruits.

Statistical analyses were performed using STATISTICA version 5.5 software. All analyses were conducted separately for all lung cancers combined and for the main cell types (squamous cell, small cell, adenocarcinoma). There were too few other histologic types of lung cancer for inclusion by cell type. Univariate logit models were used to calculate odds ratio (OR) together with 95% confidence intervals (CI) (5).

All risk factors that had a significant effect on risk in at least one histologic group of lung cancers in a univariate analysis were estimated simultaneously in a multivariate unconditional logistic regression analysis. The final multivariate model was obtained through stepwise regression (backward approach). In order to compare risks for different histologic groups, the multivariate model with the same explanatory variables was estimated for each group.

The regression models contained terms for age, pack-years of smoking (0, 1–19, ≥ 20), passive smoking during childhood (no, yes), beer consumption level (0, ≤ 50 g per week, > 50 g per week), vodka consumption level (0, ≤ 25 g per week, > 25 g per week), place of residence in urban areas only (no, yes), cancer in siblings (no, yes), and prior history of tuberculosis (no, yes). Adjustment was also made for occupational exposure to coal dust (no, yes), other dusts, (no, yes), rubber (no, yes), other chemicals (no, yes), and for employment in the metallurgical industry (no, yes).

A separate analysis (adjusted for age) was also made to estimate the influence of consumption of carrots, other vegetables, fruits and margarine, taking into consideration different levels of smoking and/or vodka drinking. Women who smoked at least 20 cigarettes a day were defined as heavy smokers. Women were considered heavy drinkers if they drank more than 25 g of vodka per week.

RESULTS

The combined set cases included 89 squamous cell carcinomas (37%), 87 small cell carcinomas (36%) and 52 adenocarcinomas (21%); the rest were mixed and other types (n = 14).

The median age for squamous cell carcinoma was 62.0 years, for small cell carcinoma 58.0 years, for adenocarcinoma 59.0 years, and for all cases the median age was 61.0. The median age for the controls was 58.0 years.

The selected characteristics of the 242 subjects and 352 controls in this study are described in Table 1. No differences were found between subjects and controls for education. A higher proportion of urban lifetime residence was observed among subjects than among controls (51.2% vs. 36.4%).

Cigarette smoking was more common among subjects (77.7%) than controls (28.7%). The age-adjusted relative risks corresponding to 1 to 19, 20 to 29, and ≥ 30 pack years of smoking were 3.02 (1.83–5.01), 12.72 (6.70–24.16), and 25.92 (14.48–46.40), respectively, as compared to those who never were smokers, thus showing the expected dose response for lifetime smoking.

There were significant differences in the intake of alcoholic beverages between subjects and controls. The proportion among vodka drinkers was 68.6% for subjects and 37.2% for controls. A larger proportion of case subjects (25.2%) than controls (17.9%) were beer drinkers.

In general, all subjects reported higher frequencies of intake of meat, processed meat, and butter than controls.

The univariate analysis (adjusted for age) showed that relative risk significantly increased with increased intake of meat, processed meat and butter for each histologic type separately and all cases of lung cancer combined. The consumption of cheeses significantly increased the risk only for adenocarcinoma [cheese: OR = 2.78 (1.35–5.75); cheese spread: OR = 2.34 (1.30–4.24)].

The risk for each histologic type separately and all cases of lung cancer combined declined markedly with increasing intake of margarine on bread, carrots and fruits. Consumption of tomatoes and other vegetables was shown

Table 1

Selected characteristic for case subjects and control subjects

Characteristic	Cases (n = 242)		Controls (n = 352)	
	n	%	n	%
Education				
University	20	8.3	46	13.1
Secondary	83	34.3	115	32.7
Vocational	38	15.7	55	15.6
Elementary	101	41.7	136	38.6
Life time residence only urban				
No	118	48.8	224	63.6
Yes	124	51.2	128	36.4
Smoking				
Never smoked	54	22.3	251	71.3
1–19 pack years	40	16.5	66	18.8
20–29 pack years	44	18.2	17	4.8
≥ 30 pack years	104	43.0	18	5.1
Intake of vodka				
Non-drinker	76	31.4	221	62.8
≤ 25 g/week	114	47.1	121	34.4
> 25 g/week	52	21.5	10	2.8
Intake of beer				
Non-drinker	181	74.8	289	82.1
≤ 50 g/week	25	10.3	53	15.1
> 50 g/week	36	14.9	10	2.8

to have a significant protective effect for both squamous cell carcinoma and adenocarcinoma, and also for all histologic types combined. The protective effect of spinach was statistically significant only for all cases of lung cancer combined. The risk of lung cancer declined with increasing milk consumption. A significant effect was observed for each histologic type separately and all types combined.

Results of multivariate standardization after controlling for potentially confounding factors showed that frequent consumption of carrots (at least five times a week) significantly lowered the risk (Table 2). The protective effects of carrots were statistically significant for each histologic type separately and all cases combined. The strongest protective effect was observed for small cell carcinoma.

The protective effect of daily consumption of other vegetables was also statistically significant but only for squamous cell carcinoma and all histologic types combined.

A significantly reduced risk was observed in women using margarine on bread. The effect of margarine against lung cancer was observed for all cell types. Furthermore, the results of multivariate analysis showed that frequent consumption (at least three times a week) of cheese spread significantly increased the risk of adenocarcinoma.

In addition, the influence of consumption of carrots, other vegetables, fruits and margarine was estimated taking into consideration different levels of smoking and/or vodka drinking (Table 3). High intake (at least five times a week) of carrots showed a significant protective effect in all exposure categories, with the exception of the group of heavy drinkers and heavy smokers where the protective effect was not statistically significant. Daily intake of other vegetables did not show significant protective effects against lung cancer in the category of heavy smokers and heavy drinkers. The protective effect from daily intake of fruits was observed when only one risk factor (smoking or drinking) was present. Margarine was shown to have a significant protective effect against lung cancer in all analysed categories of exposure, with the exception of the group of heavy drinkers and heavy smokers where the protective effect was not statistically significant.

DISCUSSION

In our study, the controls were selected from the same population as the case subjects. It should be stressed that the motivation to participate in the study was similar among subjects and controls. The control group also had some experience of cancer in their next-of-kin, and therefore, like the subjects, they were willing to give complete and accurate information.

To minimize the impact of potential biases of data collection (recall bias, systematic non-response), all information was collected by personal interviews with subjects and controls in the same place (hospital) and concurrently. Subjects were asked to recall their habitual diet as of five years before the diagnosis of cancer, and comparable time periods were required for the controls. Detailed data were collected for potentially confounding factors by obtaining as complete a life history as possible for cigarette smoking, alcohol drinking, occupational exposure as well as other variables. This facilitated control of these factors in the multivariate analysis. The interviewer was trained, and used a standardized questionnaire. This method minimizes the responder bias (recall bias) and observer bias. It should be stressed that only newly diagnosed cases were included. Memory of past events in personal histories tends to be more accurate in newly diagnosed cases than in prevalent

Table 2

Odds ratio (OR) of lung cancer by cell type according to dietary factors—multivariate analysis

Intake frequency	All cell types		Squamous cell		Small cell		Adenocarcinoma		Controls
	n	OR[a] (95% CI)	n	OR[a] (95% CI)	n	OR[a] (95% CI)	n	OR[a] (95% CI)	n
Carrots									
Rarely	221	1.00	80	1.00	80	1.00	47	1.00	174
At least 5×/week	21	0.13 (0.06–0.26)	9	0.17 (0.06–0.46)	7	0.09 (0.03–0.29)	5	0.12 (0.04–0.38)	178
Other vegetables									
Rarely	213	1.00	82	1.00	71	1.00	46	1.00	251
Every day	29	0.24 (0.11–0.52)	7	0.14 (0.04–0.49)	16	0.37 (0.13–1.08)	6	0.35 (0.11–1.12)	101
Margarine									
Rarely	203	1.00	74	1.00	73	1.00	44	1.00	146
At least 3×/week	39	0.16 (0.09–0.28)	15	0.12 (0.05–0.30)	14	0.11 (0.04–0.27)	8	0.14 (0.06–0.39)	206
Cheese spread									
Rarely	140	1.00	55	1.00	53	1.00	24	1.00	234
At least 3×/week	102	1.62 (0.94–2.81)	34	1.30 (0.57–2.96)	34	1.62 (0.67–3.90)	28	2.54 (1.16–5.58)	118

[a] Adjusted for age, pack years of smoking, passive smoking, consumption of beer and vodka, siblings with cancer, tuberculosis, place of residence, occupational exposure to coal and other dusts, rubber, acid mist, solvents, other chemicals and employment in the metallurgical industry.

Table 3

Odds ratio (OR) for lung cancer in subjects with consumption of carrots, other vegetables, fruits and margarine, according to smoking and vodka drinking

Intake frequency	Non-smoker Non-drinker Case/Control 23/179 OR[a] (95% CI)	Non-smoker Drinker Case/Control 31/72 OR[a] (95% CI)	Smoker Non-drinker Case/Control 53/42 OR[a] (95% CI)	Smoker Drinker Case/Control 135/59 OR[a] (95% CI)	Heavy smoker Heavy drinker Case/Control 42/3 OR[a] (95% CI)
Carrots					
Rarely	1.00	1.00	1.00	1.00	1.00
At least 5 ×/week	0.10 (0.03–0.36)	0.05 (0.01–0.37)	0.05 (0.01–0.24)	0.12 (0.06–0.25)	0.33 (0.02–5.01)
Other vegetables					
Rarely	1.00	1.00	1.00	1.00	1.00
Every day	0.10 (0.01–0.75)	0.25 (0.05–1.19)	0.23 (0.07–0.75)	0.32 (0.16–0.66)	0.18 (0.01–2.91)
Fruits					
Rarely	1.00	1.00	1.00	1.00	1.00
Every day	0.38 (0.15–0.98)	0.30 (0.11–0.78)	0.28 (0.12–0.69)	0.72 (0.38–1.39)	0.46 (0.03–6.56)
Margarine					
Rarely	1.00	1.00	1.00	1.00	1.00
At least 3 ×/week	0.19 (0.07–0.54)	0.23 (0.09–0.60)	0.09 (0.03–0.27)	0.11 (0.06–0.23)	0.11 (0.01–1.59)

[a] Adjusted for age.

cases. In addition, new cases are less likely to have changed their habits as a result of the disease (6).

Because lung cancer is a disease with a short survival time, validation of the answers on past diet is difficult. In this situation, as in other case-control studies on lung cancer, the reported frequency of consumption was accepted without any attempt to validate the data from other sources (7). It should be stressed that single food-frequency questionnaire measurements could characterize dietary habits for a period of at least five years. Results of studies on validity and reliability carried out by comparison with diet records or serum analyses generally show that food-frequency questionnaires can measure individual intake for a variety of nutrients (8).

Most results of cohort and case-control studies conducted in different geographical areas of the world showed a statistically significant protective association connected with frequent consumption of vegetables and/or fruits (9–15).

The relationship between consumption of vegetables and fruits and specific histologic types of lung cancer has been investigated in only a few studies, and with inconsistent results (10, 16). In some studies, which involved only or predominantly men, the protective effect was mostly limited to squamous and/or small cell carcinoma (11, 17), although a protective effect was seen also for adenocarcinoma (12, 18). The results of some studies comprising only women show that the protective association was stronger for adenocarcinoma or large cell carcinoma (9, 19, 20). However, in the studies conducted by Gao et al. (21), Steinmetz et al. (22), and Agudo et al. (15) similar relative risks were observed for frequent consumption of vegetables and fruits for each histologic subtype.

In the present study, the protective effect of carrots was seen for all histologic types, but the effect seemed to be strongest for small cell carcinoma. Daily intake of vegetables was shown to have the strongest protective effect against squamous cell carcinoma.

The protective association with a high intake of carrots has been reported by both case-control studies and cohort studies (10, 12, 13, 16–18). Carrots are an especially rich source of β-carotene, one of the carotenoids that can be converted into vitamin A, which is necessary for regulation of epithelial cell differentiation. Furthermore, the protective role of carotenoids may be related to their ability to quench singled oxygen and block the carcinogenic effect of free radicals.

Vegetables are also sources of other potentially anticarcinogenic agents such as vitamins C, E, folate and indoles, flavonoids, phenols, isoflavones and protease inhibitors (22).

It should be noted that the results of prospective studies have shown that both smoking and drinking have an influence on carotenoid levels. In the study by Stryker et al. (23), it was observed that women who smoked one pack of cigarettes a day had on average 79% of the plasma β-carotene level found among non-smokers who consumed a similar amount of carotenoids in their diet. In a similar evaluation, women who drank 20 g of alcohol per day had β-carotene levels that represented 89% of those found in non-drinkers. Aoki et al. (24) observed that serum concentration of β-carotene among non-drinking and non-smoking women was 650 μg/L. The level of β-carotene among female drinkers who were currently smoking was 401 μg/L. The results of this study suggest that smoking or alcohol drinking may affect serum carotene concentration (espe-

cially β-carotene level) either independently or synergistically.

Despite the fairly consistent data from epidemiological investigations suggesting that dietary intake of β-carotene may protect against lung cancer, the results from clinical trials have been controversial. Three trials, The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), which included only men, The Beta-Carotene and Retinol Efficacy Trial (CARET), which included men and women and The Physicians' Health Study (PHS), which included only men, provided no evidence of any beneficial effects of β-carotene supplementation on lung cancer (25–27). In addition, it was also observed that supplementation with α-tocopherol does not prevent lung cancer.

Various explanations for the results of the trials have been suggested, although none has been fully accepted. It is stressed that in the intervention studies high doses of β-carotene were used for relatively short periods. The amounts of β-carotene in the supplements used in trials were higher than the mean daily dietary intake of β-carotene. It has also been suggested that β-carotene from supplements may have different biological properties from the dietary intake of β-carotene.

In the present study, the protective effect of margarine was observed with regard to all histologic types.

Margarine is a source of vitamins A, E and β-carotene. Epidemiological studies investigating the association between lung cancer risk and diet high in vitamin E are limited in number and show inconsistent results.

The primary role of vitamin E is to protect polyunsaturated fatty acids in cell membranes from oxidative damage. Vitamin E is considered to be more effective as an antioxidant than other antioxidants such as β-carotene. In addition, Wattenberg (28) has characterized vitamin E as a cancer inhibitor that prevents the formation of carcinogens from precursor compounds. Menkes et al. (29) observed that blood levels of vitamin E in people who developed lung cancer during the following 8 years contained 12% less vitamin E than those in healthy controls. Moreover, it appeared that vitamin E levels were lower in lung cancer family members than in controls (average levels: 11.85 mg/L and 14.10 mg/L, respectively).

In the present study, women with adenocarcinoma reported a higher consumption of foods rich in saturated fat (butter, cheese, cheese spreads) than women with other histologic types of lung cancer. The results of a univariate analysis (adjusted for age) showed a significant association between consumption of the above-mentioned food products and adenocarcinoma. After a multivariate analysis it was found that only the frequent consumption of cheese spreads significantly influenced the increased risk of adenocarcinoma.

In a case-control study, Jain et al. (30) found an elevated risk of lung cancer associated with high cholesterol and fat intake. The cholesterol effect was strongest for adenocarcinoma. Also in a case-control study conducted by Alavanja et al. (14), a strongly increasing trend in the risk for lung cancer with increased saturated fat consumption among non-smoking women was observed. The effect of saturated fat was more pronounced for adenocarcinoma than for other cell types.

The biological mechanisms by which dietary fat and cholesterol may increase lung cancer are unknown. It is postulated that fat in the diet may promote (or initiate) lung carcinogenesis. Cell membrane lipid composition affects cell fluidity, permeability and gap junction intercellular communication (4).

In conclusion, the present study supports earlier observations that diet plays a role in the aetiology of lung cancer. Frequent consumption of carrots as well as margarine appeared to be protective for all histologic subtypes. Daily consumption of other vegetables also lowered the risk of lung carcinoma. Moreover, the results suggest that frequent consumption of both carrots and margarine has a protective effect against lung cancer regardless of the amount of cigarettes smoked and the quantity of vodka drunk, although the protective effects in the category of heavy smokers and heavy drinkers were not statistically significant.

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