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Dietary intake in newly diagnosed lung cancer patients

Исхрана болесника са новодијагностикованим раком плућа

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SUMMARY

Introduction/Objective Although smoking is the main risk factor for lung cancer (LC), studies have shown that diet could also play an important role.

The aims of this study was to analyze dietary intake of newly diagnosed LC patients and to compare with sex and age matched healthy controls.

Methods Sixty-nine non-treated LC patients (50 male, 19 female, aged 46–80 years), and 70 healthy controls (50 male, 20 female, aged 47–76 years) fulfilled a validated food frequency questionnaire in presence of a trained nutritionist. Nutrient intake was calculated using the Serbian Food Composition Database.

Results Similar energy intake was reported by both groups. However, the controls had significantly higher intake of total fats, saturated, monounsaturated, and n-3 polyunsaturated fatty acids (PUFA) and lower intake of carbohydrates and n-6 PUFA. Patients with LC reported markedly lower intakes of milk and dairy products, eggs, seafood, vegetables and fruits, and higher intake of grains and grain products.

Conclusion Patients with LC had significantly different dietary intake of most nutrients than healthy participants, suggesting that changes in dietary patterns could contribute to prevention of lung cancer development.

Keywords: lung cancer; dietary intake; food frequency questionnaire; fatty acids

САЖЕТАК

Увод/Циљ Иако је пушење водећи фактор ризика за рак плућа (РП), студије показују да и начин исхране игра важну улогу.

Циљ ове студије је био анализа исхрана код болесника са новодијагностикованим РП и упореди је са здравом популацијом истог пола и година старости.

Метод Шездесет-девет болесника са новооткривеним РП (50 мушкараца, 19 жена, старости 46–80 година) и 70 здравих испитаника (50 мушкараца, 20 жена, старости 47–76 година) попунило је у присуству лекара упитник о учесталости конзумирања намирница. Нутритивни унос је рачунат помоћу Српске базе података о саставу намирница.

Резултати Обе групе су имале сличан унос енергије, али је у контролној групи забележен већи унос масти, засићених, мононезасићених и n-3 полинезасићених масних киселина (ПНМК), а нижи унос угљених хидрата и n-6 ПНМК. Група болесника је имала значајно нижи унос млека и млечних производа, јаја, морских плодова, воћа и поврћа, а већи унос житарица и производа од брашна.

Закључак Болесници са раком плућа имали су значајно другачији начин исхране од здравих испитаника, што сугерише да промене у начину исхране могу да допринесу превенцији настанка канцера плућа.

Кључне речи: канцер плућа; дијетарни унос; упитник о учесталости конзумирања намирница; масне киселине

INTRODUCTION

Lifestyle factors, including diet and smoking, have long been linked to cancer development. Observational epidemiological studies have reported significant correlations between dietary habits and cancer incidence and mortality [1]. Since these risk factors are modifiable, changes in lifestyle can reduce cancer risk and can improve overall survival after diagnosis of some cancers. According to the latest recommendations, a diet for cancer prevention implies higher intake of fruits, vegetables, whole grains and pulses, with low amounts of red meat, no processed meats, and limited salt intake. In addition, a healthy diet implies the avoidance of sweetened drinks and limited intake of alcohol and energy dense foods, thereby contributing to achieving and maintaining a healthy weight, given that obesity is also a risk factor for several cancers [2]. That was in line with the results of a large European Prospective Investigation into Nutrition and Cancer (EPIC) study, where the participants with a lifestyle in agreement with the World Cancer Research Fund and the American Institute for Cancer Research recommendations for cancer prevention, had a 34% lower risk of death (95% CI: 0.59–0.75) compared with the participants within the lowest agreement to the recommendations [3].

The relationships between diet and cancer are complex. Many dietary components are consumed every day worldwide, but the amounts of bioactive components within a particular food may widely vary [4]. Besides the potential of each food component to modify cancer process at different steps, the quantity, timing, duration of exposure, as well as combinations of several micronutrients can affect the cell response [2]. Therefore, the influence of different dietary intakes is probably a combination of effects on several pathways involved in cancer development.

Increased risk of some cancer types is associated with excessive caloric intake and obesity, and experimental studies have shown that calorie restriction suppresses the carcinogenesis. Although underlying mechanisms are not clear, they may include chronic inflammation, oxidative stress, insulin resistance, changes in the metabolism of sex hormones, and increased production of cytokines by adipose tissue [5]. Diets rich in simple carbohydrates may promote carcinogenesis by increasing oxidative stress, insulin synthesis and by forming adipose tissue which is a source of inflammatory cytokines [6]. On the other hand, diet can also have anti-carcinogenic effects, especially in people who are exposed to other environmental carcinogens [7]. Thus, it is important to evaluate dietary habits in people with cancer in comparison with apparently healthy people of the same age.

Lung cancer is the leading cause of cancer-related death worldwide. The main risk factor for lung cancer is cigarette smoking, which account for about 90% of cases [8]. Tobacco smoke contains numerous reactive oxygen and nitrogen species that can induce oxidative damage of DNA and thus act as carcinogenic compounds [9]. On the other hand, antioxidant nutrients (such as carotenoids, vitamin E, C etc.) present in plant foods, scavenge free radicals and thereby protect DNA from oxidative damage caused by smoking. In this way, adequate diet might protect against lung cancer even smokers. A potentially protective effect of fruits and vegetables was observed in numerous case-control and cohort studies, including the EPIC study [10], although the NIH-AARP North American cohort study [11] did not find a significant association. Evidence of an inverse association between lung cancer and intake of carotenoid-rich vegetables was provided by the study in Chinese men [12]. In a multi-ethnic cohort, circulating carotenoid levels were inversely related to lung cancer risk in men but not in women, raising the issue of potential confounding by smoking [13]. Nevertheless, the effects of other dietary components besides carotenoid have not been thoroughly investigated, and the convincing relationship between the diet and lung cancer has not been established so far.

The aim of this study is to evaluate dietary intakes in newly diagnosed patients with lung cancer and to compare with the dietary intake reports of control participants.

METHODS

Study population

This case-control study involved 69 patients with lung cancer recruited consecutively from June 2015 to September 2016 at the Clinical Hospital Center “Bezanijska Kosa” in Belgrade, Serbia. Among them, there were 50 male and 19 female, median age 63 (46-80 years).

The inclusion criteria were histopathologically confirmed cell lung cancer and willing to complete the food frequency questionnaire, while the exclusion criteria were some other malignancy or serious chronic non-malignant diseases. The control group was composed from 70 apparently healthy age and sex matched participants, 50 men and 20 women, median age 63 (47-76 years). All study participants signed the informed consent approved by the Ethical Review Board of the Clinical Hospital Center “Bežanijska Kosa”, in accordance with the principles of the Declaration of Helsinki.

For all the patients we performed a fiberoptic bronchoscopy and obtained a biopsy sample. Out of the total of 69 patients, NSCLC was found in 41 patients (14 adenocarcinoma and 27 squamocellulare carcinoma in 27), SCLC in 18 and 10 patients had some other kind of lung carcinoma (carcinoid, metastatic malignancy, mesenchymal malignancy).

Dietary intake

Habitual dietary intake of patients and controls was assessed using a semi-quantitative, validated Food Frequency Questionnaire (FFQ) [14]. It was self-administered in the presence of a medical professional and it took approximately 30-40 minutes to complete. The questionnaire consisted of 90 food items classified in appropriate groups and additional questions regarding socio-demographic characteristics, smoking status, medical condition, as well as dietary supplements and medications use. Subjects were asked to recall their dietary habits over the preceding three months. For each item participants reported their average frequency of consumption for the specified time period on a seven-level scale with frequency categories ranging from “never” to “every day”. Selected frequency option for each item was converted to a daily equivalent with reference to a baseline coefficient of 1.0 for the “every day” category. Furthermore, for all items, participants indicated their usual portion size using standard measures, natural portions and pre-specified options presented on photographs incorporated in the questionnaire. Diet Assess & Plan, software based, validated nutritional tool was used to process the FFQs and obtain comprehensive dietary intake assessment [14]. Nutrient intake calculation was performed using the product-sum method. The estimates of amounts of food consumed per day were multiplied with nutritional value of 100 g of that food according to the Serbian Food Composition Database [15].

Statistical analysis

The results are presented as the mean±SD. Normality was tested using the Kolmogorov-Smirnov test. Unpaired Student t test was used to compare the normally distributed variables, and nonparametric Mann–Whitney U test for non-normally distributed variables analysis. The differences between the patients and the control group were considered significant at $p \leq 0.05$.

RESULTS

The characteristics of the study participants are presented in Table 1. Among 69 lung cancer (LC) patients, 50 were male and 19 female, median age 63.2 (46-80 years). Forty-one patient had

Table 1. Demographic and clinical characteristic of the study participants.

	LC patients	Control
No (M/F)	50/19	50/20
Median age (years)	63.2±7.9	63.1±7.7
Smoking status		
Smokers(M/F)	50 (39/11)	25 (19/6)
Ex smokers(M/F)	8 (8/0)	9 (7/2)
NSCLC	41	-
Adenocarcinoma	14	
Squamocellulare carcinoma	27	
SCLC	18	-
Other LC	10	-

LC- lung cancer; NSCLC- non-small cell lung cancer; SCLC- small cell lung cancer.

Table 2. Dietary intake in study participants evaluated by the validated FFQ.

	LC patients (range)	Control
Energy (kcal)	1912±644 (741-4458)	1931±444 (1109-3081)
Proteins (g)	85.3±30.6 (35.9-169.4)	83.2±21.5 (45.0-156.1)
Carbohydrates (g)	238.6±87.5 (82.8-599.5)	210.0±53.5 (74.2-434.0) *
Fats (g)	48.8±21.1 (14.5-120)	63.5±18.7 (27.7-119.3) **
SFA (g)	21.0±11.9 (3.9-79.2)	26.1±8.7 (12.0-54.1) *
MUFA (g)	23.0±14.4 (4-99)	27.7±11.7 (12.1-58.7) *
PUFA (g)	9.5±3.9 (2.9-21)	10.8±4.7 (4.1-25.0)
n-3 PUFA (mg)	594±314 (78-1633)	708±210 (352-1436) **
n-6 PUFA (mg)	5340±1852 (1828-9346)	3762±1763 (1793-11305) **
Cholesterol (mg)	342±203 (41-1125)	392±145 (141-770)

Significant statistical difference measured by unpaired Student *t*-test and Mann Whitney *U* test: * $p < 0.05$, ** $p < 0.001$

LC- lung cancer; SFA- saturated fatty acids; MUFA- monounsaturated fatty acids; PUFA- polyunsaturated fatty acids.

saturated, monosaturated, and n-3 polyunsaturated fatty acids (PUFA). Reported intake of total PUFA in both groups was into a wide range, group of patients had significantly higher intake of n-6 PUFA than the group of healthy participants.

Table 3. Dietary intake of specific food groups.

Food groups	LC patients (g)	Control (g)
Milk and dairy products	95±103	168±125 ***
Eggs	23±22	35±24 **
Meat and meat products	156±106	169±56
Seafood	9±12	18±13 ***
Fat and oils	52±32	54±28
Grains and grain products	341±139	228±68 ***
Nuts, seeds and kernel products	0.7±0.9	3.4±6.4 ***
Vegetables	160±101	190±61 *
Fruits	158±145	260±148 ***
Sugar and candies	17±22	28±19 ***

Significant statistical difference measured by unpaired Student *t*-test and Mann Whitney *U* test * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

NSCLC, 18 SCLS and 10 other types of lung cancer. Smoking status differed between the groups. In the control group, 34 out of 70 persons were smokers and ex-smokers. Among patients, 58 out of 69 were smokers and ex-smokers, and most of them (57) were heavy smokers with more than 20 pack/year.

The average daily intake of energy and macronutrients is displayed in Table 2.

Mean daily energy intake in the patients group was 1912 kcal, ranging from 741 to 4458 kcal/d. A similar energy intake was reported by the control group. However, the controls had significantly lower intake of carbohydrates and higher intake of total fats,

When evaluated dietary intake according to food groups, we found significant differences in the dietary habits between the two groups. Patients with LC reported markedly lower intakes of milk and dairy products, eggs, seafood, vegetables and fruits, and higher intake of grains and grain products. Interestingly, higher sugar intake was reported by the controls (Table 3).

DISCUSSION

This study has shown significant differences in dietary intake between apparently healthy controls and patients with newly diagnosed lung cancer. To our best knowledge, this is the first study on the relationship between dietary habits and cancer in Serbia. Patients fulfilled validated FFQ on the dietary intake in the last 3 months before diagnosis of lung cancer. Nevertheless, their dietary habits significantly differed from those of the controls.

Epidemiological studies on associations between dietary intake or biomarkers of certain macro- and micronutrients and cancer risk, have not revealed a conclusive evidence. When compare the intake among our study participants, we found similar energy and protein intake, but differences in the intake of carbohydrates and fats. The control group had markedly higher intake of all fats, in particular n-3 PUFAs, but lower intake of n-6 PUFAs. Lung cancer patients had significantly lower intake of seafood, which is the best source of n-3 PUFAs, and nuts, seeds and kernel products. Although the intake of fats and oils was similar in the two groups, the type of fats was different. In the LC group, 68 out of 69 patients reported daily intake of sunflower oil, which is the main source of n-6 PUFA in our region. Twenty-seven of them occasionally consumed olive oil and only 1 out of 69 patients use exclusively olive oil for food preparation. In the control group, 63 out of 70 subjects used sunflower oil, but 33 of them also consumed olive oil, while 7 controls consumed only olive oil. Thus the ratio between n-6 and n-3 PUFA is significantly higher in the patients group. Dietary n-6 /n-3 PUFA ratio is an important additional factor for tumorigenesis [16]. Cancer-related research on essential fatty acids (EFAs) mostly focused on the beneficial properties and mechanisms of n-3 PUFAs and the n-6/n-3 ratio. However, a limited number of studies, to date, have evaluated habitual dietary intake of n-3 and n-6 PUFA in lung cancer patients. The anti-cancer effects of long-chain n-3 PUFAs, specifically eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), have been shown in several studies [17]. Namely, diet influences cell membrane lipid composition. Intake of n-3 PUFA leads to their incorporation into membrane phospholipids [18]. EPA and DHA may alter the distribution or function of membrane-associated signaling molecules by inducing changes in physical properties of membranes, they have important anti-inflammatory properties, and can act perhaps by some other mechanism [18]. Takezaki et al. reported that cooked and raw fish consumption lowered the risk of lung adenocarcinoma in Japanese [19]. Also, they showed that fish eaters 3 or more times per week had an 81% lower risk of lung cancer than those who eat fish less than 1 time per week [19].

Cancer patients typically have lower level of n-3 PUFAs in plasma phospholipids [20]. Moreover, they have worse prognosis and n-3 supplementation improve their response to therapy and clinical outcome [21]. Many clinical trials suggest improved outcomes with n-3 PUFA supplementation in lung cancer patients undergoing chemotherapy [22, 23]. However, the mechanism

how n-3 PUFAs selectively modify the response of tumor cells, but not normal host tissues, to chemotherapeutic agents remains to be elucidated [24].

On the other hand, dietary-related disease caused by the excessive intake of n-6 PUFAs in the Western world has recently come to attention. Although linoleic acid (LA; C18:2 n-6) is as an EFA, it was associated with increased cancer incidence and tumor progression [20]. It is interesting to note that LA supplementation upregulates pathways involving EGFR and PI3K that are already major targets in cancer therapeutic development [25]. Mouradian et al. have identified a series of signaling events initiated by the LA-induced upregulation of COX activity and prostaglandin E2 synthesis, which are involved in enhancement of cell growth in models of human breast and lung cancers [26]. In accordance with these findings, our patients with LC had higher n-6 PUFAs intake. This suggests that nutrition, specifically dietary modifications of PUFAs intake, should be considered as an adjuvant treatment of cancer. Nevertheless, a recent meta-analysis of 8 prospective cohort studies showed that a high PUFA intake was not associated with lung cancer (RR 0.91; 95% CI 0.78–1.06) [27], but the authors did not analyze n-3 and n-6 PUFAs separately. This study has given two important inputs for future studies: to take cooking methods into account of assessing PUFA intake and to analyze the impact of PUFA intake on specific histological or cell types of lung cancer, in order to provide clear dietary guidelines for the prevention.

Several studies have investigated the relationship between milk and dairy consumption and LC risk, but they have produced conflicting results. Two recent meta analyses have found no significant associations between intake of dairy products and the risk of lung cancer [28,29]. This is in accordance with our results that the control group had higher intake of milk and dairy products. However, it should be noted that both groups had consumption of these products which is below the current recommendations. Fruits and vegetables are traditionally recognized as cancer protective. In accordance, the control subjects had higher intake of vegetables and in particular of fruits than the LC patients. A recent meta-analysis of 18 studies has confirmed protective effects of vegetables and fruits intake and lung cancer, with the summary RR estimates of 0.86 (95% CI 0.78–0.94) [30]. The mechanisms of the anti-cancer effects of fruits and vegetables have not been thoroughly investigated. The suggested mechanisms are thought to be mediated by multiple components, such as beta-carotene, vitamins C and E, fiber, and phytochemicals, and include modulation of DNA methylation, protection against oxidative stress and DNA damage, promotion of apoptosis and induction of detoxifying enzymes [7].

Although LC patients had lower intake of fruits, vegetables and even sugars, they had higher intake of carbohydrates, which could be attributed to grains and grain products. There are some evidences that reducing dietary carbohydrates intake could suppress, or at least delay the occurrence of cancer [31]. Also, the proliferation of already existing tumor cells could slow down. In lung cancer, studies have mostly been focused on fruit, vegetables and related micronutrients, with little reference to carbohydrates. A recent study has revealed that people who often consume foods with high

glycemic index (GI) had a 49% higher risk of developing lung cancer, even if they are non-smokers [32]. However, our patients had a negligible intake of low GI foods (ground whole wheat bread, rolled or steel-cut oatmeal, most fruits, and non-starchy vegetables) and higher intake of refined grains and higher GI foods (white bread, bakery products of refined wheat flour, white rice, potatoes). In line with this, higher consumption of whole grains and fruits was significantly inversely associated with lung cancer risk for several of the diet indices [33]. A possible reason is that higher GI foods rapidly elevate blood glucose and insulin levels after a meal, that in turns raises insulin-like growth factor 1 (IGF-1). IGF-1 can directly promote tumor cell proliferation via the insulin/IGF-1 signaling pathway and thus is linked to an increased lung cancer risk.

The limitation of this study is a relatively low number of study participants. We did not calculate associations (odds ratios) between specific foods and lung cancer, since the idea was to compare dietary habits between the patients and matched healthy subjects. In addition, dietary intake is assessed using FFQ after cancer diagnosis, and they are more prone to recall and selection biases than are prospective observational studies.

CONCLUSION

Patients with LC had significantly different dietary intake of most nutrients than healthy participants, suggesting that changes in dietary patterns could contribute to prevention of lung cancer development.

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