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The role of selected risk factors for development of oesophageal cancer

Research Article

Helena Kollárová[1], Kateřina Azeem[1]*, Silvie Magnusková[1], Hana Tomášková[2], Jarmila Ševčíková[1], Dagmar Horáková[1], Vojtěch Kamarád[3], Vladimír Janout[1]

1 Department of Preventive Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc, Hněvotínská 3, Olomouc, 775 15, Czech Republic

2 Department of Epidemiology and Public Health, Faculty of Medicine, University of Ostrava, Syllabova 19, Ostrava, 703 00, Czech Republic

3 Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Ostrava, Syllabova 19, Ostrava, 703 00, Czech Republic

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Abstract: A hospital-based analytical observational case-control study of 88 oesophageal cancer cases and 200 controls was conducted in the University Hospital Olomouc. A standardized questionnaire was used. The adjusted odds ratio (OR) are calculated by logistic regression. The adjusted odds ratios for tobacco smoking were 6.20 (95% CI 2.78–13.83), 10.64 (95% CI 3.46–32.72) and 3.53 (95% CI 1.26–9.88) for oesophageal cancer, for oesophageal squamous cell carcinoma, and oesophageal adenocarcinoma, respectively. An inverse association with overweight and obesity was found in both histological types. In adenocarcinoma, there was a relatively strong positive association with a statistically significant result for alcohol consumption only in a group consuming more than 300 g of alcohol weekly; the OR was 5.81 (95% CI 1.17–28.84). The strong, statistically significant association was found in alcohol consumption regardless of histological type: the OR was 4.41 (95% CI 1.09–17.84). In a group with 20 or more X-ray exposures, there was a very strong statistically significant positive association. In vegetable consumption, an inverse association was found that was statistically significant only if more than 8 portions of vegetables were eaten weekly, ORs were 0.02–0.11.

Keywords: *Oesophageal adenocarcinoma • Oesophageal squamous cell carcinoma • Risk factor • Protective factor • Case-control study • Analysis*

1. Introduction

Oesophageal cancer mortality rates in the Czech Republic have increased and are expected to continue to rise. According to current data, the incidence of oesophageal cancer increases by 6.6% per year [1]. In 1977, the crude incidence rates were 3.13/100,000 in males and 0.4/100,000 in females. Thirty-one years later, the rates were 8.1/100,000 and 1.9/100,000, respectively [2]. In 2009, the standardized incidence rates for malignant oesophageal cancer were 5.88/100,000 in males and 0.92/100,000 in females [2]. There was also a steady increase in relative incidence with age, from 35 years in males and 45 years in females [3].

While squamous cell carcinoma remains the predominant histological type of oesophageal cancer in the Czech Republic, the incidence of oesophageal adenocarcinoma is still increasing [4]. Squamous cell carcinoma and oesophageal adenocarcinoma have distinct risk factors. The increase in oesophageal adenocarcinoma rates is thought to be linked to increasing prevalence of obesity and overweight. These conditions are associated with a higher prevalence of gastro-oesophageal reflux disease, which is considered as the primary causal factor for oesophageal adenocarcinoma [5-9]. Gastro-oesophageal reflux is the predominant risk factor for Barrett's oesophagus, which is a precursor of oesophageal adenocarcinoma [10]. Male gender is a well recognized risk factor for oesophageal adenocarcinoma,

* *E-mail: mitroslo@eunet.rs*

which is approximately six- to eight-fold more frequent in males than in females [11].

It is assumed that diabetes mellitus is a risk factor for oesophageal cancer; however, metabolic alterations correlated with diabetes (hyperglycaemia, hyperinsulinemia), as well as systemic inflammation secondary to abdominal obesity, may be responsible for the risk increase [12]. By contrast, oesophageal squamous cell carcinoma is, in many cases, considered to be induced in the mucosa by chronic exposure to irritants such as tobacco smoke and alcohol (mainly concentrated) [13,14]. Consuming hot beverages and using high-temperature cooking methods, including barbecuing and frying, might increase the risk of chronic irritation and susceptibility to carcinogenesis [15]. HPV infection may also play an important role in the carcinogenesis and development of oesophageal squamous cell carcinoma [16,17].

Based on histological reports, smoking at the same time as consuming excessive ammounts of alcohol is the major risk factor for oesophageal squamous cell carcinoma. Associations between alcohol and tobacco smoking and oesophageal adenocarcinoma are less consistent but generally indicate that tobacco smoking is a moderate risk factor and alcohol has no association [18]. Many of the known risk factors for oesophageal cancer, such as male sex or advanced age, are difficult or impossible to modify, whereas others, including tobacco smoking, alcohol consumption, obesity and possibly decreased intakes of fruit and vegetables, are more amenable to intervention. An inverse association has been found between aspirin or NSAIDs (non-steroidal anti-inflammatory drugs) and risk of oesophageal adenocarcinoma [10,19].

The selected cytokines [20], portal hypertension [21] and estrogen expression [22] belong among the suspected risk factors that have a weak association with oesophageal cancer. Dietary patterns have been thought to account for about 30% of cancers in Western countries [23], making a poor diet a preventable cause of cancer [24]. Ionizing radiation exposure is a risk factor for the development of oesophageal squamous cell carcinoma [25-27]. Nutrition provides both protective and harmful factors and a possible link between oesophageal cancer and diet has been suggested based on a number of studies [28-32]. However, epidemiological evidence remains limited. In the presented study, the protective effect of vegetable and fruit consumption was studied.

Given the increasing incidence of oesophageal cancer in the Czech Republic, a knowledge of both risk and protective factors is essential for implementing preventive measures. Therefore, this study investigated selected risk factors for oesophageal cancer such as age, sex, nutrition, alcohol consumption, tobacco smoking, X-ray exposure, and BMI in two major histological types of oesophageal cancer—squamous cell carcinoma and adenocarcinoma. The unique approach of the present work lies in the analysis of risk factors in relation to different histological types of the oesophageal cancer.

2. Materials and methods

2.1 Subjects

A hospital-based case-control study was conducted in the University Hospital, Olomouc, between March 2000 and November 2002. Initially, 90 patients were identified as eligible for participation; the response rate was 98%. The case group comprised 88 newly diagnosed oesophageal cancer cases (76 males and 12 females). To capture the studied factors in the control group, its size was set at 200 (123 males, 77 females). Of the 88 incident oesophageal cancer cases ascertained (ICD-O-2 C15), 48 cases represented oesophageal squamous cell carcinoma and 34 cases were classified as oesophageal adenocarcinoma. Six cases were excluded from the analysis because the histological type either was missing, was in situ carcinoma, or was not squamous cell carcinoma.

Each case had at least one matched control. Eligible controls (n =200) were patients admitted to the same hospital as cases for conditions unrelated to smoking and alcohol. The controls were recruited within 3 months from the diagnosis made in oesophageal cancer patients. The inclusion criteria for the control group was health status, with the further conditions that the subjects had no malignancies, were hospitalized for reasons unrelated to the studied disease and had no other life-threatening diseases. Controls were selected from the following hospital departments: Department of Dermatology and Venereology (psoriasis, atopic dermatitis), Otolaryngology (hypoacusis, inflammatory diseases), Orthopedics (states after injuries), Neurology (vertebral syndrome), and the Department of Rehabilitation and Sport Medicine. A control with congruent age (a possible deviation of 3 years) and gender was assigned for each case. Despite that analyses were carried out regardless of gender and were not pair selections, the proportion of females in controls was not identical with the ratio in the group of cases. For assessment of ratio of oesophageal cancer cases between males and females, only the aspect of ratio in oesophageal cancer group is important. The mean ages were 59 years (range 34–81) for cases and 60 years (range 27–79) for controls. The study was approved by the Research Ethics Committee of the Uni-

versity Hospital and Palacky University Olomouc and informed consent was obtained from all participants prior to their enrolment.

2.2 Exposure assesment

Each case or control was interviewed by a trained interviewer using a standardized questionnaire to obtain information about the patient's demographic characteristics, dietary habits, smoking status, alcohol consumption and number of X-ray examinations; the BMI at two years before oesophageal cancer development was calculated. Standard BMI categories were used for the analysis (normal weight ≥ 18.5 kg/m², overweight 25–30 kg/m², obesity > 30 kg/m²). A non-smoker was defined as a person who had never smoked or had stopped smoking 20 or more years earlier. An ex-smoker was a person who had ceased smoking 5 to 19 years earlier, whereas a current smoker was someone who smoked or had stopped fewer than 5 years before the study.

Alcohol consumption was assessed by asking whether the person drank alcohol; if yes, he/she was regarded as a consumer. In the present study, the type of alcoholic drink was asked (wine, beer, spirits); however, for comparability of exposure, the measure of consumption was transferred to number of grams of spirit per week. Consumption was calculated as the average number of doses per week, with one dose of alcohol being equal to 20 g of ethanol, corresponding to 500 ml of beer, 200 ml of wine or 50 ml of spirit. Alcohol consumption was categorized into four groups (0-3) according to grams of pure alcohol per week (0=0 g, 1=1–99 g, 2=100–299 g, 3= ≥300 g).

The study aimed to determine whether exposure to X-ray radiation increases the risk of oesophageal cancer, so exposure to ionizing radiation for occupational reasons was ascertained. The subjects answered the question whether they underwent a X-ray investigations as part of their occupation, and if yes, how many times it occurred. The subjects were classified into groups based on the number of X-ray examinations they had undergone: 1–9, 10–19, and 20 or more, as reported by the subjects. Most frequently, the patients had undergone lung X-rays.

The questionaire also investigated the characteristics of health status and whether participants (both cases and controls) underwent X-ray examination because of their heath conditions; CT scans were not included. X-ray examinations carried out in the practice of the subject's occupation were included in the analysis. Also included were X-ray examinations during regular preventive examinations within health state monitoring, performed by physicians who provided company health care. Study participants were selected from the same region to avoid any influence of difference in radioactive backgrounds.

Table 1. Distribution of socio-demographic characteristics and other exposure variables among case and control subjects.

Characteristics	Category	Cases total		Oesophageal squamous cell carcinoma		Oesophageal adenocarcinoma		Undefined		Controls	
		n=88 number	%	n=48 number	%	n=34 number	%	n=6 number	%	n=200 number	%
Age group	≤49	10	11.4	7	14.6	2	5.9	1	16.7	23	11.5
	50–64	53	60.2	28	58.3	21	61.8	4	66.7	102	51.0
	65–74	21	23.9	12	25.0	8	23.5	1	16.7	57	28.5
	≥75	4	4.5	1	2.1	3	8.8	0	0	18	9.0
Sex	Males	76	86.4	41	85.4	30	88.2	5	83.3	123	61.5
	Females	12	13.6	7	14.6	4	11.8	1	16.7	77	38.5
Smoking	Non-smokers	17	19.3	7	14.6	9	26.5	1	16.7	117	58,5
	Ex-smokers	10	11.4	3	6.2	6	17.6	1	16.7	23	11,5
	Smokers	61	69.3	38	79.2	19	55.9	4	66.7	60	30
Alcohol	Abstainers	2	2.3	1	2.1	1	2.9	0	0	45	22.5
	Consumers	86	97.7	47	97.9	33	97.1	6	100	155	77.5
BMI	<25	48	54.5	28	58.3	16	47.1	4	66.7	57	28.5
	25–30	31	35.2	15	31.3	14	41.2	2	33.3	94	47
	>30	9	10.2	5	10.4	4	11.8	0	0	49	24.5
X-ray	0	40	45.5	18	37.5	18	53.9	4	66.7	147	73.5
	1–9	7	8.0	4	8.3	3	8.8	0	0	15	7.5
	10–19	23	26.1	16	33.3	7	20.6	0	0	25	12.5
	≥20	18	20.4	10	20.8	6	17.7	2	33.3	13	6.5

Because adequate fruit and vegetable consumption is considered a protective factor, the study ascertained how frequently fresh fruit and vegetables were eaten. The subjects were divided into groups according to their weekly consumption of fresh fruit and vegetables as follows: low (1–5 portions/week), moderate (6–7) and high (8 or more).

2.3 Statistical methods and experimental procedures

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated and adjusted for potential confounders, including age, sex, alcohol consumption, tobacco smoking, fruit and vegetable consumption, BMI, and X-ray exposure, using multivariate logistic regression. Tests for trends in the ORs across exposure strata were calculated for ordinal variables by using logistic models. Statistical significance was set at 0.05. All reported P values are from two-sided tests. Statistical analyses were performed using the Stata software (version 10). Multivariate logistic regression was used to calculate ORs and 95% CIs.

3. Results

Selected characteristics of case and control subjects are presented in Table 1. Table 2 shows the influence that age, tobacco smoking, BMI, alcohol consumption, X-ray exposure, and vegetable and fruit consumption have on the risk of oesophageal cancer by adjusted odds ratio (logistic regression). When analyzing the risk for the development of oesophageal cancer depending on age, no statistically significant difference was found. However, the study suggested the highest risk for in the age group 65-74.

In ex-smokers, there was a significant positive association for those with oesophageal adenocarcinoma,

Table 2. Effects of age, tobacco smoking, BMI, alcohol consumption, X-ray exposure, vegetable and fruit on the risk of oesophageal cancer by adjusted odds ratio (logistic regression).

Risk factors	Category	Oesophageal squamous cell carcinoma		Oesophageal adenocarcinoma		Oesophageal carcinoma	
		OR	95% CI	OR	95% CI	OR	95% CI
Age	≤49	1*		1*		1*	
	50–64	1.05	0.28–3.90	2.26	0.43–11.78	1.34	0.47–3.78
	65–74	2.22	0.47–10.46	2.15	0.35–13.26	1.53	0.45–5.17
	≥75	0.16	0.01–3.98	2.44	0.28–21.51	0.84	0.14–4.85
Smoking**	Non-smokers	1*		1*		1*	
	Ex-smokers	1.52	0.24–9.71	3.77	0.99–14.45	2.63	0.83–8.40
	Smokers	10.64	3.46–32.72	3.53	1.26–9.88	6.20	2.78–13.83
BMI	18–24	1*		1*		1*	
	25–30	0.31	0.12–0.82	0.44	0.17–1.14	0.32	0.15–0.68
	>30	0.09	0.02–0.37	0.16	0.04–0.66	0.13	0.05–0.39
Alcohol	Abstainers	1*		1*		1*	
	1–99 g/week	3.30	0.59–18.50	4.31	0.99–18.72	3.09	0.99–9.69
	100–299 g/week	3.76	0.75–18.91	2.24	0.51–9.85	1.92	0.59–6.28
	≥300 g/week	5.34	0.81–35.24	5.81	1.17–28.85	4.41	1.09–17.84
X-ray	0	1*		1*		1*	
	1–9	7.50	1.60–35.22	1.97	0.37–10.53	3.72	1.12–12.33
	10–19	4.06	1.38–11.92	2.37	0.75–7.43	2.28	0.95–5.49
	≥20	9.08	2.33–35.35	4.93	1.27–19.04	5.74	1.98–16.61
Vegetable	No consumption	1*		1*		1*	
	Low consumption	0.37	0.11–1.25	0.50	0.14–1.75	0.32	0.12–0.86
	Moderate consumption	0.70	0.18–2.78	0.68	0.20–2.29	0.45	0.15–1.30
	High consumption	0.08	0.02–0.36	0.11	0.03–0.43	0.07	0.02–0.22
Fruit	No consumption	1*		1*		1*	
	Moderate consumption	+		+		2.68	1.01–7.12
	High consumption	1.00	0.89–1.13	0.91	0.85–0.97	1.34	0.42–4.24

1 Basic category, + analysis not performed due to small numbers.*
*** A non-smoker - a person who has never smoked or stopped smoking 20 or more years earlier, an ex-smoker - a person who ceased smoking 5 to 19 years ago, current smoker - person who smokes or stopped less than 5 years before the study.*

but the result was of borderline statistical significance. For oesophageal squamous cell carcinoma, no association was found. Tobacco smoking was a significant risk factor for current smokers with both types of cancer, also regardless of histological type. In squamous cell carcinoma, the OR was 10.64 (95% CI 3.46–32.72), suggesting a very strong positive association. The OR for adenocarcinoma was 3.53 (95% CI 1.26–9.88), confirming that smoking was a significant risk factor for this type of cancer as well. Regardless of histological type, the OR was 6.20 (95% CI 2.78-13.83).

When analyzing whether overweight and obesity are related to oesophageal squamous cell carcinoma and adenocarcinoma, an inverse association was revealed for both histological types, and regardless of histological type, the effect of overweight was statistically insignificant for adenocarcinoma.

A strong and statistically significant association was found for alcohol consumption regardless of histological type: OR 4.41 (95% CI 1.09–17.84). The study suggested a positive but statistically insignificant association between alcohol consumption and the development of oesophageal squamous cell carcinoma. Data suggested a dose-response relationship for frequency of cumulative consumption of alcohol in the case of oesophageal squamous cell carcinoma. In adenocarcinoma, there was a relatively strong positive association, with a statistically significant result only in a group consuming 300 or more grams of alcohol weekly: the OR was 5.81 (95% CI 1.17–28.84).

The analyses also ascertained the numbers of X-ray examinations undergone for occupational reasons. Excessive exposure was defined as 20 or more X-ray examinations. Such numbers were reported by 16 patients with oesophageal adenocarcinoma and 13 among the controls. A strong positive association was found regardless of histological type. Persons in the group with the highest X-ray exposure, both those with squamous cell carcinoma and those with adenocarcinoma, were found to have a very strong statistically significant positive association as compared with those who had not undergone X-ray examinations. Particularly in squamous cell carcinoma, the number of X-ray examinations appears to be a significant risk factor, despite the fact that the association may be masked by smoking as a stronger factor. The association remained strong even after adjusting for other risk factors.

The risk for developing squamous cell carcinoma for persons who had undergone X-ray examinations in carrying out their occupation was statistically significant. The analysis suggested a potential relationship between higher X-ray exposure and an increased risk for the development of squamous cell carcinoma when compared with persons who had not undergone X-ray examinations. In the case of oesophageal adenocarcinoma, the association was statistically significant only for the most exposed individuals.

Data analysis showed no protective effect of fruit consumption against either of the two oesophageal cancer types. There was an inverse association for vegetable consumption, but statistically significant only if more than 8 portions of vegetables were eaten weekly, both for squamous cell carcinoma and adenocarcinoma. The protective effect of vegetable consumption was also found in the analysis regardless of histological type: OR 0.07 (95% CI 0.02–0.22) was found for consumption of 8 or more servings per week. The protective effect was not found in consumption of fruit.

Because smoking and alcohol consumption are among the factors with the strongest association, all studied factors were analyzed using logistic regression supplemented by multivariable analysis focused only on smoking, alcohol consumption, and the interaction of smoking and alcohol consumption. Due to the extent of a sample this analysis was made regardless of histological types. The results of this analysis are shown in Table 3.

Table 3. Effects of tobacco smoking and alcohol consumption on the risk of oesophageal cancer by crude odds ratio (multivariable analysis).

Risk factors	Category	Oesophageal carcinoma	
		OR	95% CI
Smoking	Non-smokers	1*	
	Smokers	5.84	2.93-11.66
Alcohol	Abstainers	1*	
	Consumers	3.14	1.85-5.35
Smoking and alcohol	Non-smokers, abstainers	1*	
	Non-smokers, alcohol consumer	2.78	0.77-10.02
	Smokers, abstainers	5.23	1.98-13.87
	Smokers, alcohol consumer	10.69	4.30-26.58

1 Basic category.*

4. Discussion

Oesophageal cancer is an advanced-age malignancy characterized by a rapid course and high fatality rates. Worldwide, the peak is between 50 and 70 years of age [33,34]. This trend was confirmed by the presented study. The highest incidence was in the 50- to 64-year age group, followed by that in the 65- to 74-year age group; these results are consistent with data reported by Coleman et al. and Ferlay et al. [33,34]. Oesophageal cancer is also more frequently observed in males. The reported male:female ratio for oesophageal adenocar-

cinoma is 6:1 to 8:1 [11]. The present study showed a similar ratio of 5.8:1. For oesophageal squamous cell carcinoma, the ratio was calculated to be 7.5:1; and 6.3:1 for both types of oesophageal cancer.

According to Hashibe et al., the risk of oesophageal squamous cell carcinoma may be increased by approximately 7-fold for current smokers as compared with non-smokers in Central and Eastern Europe, with smoking being the most significant risk factor for the development of oesophageal squamous cell carcinoma. This present study showed that the effect of tobacco smoking is much more pronounced in squamous cell carcinoma than in adenocarcinoma. The OR was 10, confirming results from other studies [15,35]. Lee et al. agrees that five to ten years after smoking cessation, the risk for oesophageal cancer decreases quite rapidly [36,37], which is consistent with findings in this study. In the present analysis, the non-smoker group included individuals who had not smoked for more than 20 years. Those who had stopped smoking 5 to 19 years earlier were at a significantly lower risk of squamous cell carcinoma than those who remained smokers. In current smokers, the OR reached 10.64, suggesting an extremely high risk.

Although smokers have a less significant increase in the risk of developing oesophageal adenocarcinoma when compared with that for squamous cell carcinoma, the study showed a 3.5-fold higher risk. Earlier studies reported a 2-fold increase in the risk for oesophageal carcinoma on average [6,15,38-40] as well as an increasing risk associated with increasing intensity and duration of smoking [40]. Such a dose-response trend was not confirmed in the group analyzed in this study. Jankowski et al. stated that, unlike in squamous cell carcinoma, the risk of adenocarcinoma decreases only about 30 years after smoking cessation [37]; that trend can be observed in the present study as well.

Individuals with oesophageal squamous cell carcinoma tend to have lower BMI [41,42]; this inverse association was also confirmed by the present study. Lower values for BMI in the study were not associated with cachexia, which is often present in the underlying disease [43], because the values for the BMI calculation were considered on the basis as the BMI 2 years before the onset of disease. Rather, it could be related to higher prevalence of smoking and alcohol consumption in the population.

The increase in obesity in Western countries is accompanied by a higher incidence of oesophageal adenocarcinoma. Two meta-analyses confirmed the relationship between overweight (BMI 25–30 kg/m^2), obesity (BMI > 30 kg/m^2) and a higher incidence of oesophageal adenocarcinoma [9,44]. In such individuals, the risk is 2- to 3-fold higher and continues to rise with increasing BMI [44]. This positive association between higher BMI and oesophageal adenocarcinoma was not found in the present study: we found an inverse association between obesity and adenocarcinoma. An inverse association was also suggested in overweight persons, but the result was not statistically significant. However, this may be due to the high proportion of overweight (n=94, 47%) and obese (n=49, 24.5%) controls in the study. The number of participants with overweight and obesity in oesophageal cancer case group was 45.4%, while in the control group that was 71.5%. The high BMI in the control group may be due to the high prevalence of people with excess weight in the population (around 52%) or to the design of the study: overweight and obesity may be more frequent reasons for hospitalization. Therefore, the association in the present study may be underestimated [45,46].

According to the International Agency for Research on Cancer (IARC), alcohol is a risk factor for the development of oesophageal squamous cell carcinoma [47]. The risk increases with a rise in daily alcohol consumption. Excess alcohol consumption (more than 39 g of alcohol per day) led to a 3- to 5-fold higher risk [15,29]. This trend was apparent in the present study as well. Higher alcohol consumption was associated with an increased risk for the development of oesophageal carcinoma. Similarly, alcohol consumption was found to increase the risk for oesophageal adenocarcinoma. There was a statistically significant positive association in the group consuming 300 or more grams of pure alcohol per week; the results were not statistically significant if less alcohol was consumed. Nevertheless, for squamous cell carcinoma, the results were below the level of statistical significance. The relative risk is increased if alcohol is consumed together with smoking because of a synergistic effect of the two factors [36,48,49]. There was a significant association between oesophageal squamous cell carcinoma and smoking. However, the association with alcohol was only suggested. By contrast, adenocarcinoma was found to be significantly associated with both high alcohol consumption and heavy smoking.

Tables 2 and 3 show the multivariable analysis wherein the individual risk factors are analyzed taking other factors into account. To distinguish separately the relationship between smoking, alcohol consumption, and their interaction is difficult because most smokers also consumed alcohol, and taking into consideration the extent of a studied sample, there is a problem with small numbers for subsequent analysis. However, the results in Table 3 show that smoking and alcohol consumption are among the strongest risk factors, and also that there was a statistically significant difference between smokers and drinkers in the group with oesophageal cancer compared with the control group.

Ionizing radiation is reported to be a risk factor for the development of cancer in general. People may be exposed to both naturally occurring radionuclides (natural background radiation) and artificial sources of radiation. The average annual per capita dose from natural sources is approximately 2.4 mSv; the average dose from artificial sources of ionizing radiation is estimated at approximately 0.6 mSv/year [25]. Background radiation is not understood to be a factor causing a significant risk for the development of cancer in a particular individual. Oesophageal cancer is a rare secondary malignancy developing after exposure to ionizing radiation [50]. Cases due to irradiation account for less than 1% of all oesophageal cancer cases [51].

To date, no epidemiological study has provided direct evidence that a carcinoma developed in association with the use of radiological methods in medicine [26]. Santibañez et al. found a statistically significant increase in the risk of oesophageal squamous cell carcinoma for ionizing radiation (p=0.05) [52]. The present study analyzed exposure to X-ray examinations. In 20 or more X-ray examinations, there was a very strong statistically significant positive association for both squamous cell cancer and adenocarcinoma. In the case of squamous cell carcinoma, all levels of exposure were associated with statistically significant results. However, adenocarcinoma was only statistically significantly associated with exposure to 20 or more X-ray examinations. Risk factors such as tobacco smoking, alcohol and chronic inflammatory diseases are likely to have a much stronger effect than medical X-ray exposure. In the present study, only information self-reported by the subjects could be analyzed. Therefore, specific doses of irradiation and background radiation were not considered. When interviewed to fill in the questionnaires, the subjects confirmed that they were mostly exposed during regular check-ups with chest radiographs. Given the inclusion criteria demanding that cancer patients and controls were from identical places, the effect of radiation background was assumed to be the same in both groups and did not influence the results.

Inadequate intake of fruit and vegetables is generally associated with a higher risk for the development of oesophageal cancer [53,54]. WCRF-AICR (World Cancer Research Fund / American Institute for Cancer Research Joint Committee) [55] as well as COMA (Committee on Medical Aspects of Food and Nutrition Policy) [56] have concluded that fruit and vegetable consumption clearly has a protective effect on the development of oesophageal cancer. Hajizadeh et al. found a protective effect of fruit (but not vegetable) consumption on the incidence of oesophageal squamous cell carcinoma [57]. The present study analyzed potential protective effects of fresh fruit and vegetable consumption. While logistic regression revealed no protective effect of fruit, there was a statistically significant inverse association with both squamous cell carcinoma and adenocarcinoma if 8 or more portions of vegetables were eaten each week, despite the fact that daily consumption did not reach the recommended number of portions. According to Brown et al., lifestyle modifications, especially a lower intake of alcoholic beverages, would markedly decrease the incidence of oesophageal squamous cell carcinoma incidence [29]. The findings in the present study, which suggested that increased vegetable intake was associated with a lower incidence of oesophageal cancer, are consistent with a recently published report by Anderson et al. [58].

The effects of individual factors on the incidence of both oesophageal cancer types vary. There are multiple factors; however, in the present analysis, we are focused on the main risk and protective factors. Since the development of cancers is a multifactorial process, it may be assumed that individual effects are clustered and modified in oesophageal cancer as well. Knowing such effects and their interaction may be useful for prevention of oesophageal cancer.

The analysis was limited by the use of a questionnaire, that is, information self-reported by subjects enrolled in the study, and is thereby potentially biased. The bias was minimized by using same type of questionnaire for both oesophageal cancer patients and control subjects and that it was filled in by a trained interviewer. In spite of certain limitations, the analysis provided findings consistent with earlier studies and thus suggests potential associations.

The aim of epidemiological studies is comparison with the general population and therefore controls, although the hospitalized persons, should have less severe disease to approach that of the general population.

In the past, squamous cell carcinoma accounted for 90% of all oesophageal cancer cases. Although the incidence of oesophageal squamous cell carcinoma has decreased in developed countries, it remains the predominant type of oesophageal cancer in developing countries. Over the last three decades, there has been a significant rise in the incidence of oesophageal adenocarcinoma, currently accounting for up to 60% of all cases of oesophageal cancer in Western countries. This type is more prevalent in Caucasian males, in whom it is mainly associated with obesity. Although obesity was not found to be a risk factor for oesophageal adenocarcinoma in the present study, there was a clearly significant increase in its incidence. The study comprised 39% of individuals with oesophageal adenocarcinoma and 55% of those with squamous cell

carcinoma (6% of cases were not histologically classified). That is why research into risk and protective factors for oesophageal cancer is currently a priority in preventive medicine.

To date, the evaluation of selected risk factors in relation to different histological types in the Czech population has not been performed. Therefore, our results were compared with data from the countries other than the Czech Republic. However, even elsewhere there are only few studies on risk factors in relation to different histological types, and the results are very limited. In this context, our study is exceptional. The study evaluated not only risk factors for oesophageal squamous cell carcinoma and oesophageal adenocarcinoma but also assessed protective factors for both forms of oesophageal cancer. Increased consumption of vegetables (8 or more portions of vegetables per week), as determined in our study, confirmed their significant protective role against cancer development. Even though 8 portions of vegetables per week is only a fraction of dose recommended by WHO (500 g of vegetables and fruit daily), vegetables in general, were shown to be protective against both types of oesophageal cancer. Our findings were strengthened by a logistic regression model adjusted for possible confounders with regard to age, sex, alcohol consumption, tobacco smoking, fruit and vegetable consumption, BMI and X-ray exposure.

In conclusion, the study found that tobacco smoking, high BMI, alcohol consumption, X-ray exposure and vegetable and fruit consumption may influence the risk of oesophageal cancer. Tobacco smoking increases the risk of oesophageal cancer, especially squamous cell carcinoma. Associations were found between X-ray exposure and both oesophageal squamous cell carcinoma and oesophageal adenocarcinoma; in the case of adenocarcinoma, however, the result was statistically significant only in the group with 20 or more X-ray examinations. Higher BMI was found to be a protective factor for oesophageal cancer. BMI is a complex issue, and (lower) BMI cannot be separately identified as a protective or risk factor because those factors work simultaneously, or because other environmental factors or the work environment can contribute.

Consumption of 8 or more portions of vegetables weekly showed a strong protective effect against oesophageal cancer. No association was found between the risk of oesophageal cancer and fruit consumption. It is unlikely that the exact nature of the relationship between vegetable consumption and oesophageal cancer could be determined in retrospective studies, suggesting the need for large-scale prospective studies of this relationship in future research.

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