

# Risk Factors for the Occurrence of Undifferentiated Carcinoma of Nasopharyngeal Type: A Case-Control Study

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## SUMMARY

**Introduction** The incidence rate of nasopharyngeal carcinoma in Serbia is less than one per 100,000 citizens, which classifies it as a region with low incidence for this disease.

**Objective** The aim of this study was to test some hypotheses of the risk factors for undifferentiated carcinoma of nasopharyngeal type (UCNT) in the low incidence population.

**Methods** A case-control study was used for the research. The study included 45 cases with histopathological diagnosis of UCNT and 90 controls. Cases and the controls were individually matched by sex, age ( $\pm 3$  years), and place of residence (city-village). Data were gathered about sociodemographic characteristics, occupational exposure to harmful agents, habits, diet, personal history, and family history. In the analysis of the data, conditional univariate and multivariate logistic regression analyses were applied.

**Results** According to the results of multivariate logistic regression analysis UCNT was significantly positively associated with "passive smoking" of tobacco in the family during childhood, frequent consumption of industrially manufactured food additives for enhancing flavour and frequent consumption of white bread. UCNT was significantly negatively associated with frequent consumption of margarine, olive oil and cornbread.

**Conclusion** In our low incidence population, an independent risk factor for the occurrence of UCNT was "passive smoking" of tobacco in the family during childhood, use of industrially manufactured food with additives for enhancing flavour and consumption of white bread. Multicentric study enrolling a greater number of cases would be desirable.

**Keywords:** undifferentiated carcinoma of nasopharyngeal type; risk factors; case-control study; diet; smoking

## INTRODUCTION

In Southern Asia, North Africa, and among the Eskimo population, nasopharyngeal carcinoma (NPC) is a major public health issue, with an annual incidence rate as high as 20/100,000 [1]. In contrast, the incidence rate of NPC in Serbia is less than one per 100,000 citizens, which classifies it as a region with low incidence for this disease [2, 3]. Although numerous studies exist that describe possible etiological factors in the appearance of NPC, the results are often contradictory, and therefore their influence is insufficiently known [4]. In the aetiology of this disease, a great significance is attributed to genetic factors [5] and to environmental factors, such as: diet [6-10], "active and passive smoking" [11, 12, 13] on-the-job exposure to formaldehyde, chemical solvents, pesticides, tree dust, products of combustion [14, 15], Chinese medicines (Euphorbiaceae and Thymelaeaceae as usual ingredients), height above sea level, incense [16], viral infections provoked by Epstein-Barr virus (EBV), and human papilloma virus (HPV) [17].

However, most of the epidemiological studies of environmental factors have focused on population with a high risk of the disease. Studying a population, which is at low risk, may facili-

tate detecting additional risk factors, which in a high-risk population would otherwise be overwhelmed by the action of other causal pathways, such as genetic susceptibility and childhood diet. Infection with EBV and genetic susceptibility appear to play a major role in the high incidence populations of NPC, but migration studies suggest that environmental factors are also important [18].

## OBJECTIVE

The aim of this study was to test some hypotheses of the risk factors for undifferentiated carcinoma of nasopharyngeal type (UCNT) in the low incidence population [19, 20].

## METHODS

A case-control study was used for the research. The case group was comprised of 45 patients, that were of Serbian nationality who had a histopathological diagnosis of UCNT. The research was conducted at the Institute of Otorhinolaryngology and Maxillofacial Surgery of the Clinical Centre of Serbia in Belgrade, during the period 2001-2003. Only new patients with this diagnosis were

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taken into consideration. The control group included 90 individuals with orthopaedic disorders and injuries who did not suffer from malignant diseases, and who were treated at the Institute of Orthopaedic Surgery "Banjica" in Belgrade and the Institute of Orthopaedic Surgery and Traumatology, Clinical Centre of Serbia, in Belgrade. Cases and controls were matched by sex, age ( $\pm 3$  years), and place of residence (city-village). The Institutional ethics committee approved this study. Controls were interviewed within the same week as the cases and in the same conditions. A single doctor interviewed all the subjects. A structural questionnaire was used. Data were gathered about sociodemographic characteristics (sex, age, place of residence, nationality, marital status, education, occupation, socio-economic conditions), occupational exposure to harmful agents (formaldehyde, dust, wood dust, solvents, harmful gases, pesticides, age at start of exposure, total duration of exposure), habits (current smoker, former smoker, average number of cigarettes smoked per day, duration of smoking, "passive smoking" in childhood, "passive smoking" at place of work, total time of exposure to "passive smoking" in years, coffee consumption, average number of cups of coffee per day, total duration of coffee consumption, alcohol consumption, type of alcoholic beverage, average weekly consumption of alcoholic beverages, total duration of consumption of specific types of alcoholic beverage), diet (frequency consumption of about 100 food items including non-alcoholic beverages and spices, as well as manner in which food is prepared: grilled, fried, stewed, boiled), personal history (chronic rhinosinusitis, chronic purulent inflammation of the middle ear, herpes simplex virus infection, surgical tonsillectomy), and family history (malignant tumours of the otorhino-

laryngology region and malignant tumours outside of the otorhinolaryngology region). The data on diet covered a period of a year preceding the diagnosis of UCNT, and the same period for matched controls. Dietary data were collected using a food frequency questionnaire (FFQ). FFQ is one of the most commonly used tools in epidemiologic studies of nasopharyngeal carcinoma [21-24] to assess long-term nutritional exposure. For all food categories subjects were asked to choose between three frequency categories (never or seldom; from 2-3 times per month to 1-3 times per week; 4-7 times per week). Current smokers were defined as individuals who smoked in the previous 12 months and included those who quit within the past year. Former smokers were defined as those who had quit more than a year earlier. In the analysis of the data, conditional univariate and multivariate logistic regression analyses were applied.

## RESULTS

Out of 45 UCNT cases, 29 were men and 16 were women. Nine cases were younger than 40 years, 25 were in the age group 41-60, and 11 were 61 or more years old.

Variables significantly ( $p \leq 0.10$ ) related to UCNT, according to univariate logistic regression analysis, are presented in Tables 1 and 2.

Patients in the group with UCNT (cases) and patients in the control group (control) differ in the consumption frequency of 19 food items, including beverages and spices (Table 1).

Out of the other factors investigated, "passive smoking" during childhood, chronic rhinosinusitis and positive family

**Table 1.** Food items significantly\* related to undifferentiated carcinoma of nasopharyngeal type according to univariate conditional logistic regression analysis (45 cases compared with 90 controls)

Food item	Frequency of consumption (%)						p
	Never or seldom		Moderately frequent**		Frequently***		
	Cases	Controls	Cases	Controls	Cases	Controls	
Coca-cola	80.5	64.0	17.1	31.5	2.4	4.5	0.0382
Salt	4.6	2.2	54.5	75.6	40.9	22.2	0.0772
Pepper	9.1	21.1	61.4	62.2	29.5	16.7	0.0306
Paprika	6.8	14.4	72.8	73.4	20.4	12.2	0.0998
Canned fish	46.6	38.2	51.2	59.6	2.2	2.2	0.0395
Hot dog	42.2	13.6	48.9	80.7	8.9	5.7	0.0361
Ham	97.8	88.5	2.2	11.5	0.0	0.0	0.0577
Yogurt	11.1	5.6	55.6	43.8	33.3	50.6	0.0595
Butter	76.8	62.9	18.6	33.7	4.6	3.4	0.0714
Egg	11.1	1.1	55.6	55.6	33.3	43.3	0.0381
Stewed meat	43.1	22.2	54.6	71.2	2.3	6.6	0.0201
Margarine	40.5	20.0	47.6	70.0	11.9	10.0	0.0208
Olive oil	11.4	2.2	36.4	28.9	52.2	68.9	0.0208
Grapefruit	94.6	83.3	5.4	13.1	0.0	3.6	0.0955
Peanut	60.5	37.7	39.5	48.2	0.0	14.1	0.0024
Hazelnut	74.4	59.8	25.6	37.8	0.0	2.4	0.0304
Rice	11.1	13.3	77.8	85.6	11.1	1.1	0.0206
White wheat bread	18.6	38.9	25.6	24.4	55.8	36.7	0.0080
Half wheat bread	44.4	30.0	22.3	21.1	33.3	48.9	0.0371
Rye bread	83.7	77.8	16.3	20.0	0.0	2.2	0.0837
Cornbread	60.0	46.0	37.5	52.9	2.5	1.1	0.0217
Industrially manufactured food additives for enhancing flavour	0.0	5.6	65.1	85.5	34.9	8.9	0.0003

\* $p \leq 0.10$ ; \*\*from 2-3 times per month to 1-3 times per week; \*\*\*4-7 times per week

**Table 2.** Variables significantly\* related to undifferentiated carcinoma of nasopharyngeal type according to univariate conditional logistic regression analysis (45 cases compared with 90 controls)

Variable	Cases	Controls	p
"Passive smoking" in childhood	29 (64.4%)	44 (48.9%)	0.0892
Exposure to "passive smoking" (>20 years)	27 (65.9%)	41 (45.6%)	0.0235
Chronic rhinosinusitis	8 (17.8%)	5 (5.6%)	0.0309
Family history positive on malignant tumours outside the ORL** region	19 (42.2%)	20 (22.7%)	0.0211

\*  $p \leq 0.10$ ; \*\*otorhinolaryngology

history for malignant tumours outside of the otorhinolaryngology region were more frequently reported by cases. The total exposure time to "passive smoking" was longer in cases than in their controls (Table 2).

Variables, which were according to univariate logistic regression analysis significantly related to nasopharyngeal carcinoma at the level of  $p \leq 0.10$ , were included in the multivariate logistic regression analysis. Several models for multivariate analysis were used: the first model comprised variables concerning "passive smoking", past medical history and family history, and the next four models included food items (a – meat, milk and dairy products, eggs and various types of fat; b – fruits and vegetables; c – cereals, and d – spices). Variables, which were significantly associated with nasopharyngeal cancer in each of these multivariate analyses, were included in the final model (consumption frequency of eggs, margarine, olive oil, rice, white bread, cornbread, peanuts and industrially manufactured food additives for enhancing flavor, as well as "passive smoking" in the family during childhood, chronic rhinosinusitis and positive family history for malignant tumours outside of the otorhinolaryngology region).

According to the results of the multivariate logistic regression analysis, UCNT was significantly positively associated with "passive smoking" during childhood, frequent consumption of industrially manufactured food additives for enhancing flavour and frequent consumption of white bread. UCNT was significantly negatively associated with frequent consumption of margarine, olive oil and cornbread (Table 3).

## DISCUSSION

Smoking is considered to be a risk factor for the occurrence of NPC. According to the findings of a study conducted in Shanghai [12], the risk of the development of NPC in current smokers was 30% greater than in non-smokers ( $OR=1.28$ ), and in smokers who smoked more than 30 cigarettes per day, the risk of developing NPC was 90% ( $OR=1.87$ ) greater than in non-smokers. The work of numerous authors suggests that the nasopharynx is less susceptible to the carcinogenic effects of tobacco smoke than other parts of the respiratory tract.

In the present study, active smoking was not found to be an independent risk factor for UNCT. In fact there was a

**Table 3.** Risk factors for undifferentiated carcinoma of nasopharyngeal type according to multivariate conditional regression analysis

Variable	Odds error	95% CI	p
"Passive smoking" during childhood*	4.04	1.10-14.85	0.0356
Industrially manufactured food additives for enhancing flavour**	43.93	6.01-321.25	0.0002
Margarine***	0.60	0.36-1.00	0.0487
Olive oil***	0.42	0.19-0.91	0.0275
White bread***	1.63	1.07-2.49	0.0234
Cornbread***	0.54	0.33-0.89	0.0159

\* yes/no; \*\*daily/periodically/none; \*\*\*frequently/moderately frequent/rare or never

greater percent of active smokers in the group control, which can be explained by the fact that there was a greater percent of individuals who were "ex-smokers" in the group cases.

Active smokers were not analysed separately, because patients included in the study were included as incidence cases, that is, those in whom UNCT was diagnosed for the first time in the specified period. Since some of these cases were diagnosed in a later stage of the disease, it was difficult to specify their smoking status correctly, since it is possible that they quit smoking for reasons that can be associated with the illness, but before they were diagnosed. In the compared groups the percent of individuals who are active smokers and ex-smokers is nearly identical, as a result this shows that there is no link between smoking and UCNT.

Little is known about the link between "passive smoking" and the occurrence of NPC. Some studies [12], but not all [11], found that living with a cigarette smoker ("passive smoking" during childhood) was a significant and independent risk factor for NPC. Interestingly enough, some studies demonstrated that in women, but not in men, the risk for the occurrence of NPC was significantly linked with the smoking of parents and other members of the household during the childhood ( $OR=2.72-3.36$ ) and with the smoking of the husband and colleagues at work ( $OR=2.84-3.17$ ) [12]. In our study, "passive smoking" was also an independent risk factor for UCNT. Individuals that were exposed to "passive smoking" within the family during childhood in the group cases are significantly more frequent than individuals from the group control.

Our results point out that frequent (4-7 times per week) consumption of white bread represents an independent risk factor for the occurrence of UCNT, while moderately frequent (1-3 times per week) consumption of cornbread reduces the risk of UCNT. Consumption of whole grains reduces the risk of malignant illnesses, while consumption of white bread and glazed rice increases the risk, microbiologists claim [25]. Some authors cite that a central place in diet should be made up of whole grains: brown rice, rye, barley, oats, millet, buckwheat, and maize; vegetables and legumes; hard-shelled fruit (almonds, hazelnuts, peanuts, pumpkins, and sunflower seeds), and algae. Whole grains contain different vitamins. Deficiencies in A and B vitamins cause damage to lysosomal membranes thus releasing enzymes which enter the nuclei and cause chromosomal abnormalities [16]. The effects of whole grains

on cancer prevention are probably not limited to dietary fiber effects but may also involve effects on oestrogen metabolism, glucose and insulin metabolism, and oxidative processes [26, 27].

An independent risk factor for the occurrence of UCNT, in the present study, was consumption of industrially manufactured food additives for enhancing flavour, whose primary ingredients, according to the declaration of the manufacturers, is cooking salt (up to 56 percent), dried vegetables and spices, flavour enhancers (monosodium-glutamate and disodium-inosinate), carbohydrates, and colour (riboflavin).

Studies conducted in Asia reported that the risk of NPC is increased in persons who frequently consume salted fish, which contains high levels of S-nitrate compounds, whose metabolites are carcinogenic. The result of a study from Sweden carried out on experimental rats (Sprague-Dawley), which were fed with Chinese salted fish, supports the hypothesis that this food is a possible risk factor for the onset of NPC [28].

Salted duck eggs, salted leafy vegetables, and salted roots, were independent risk factors of NPC, but only when they were consumed during infancy, and not later [6].

Sodium-nitrites (preservatives) ingested via food can form nitrous acid in combination with gastric acid. Secondary amines, or compounds with secondary amino group (most frequently from ingested food), are found in the stomach, and these, in contact with nitrous acid, can form nitrosamines, which can, by way of blood circulation, reach distant places within the human organism, for example, the nasopharynx. Therefore, one must be cautious when using nitrites as a preservative or other compounds that are derivatives of nitrous acid.

It is likely that some preserved food items can contain high concentrations of nitrosamine precursors, and substances that induce replication of EBV [29]. Substances which activate EBV were discovered in salted fish and salted mutton, and these food items are frequently present in the diet of those who live in the Maghreb countries [30], where NPC incidence is high.

According to the results of several case-control studies [12], inflammatory along with benign diseases of the ear and nose were related with the occurrence of NPC. In the present study, chronic rhinosinusitis was significantly more frequently present in UCNT cases than in their controls. However, this association was not an independent one.

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In the native population of Alaska (Eskimos, Indians, and Aleuts) the risk for the occurrence of NPC was increased among the relatives of the patients. In Eskimos, relatives of the patients with NPC were at a three-time greater risk for NPC compared to the population as a whole [31]. In China, NPC was significantly more frequent in first-degree relatives, particularly in the mothers of the cases, than in their controls [12]. In the present study, there were significantly more malignant diseases among the relatives of NPC patients than among the relatives of controls, but this relationship was not found to be an independent one.

It is known that full-fat milk contains saturated fats, which can be a potential risk factor in the occurrence of carcinomas. On the other hand, vegetable oils seem to act protectively. In particular, the protective role of olive oil should be pointed out, because it contains antioxidants. In the present study, frequent consumption of margarine and olive oil was inversely related with the occurrence of UCNT. This association was independent from other factors.

Numerous studies have proved that insufficient consumption of food rich in vitamins A, C, E, and beta-carotene, leads to an increased risk for the occurrence of various malignant tumours [6, 8, 9]. In the present study, individuals from control group, more frequently than cases, consumed kale, spinach, courgettes, radishes, grapefruit, fresh figs, hazelnuts, peanuts as well as seasonal fruit and vegetables - green lettuce, spring onions, green peppers and apples. However, an inverse link between these food items and UCNT was not independent.

## CONCLUSION

Although this case-control study is a small one (UCNT is not a frequent malignancy), the results obtained through this study are mainly in agreement with the results obtained from other studies of nasopharyngeal carcinomas. However, we believe a multicentric study enrolling greater number of cases would be most desirable.

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## Фактори ризика за настанак недиференцираног карцинома назофаринкса: анамнестичка студија

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### КРАТАК САДРЖАЈ

**Увод** У Србији је стопа инциденције карцинома назофаринкса мања од један на 100.000 становника, што је сврстава у регије с ниским инциденцијом за ово обољење.

**Циљ рада** Циљ студије је био да се укаже на могуће факторе ризика који доводе до настанка недиференцираног карцинома назофаринкса (НКН) у популацији с ниским ризиком за ово обољење.

**Методе рада** Истраживање је урађено као анамнестичка студија која је обухватила 45 особа с хистолошки потврђеним НКН и 90 здравих испитаника, који су чинили контролну групу. Оболели и испитаници контролне групе су међусобно упарени по узрасту ( $\pm 3$  године), полу и месту становања. Прикупљени су подаци о социодемографским одликама, професионалној изложености штетним агенсима, навикама, исхрани,

личној и породичној анамнези. У статистичкој обради података примењене су униваријантна и мултиваријантна логистичка регресиона анализа.

**Резултати** Резултати анализе су показали да су независни фактори ризика за настанак НКН тзв. пасивно пушење дувана у породици током детињства, честа употреба индустријски припремљеног додатка јелима за побољшање укуса хране и често конзумирање белог хлеба. НКН је значајно инверзно повезан с честим конзумирањем маргарина, маслиновог уља и кукурузног хлеба.

**Закључак** У нашој популацији је низак ризик за појаву НКН, али би било пожељно да се уради мултицентрична студија која би обухватила већи број испитаника.

**Кључне речи:** недиференцирани карцином назофаринкса; фактори ризика; анамнестичка студија; исхрана; пушење