RESEARCH COMMUNICATION

Risk Factors of Nasopharyngeal Carcinoma in Turkey - an Epidemiological Survey of the Anatolian Society of Medical Oncology

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Abstract

Background: Nasopharyngeal carcinoma is a rare disease in most parts of the world with a multifactorial etiology involving an interaction of genetic, viral, environmental and dietary risk factors. This is the first epidemiologic study aimed to evaluate the risk factors of nasopharyngeal carcinoma in the Turkish population. Methods: We conducted a multicentric, retrospective, case-control study using a standardized questionnaire which captured age, sex, occupation, household type, blood group, dietary habits, smoking, alcohol consumption and oral hygiene. The study included 183 cases and 183 healthy controls matched by sex and age. Multiple logistic regression and univariate analysis were employed. Results: The peak age incidence was 40-50 years and the male to female ratio was 2:1. We observed significant associations between elevated nasopharyngeal carcinoma risk and low socioeconomic status, rural household type (OR:3.95, p<0.001), farming (OR:4.24, p<0.001) and smoking (OR:3.15, p<0.001). Consumption of french fries (OR:1.44, p=0.024), fried meat (OR:1.05, p=0.023) and tea (OR:5.55, p<0.001) were associated with elevated risk, while fresh fruit consumption was associated with reduced risk (OR:0.59, p=0.011). An irregular meal pattern was also a risk factor (OR:1.75, p=0.012). There were no significant associations between consumption of grain, diary products, alcohol and nasopharyngeal carcinoma risk (p>0.05); furthermore salty foods had a borderline p value (OR:2.14, p=0.053). Blood type A increased the risk (OR:2.03, p=0.002) while blood type 0 was a protective factor (OR:0.53, p=0.009). Rare habit of teeth brushing (OR:6.17, p<0.001) and ≥10 decayed teeth before diagnosis (OR:2.17, p<0.001) increased the risk. Conclusions: The nasopharyngeal carcinoma risk factors described in the literature are also applicable for the Turkish population. People with type A blood are at risk in Turkey. Salted foods have also a border risk out of the endemic regions. This is the only study showing that poor oral hygene is a serious risk factor for nasopharyngeal carcinoma.

Keywords: Nasopharyngeal carcinoma - epidemiology - etiology - risk factor - Turkey

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Introduction

Nasopharyngeal carcinoma (NPC) is rare in most parts of the world, where incidence rates are generally less than 1 per 100.000 person-years. However, in southern China, southeastern Asia, middle-east and north Africa the rates can be as high as 20 to 50 per 100.000 person-years. The distinctive geographic and ethnic distribution of NPC worldwide suggests that genetic predisposition, dietary and enviromental factors, and Epstein-Barr virus (EBV) all have been associated with the pathogenesis of this tumor (Jeannel et al., 1999; Chang and Adami, 2006). An epidemiological survey revealing data for NPC etiology in Turkey has not been evaluated yet. Here, we have performed the first, multicentric, retrospective case-control study to examine the risk factors for NPC in Turkish population.

Materials and Methods

Study population

183 patients diagnosed with histologically proven NPC and 183 NPC-free controls were enrolled in the study. Cases were identified from medical records of

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Training and Research Hospitals of Ministry of Health and Medical Faculty Hospitals in the Anatolian region of Turkey. Controls were randomly selected from NPC-free persons who came to the hospitals to visit or to take care of the patients (usually family members), or admitted to the same hospital for other diseases, frequency-matched to cases by sex and age.

Data collection

Medical doctors conducted a face-to-face interview using a standardized questionnaire retrospectively. The questionnaire was captured age, sex, blood group, lifestyles; including dietary habits (diary products, fresh fruit, fried meat, french fries, grain, tea and salty foods), smoking habits, alcohol consumption and oral hygiene up to the time of the diagnosis. Also inquired were household type, occupation and socioeconomic status.

Information on diary products, fresh fruit, fried meat, french fries, grain, salty foods and alcohol captured frequency of consumption (daily, 3-4 times a week, 1-2 times a week, 1-2 times a month, rarely or never). Questions on tea also captured frequency of consumption (never, 1-5 glass/day, 6-9 glass/day, 10-19 glass/day, 20-29 glass/day, >30 glass/day). Data on cigarette smoking included current and past smoking habits and the number of cigarettes smoked per day. Household type was designated as rural or urban residency. Subjects were asked to choose between three categories for socioeconomic status (low, middle or high). Occupational status were divided into five groups (farmer, clerk, worker, housewife, other). Questions on the number of decayed teeth captured the level (none, 1-4, 5-9, 10-19, >20) and teeth brushing frequency (daily, weekly or rarely). No dental examination was performed as part of this survey.

Statistical analysis

Data were entered in a database and analyzed with Statistical Package for Social Science for Windows (SPSS, version 15.0) program. Males and females compared using non-parametric tests. The association of individual risk factors for NPC was analyzed using multiple logistic regressions, with the control group. A corresponding univariate analysis, including measures for all risk factors, was also explored. Reported measures of association are odds ratio (OR), 95% confidence interval (CI) and p value. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 183 NPC patients (males 66.7%; females 33.3%) and 183 healthy controls (males 64.5%; females 35.5%) were evaluated. The mean age of patients at NPC diagnosis was 44.9±12.9 (range, 18-75) years, and controls at enrollment was 43.9±12.8 (range, 19-76) years (p=0.445). The peak age incidence for NPC was 40-50 years (36.3%). The male to female ratio was 2:1 for cases and 1.8:1 for controls (p=0.660).

Cervical lymphadenopathy (46.1%), hearing loss (30.4%) and epistaxis (14.7%) were the most common presentations. Using the World Health Organization (WHO) classification for NPC criteria, the most prevalent WHO histology type was type III (69.6%), followed by WHO type II (29.4%) and WHO type I (1.0%).

Table 1. Sociodemographic Characteristics of Patients and Controls

Sociodemographic Characteristics	Patients		Controls		OR[a]	95% CI[b]	P value
	N	%	N	%			
Sex							0,660
Male	122	66,67	118	64,48	1,0		
Female	61	33,33	65	35,52	0,91	0,59-1,39	
Household type							<0,001*
Urban	69	37,70	129	70,49	1,0		
Rural	114	62,30	54	29,51	3,95	2,55-6,11	
Socioeconomic status							<0,001*
Low	67	36,61	32	17,49	1,0		
Middle	115	62,84	145	79,23	0,08	0,01-0,69	
High	1	0,55	6	3,28	0,21	0,03-1,77	
Profession							
Farmer	39	21,31	11	6,01	4,24	2,09-8,57	<0,001*
Worker	23	12,57	31	16,94	0,71	0,39-1,26	0,240
Clerk	28	15,30	50	27,32	0,48	0,29-0,81	0,005*
Housewife	39	21,31	38	20,77	1,03	0,63-1,71	0,898
Others	54	29,51	53	28,96	1,03	0,65-1,61	0,909

[a]Odds Ratio; [b]Confidence interval; *Statistically significant difference

Patients were predominantly from a rural background (62.3%), whereas controls were mainly from urban areas (70.5%) (p<0.001). In the occupation groups only farmers (21.3%) were found to have a significant elevated risk of NPC (OR 4.24, 95% CI:2.09-8.57; p<0.001). Furthermore, furnishers (3.6%) and automobile repairmen (3.3%) were the striking jobs in the patients group. There was a statistically significant difference between those with low to middle socioecomic status (36.6% and 62.8%, respectively) predominating the patient group, and those with middle socioeconomic status (79.2%) including the majority of the control group (p<0.001). The demographic characteristics and socioeconomic status of the study population were shown in Table 1.

Table 2 presents the association between dietary factors as well as smoking and alcohol use and NPC risk in the case-control dataset. When males and females were compared as per dietary habits, it was noted that they did not differ in any of the variables mentioned, except for alcohol consumption and smoking. Males tended to consume alcohol and smoke cigarette more frequently than females (p< 0.001 and p<0.03 respectively).

In a multivariate logistic regression analysis, consumption of french fries weekly or more (OR 1.44, 95% CI: 0.91-2.28; p=0.024), fried meat (OR 1.83 95% CI: 1.16-2.87 for monthly or biweekly and OR 1.05 %95 CI: 0.57-1.93 for weekly or more consumption; p=0.023) and tea (OR 5.55, 95% CI: 2.16-14.24 for <10 glass/day and OR 1.31, 95% CI: 0.67-2.57 for >10 glass/day; p<0.001) were associated with significantly elevated risk of NPC; while consumption of fresh fruit (OR 0.22, 95% CI: 0.06-0.81 for monthly or biweekly consumption and OR 0.59, 95% CI: 0.38-0.94 for weekly or more consumption; p=0.011) was associated with reduced risk. An irregular meal pattern (40.9% vs.28.4%) was also noted to be a risk

Table 2. Odds Ratios for the Association of Dietary Habits, Smoking and Alcohol Use to Risk of NPC

Dietary habit /Frequency	Patients N	Patients %	Controls N	Controls %	OR[a]	95% CI[b]	P value
Meal pattern							0,012*
Regular	108	59,02	131	71,58	1,0		
Irregular	75	40,98	52	28,42	1,75	1,13-2,71	
Dairy products							0,393
Never	7	3,83	6	3,28	1,0		
Monthly or biweekly	81	44,26	69	37,70	0,75	0,25-2,32	
Weekly or more	95	51,91	108	59,02	0,74	0,49-1,14	
Fresh fruit							0,011*
Never	11	6,01	3	1,64	1,0		
Monthly or biweekly	65	35,52	48	26,23	0,22	0,06-0,81	
Weekly or more	107	58,47	132	72,13	0,59	0,38-0,94	
Grain							0,287
Never	2	1,09	5	2,73	1,0		
Monthly or biweekly	52	28,42	61	33,33	2,76	0,53-14,48	
Weekly or more	129	70,49	117	63,93	1,29	0,83-2,02	
French fries							0,024*
Never	38	20,77	22	12,02	1,0		
Monthly or biweekly	79	43,17	102	55,74	0,65	0,34-1,22	
Weekly or more	66	36,07	59	32,24	1,44	0,91-2,28	
Fried meat							0,023*
Never	63	34,43	89	48,63	1,0		
Monthly or biweekly	32	17,49	26	14,21	1,83	1,16-2,87	
Weekly or more	88	48,09	68	37,16	1,05	0,57-1,93	
Salty foods							0,053
Never	21	11,48	38	20,77	1,0		
Monthly or biweekly	71	38,80	85	46,45	2,14	1,14-4,04	
Weekly or more	91	49,73	60	32,79	1,11	0,70-1,74	
Tea consumption							<0,001*
Never	10	5,46	37	20,22	1,0		
<10 glass/day	149	81,42	130	71,04	5,55	2,16-14,24	
10 glass/day or more	24	13,11	16	8,74	1,31	0,67-2,57	
Alcohol use							0,272
Never	149	81,42	160	87,43	1,0		
Rarely	30	16,39	21	11,48	2,15	0,39-11,89	
Daily	4	2,19	2	1,09	1,40	0,24-8,36	
Smoking							<0,001*
No	68	37,16	119	65,03	1,0		
Yes	115	62,84	64	34,97	3,15	2,05-4,82	

[a]Odds Ratio; [b]Confidence interval; *Statistically significant difference

Table 3. Distribution of Blood Type in Patients and Control

Blood type	Patients N	Patients %	Controls N	Controls %	OR[a]	95% CI[b]	P value
A	78	42,62	49	26,78	2,03	1,31-3,15	0,002*
B	25	13,66	36	19,67	0,65	0,37-1,13	0,125
0	37	20,22	59	32,24	0,53	0,33-0,86	0,009*
AB	9	4,92	12	6,56	0,74	0,30-1,79	0,502

[a]Odds Ratio; [b]Confidence interval; *Statistically significant

Table 4. Comparison of Oral Care in Patients and Controls

Oral care /Frequency	Patients N	Patients %	Controls N	Controls %	OR[a]	95% CI[b]	P value
Teeth brushing							<0,001*
Daily	35	19,13	89	48,63	1,0		
Weekly	97	53,01	40	21,86	2,57	1,51-4,37	
Rarely	51	27,87	54	29,51	6,17	3,60-10,55	
Number of decayed teeth							<0,001*
None	27	14,75	56	30,60	1,0		
1-9	95	51,91	98	53,55	4,36	2,31-8,25	
10 or more	61	33,33	29	15,85	2,17	1,28-3,67	

[a]Odds Ratio; [b]Confidence interval; *Statistically significant difference

factor for NPC (OR 1.75 95% CI: 1.13-2.71; p=0.012). There were no statistically significant associations between consumptions of grain, diary products and NPC risk (p=0.287 and p=0.393, respectively); furthermore salty foods had a borderline p value (p=0.053).

A substantial proportion of the patients were smokers (62.8%) with the mean of 18.92±6.62 pack-year. Cigarette smoking was found to be significantly associated with increased NPC risk (OR 3.15 95% CI: 2.05-4.82; p<0.001) in our study population. On the other hand, there was no significant association between alcohol consumption and NPC (p=0.272).

The most common blood type in NPC patients was A (42.6%), following 0 (20.2%), B (13.7%) and AB (4.9%). While blood type A was significantly associated with increased risk of NPC (OR 2.03 95% CI:1.31-3.15;

p=0.002), blood type 0 was associated with significant reduced risk (OR 0.53 95% CI:0.33-0.86; p=0.009) in the study population. Table 3 lists the distribution of blood types in NPC cases and controls.

Teeth brushing and number of decayed teeth were evaluated for association between oral hyigene and NPC risk. Both factors significantly increased the NPC risk (OR 6.17 95% CI:3.60-10.55; p<0.001 and OR 2.17 95% CI: 1.28-3.67; p<0.001 respectively). Females tended to brush their teeth more than males (p=0.034), though the number of decayed teeth did not differ between sexes (p=0.477). Table 4 shows the association between oral care and the risk of NPC.

Discussion

This is the first epidemiologic study in Turkey, designed to determine the risk factors for NPC. In Turkish population, most of the patients were middle-aged males with a low to median socioeconomic status, who were from rural areas. It has been reported that lower socio-economic level is an important confounding factor for NPC in China, Macau, Greenland and Tunisia (Jeannel et al., 1999; Feng et al., 2007). The peak age incidence was 40-50 years and the male to female ratio was 2:1. In almost all populations surveyed, the incidence of NPC is 2- to 3-fold higher in males than in females (Parkin et al., 2002).

In the studies from NPC-endemic areas, the relative risk of NPC associated with consumption of salt-preserved fish is generally ranged from 1.8 to 7.5, however salt-preserved fish have not been consumed in Turkey (Armstrong et al., 1998; Yuan et al., 2000; Zou et al., 2000 Feng et al., 2007). As dietary habits of Turkish population are extremely different from Cantonese diet, this was not evaluated. In the present study, consumptions of french fries and fried meat were associated with increased NPC risk. Fried foods accumulate significant levels of nitrosamines as well as heterocyclic amines which the carcinogenic potentials were supported by experiments in rats (Zheng et al., 1994; Zou et al., 1994; Armstrong et al., 1998; Ward et al., 2000). Our results support that fried meat was especially important risk factor for southeastern Anatolian region of Turkey. Interestingly, we found a strong association between tea and elevated NPC risk, however tea consumption was associated with a decreased occurrence of NPC (Ruan et al., 2010).

The patients tended to consume fresh fruits less frequently than controls, that was associated with a significantly reduced relative risk of NPC. In contrast to preserved foods, frequent consumption of fresh fruits were associated with a lower risk of NPC in previous studies. The protective effect of fruits were attributed to antioxidant effects, prevention of nitrosamine formation, and other anticarcinogenic properties (Armstrong et al., 1998; Yuan et al., 2000; Gallicchio et al., 2006; Farrow et al., 1998).

The majority of patients had a story of smoking for a prolonged duration of time. A number of case-control studies examining cigarette smoking and risk of NPC in a variety of populations reported an increased risk of 2- to 6-fold, establishing tobacco smoke as a consensus risk factor for NPC (Vaughan et al., 1996; Cheng et al., 1999; Armstrong et al., 2000; Yuan et al., 2000). On the other hand, most of case-control studies found no association between alcohol consumption and NPC (Zheng, Yan et al., 1994; Cheng et al., 1999; Zou et al., 2000). In our study, cigarette smoking was found to be significantly associated with increased risk whereas no significant association was found between alcohol consumption and NPC. These findings are consistent with the literature.

A conspicuous finding in our study was the association between blood type A and elevated NPC risk. Furthermore blood type 0 was associated with a protective effect in our study group. As far as we know, there is only one report examining the association between blood type and NPC risk in the literature (Seow et al., 1964). The authors found no association, however, so that further studies appear warranted to further assess the possible relationship evidenced here.

Poor oral hygiene was found to be a strong risk factor for NPC in the present study. Several studies evaluated the deficient oral and dental hygiene in NPC patients undergoing radiotherapy (Shieh et al., 1997; Wang et al., 2008), however, in our view, this is the first study showing the association between increased risk of NPC and poor oral care.

Occupational exposure to fumes and solvents overall was associated with a 2- to 6-fold higher risk of NPC [Chang and Adami, 2006]. The excess of NPC incidence or mortality was reported among welders, metal workers, bakers, agricultural workers and wood workers (Yu et al., 1990; Zheng et al., 1992). However, chemical exposures were not interrogated in this study, farmers, furnishers and automobile repairmen were frequent among patients.

It has been well established that reactivation of Epstein-Barr virus (EBV) in the epithelial mucosal lining of the nasopharynx is strongly associated with NPC. In fact, it is difficult to entirely explain its geographical distribution by EBV infection. Therefore, it is strongly suspected that NPC risk is affected by cofactors in addition to EBV infection (Zeng, 1985; Hildesheim and Levine, 1993). This, as well as lack of testing for EBV was the main limitation of our study and should be addressed with further studies.

In conclusion, we observed significant associations between elevated NPC risk and rural household type, low socioeconomic status and dietary factors (irregular meal pattern, consumption of more fried foods, tea and fewer fresh fruit). The risk factors described in the literature are also acceptable for Turkish population. People with type A blood is at risk in Turkey. Salted foods have also a border risk out of the endemic regions. This is the only study showing that poor oral hygene is a serious risk factor for nasopharyngeal carcinoma. The study has provided a clear view to the NPC etiology in Turkish population, thus primary preventive strategy may be developed

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