

Nasopharyngeal Carcinoma – Analysis of Risk Factors and Immunological Markers

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Rezumat

Carcinomul nazofaringian – analiza factorilor de risc și a markerilor imunologici

Scop: Inventarierea factorilor de risc asociați CNF prezenți la pacienții tratați în cadrul clinicii ORL a Spitalului Clinic Colțea București cu evidențierea similarităților și diferențelor față de datele existente la ora actuală la nivel mondial.

Pacienți și metode: Am analizat retrospectiv 178 de cazuri din perioada 2003-2011 ce au îndeplinit criteriile de includere în cadrul grupului nostru de studiu.

Rezultate și discuții: Grupul nostru de studiu a prezentat numeroase caracteristici specifice (un număr mai mare de cazuri cu vârsta peste 60 ani decât pacienți tineri; o scădere lineară a numărului de cazuri pentru grupa de vârstă 30-39 ani; aproximativ 1/3 din cazuri nu au prezentat nici un factor de risc; > 10% din cazuri au fost asociate cu limfoame, etc.).

Concluzii: Caracteristicile imunohistochimice identificate la pacienții noștri cu forme de CNF nediferențiat sunt: MNF116, CK19, S100, CD34betaE12, Ki67, EBV pozitiv; restul markerilor fiind negativi (CerB2, EGFR, COX2, p53, CK7, CD117, VGFR, PCNA, L26/CD20, UHCL1, CD15, CD30, VIM, TTF1, CLA, CK17, CEA, LMP, CD79a, EMA).

Cuvinte cheie: carcinom nazofaringian, factori de risc, VEB, limfom, markeri imunologici

Abstract

Purpose: To analyze the risk factors associated with Nasopharyngeal Carcinoma (NPC) in patients admitted to the ENT Department at Coltea Clinical Hospital in order to assess the similarities and differences as compared to the epidemiological data internationally reported.

Patients and methods: This is a retrospective study on 178 cases that met the inclusion criteria from 2003 to 2011.

Results and discussions: There are a number of specific characteristics noticed in our study group: a larger number of cases aged over 60 than younger patients; a linear fall in number of the cases aged between 30-39 years; approximately one third of the cases did not have any of the traditional risk factors; more than 10% of the cases were associated with lymphoma, etc.

Conclusions: The immunologic pattern of our patients presenting undifferentiated NPC is the following: MNF116, CK19, S100, CD34betaE12, Ki67, EBV positive. The rest of the markers were negative (CerB2, EGFR, COX2, p53, CK7, CD117, VGFR, PCNA, L26/CD20, UHCL1, CD15, CD30, VIM, TTF1, CLA, CK17, CEA, LMP, CD79a, EMA).

Key words: nasopharyngeal carcinoma (NCP), risk factors, EBV, lymphoma, immunologic markers

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Introduction

Incidence rates for NPC vary enormously among different populations. In endemic areas the numbers can be fifty times higher than in other areas. The highest incidence is found in southern China. In Hong Kong, NPC reaches 30 cases/100.000 men. This disease is 3 times more frequent in men than in women. NPC evolves at a much younger age than other forms of cancer as it has the highest incidence below the age of 50. The incidence rises after the second decade and reaches a plateau for both sexes till the age of 50 when it drops gradually. (1)

The development of NPC is the result of a complex interaction between genetic factors, early EBV infection and environmental carcinogens. Genetic susceptibility plays an important role in NPC pathogenesis. HLA alleles such as A2, A33, B46, B58, Cw1 and DR3 are often present in NPC patients. (2) A2, Cw1, B46 haplotype is associated with an earlier age of debut. On the other hand A2 haplotype without B46 or B58 has a better survival rate. (3) The discovery of EBV receptors on pharyngeal epithelial cells has established the connection between EBV and NPC. (4,5) In Hong Kong the incidence for both sexes has dropped rapidly with approximately 30% in the last 20 years but the age distribution pattern has remained unchanged. A possible explanation may be the fact that the individual level of exposure to carcinogens has dropped but the mechanism of exposure is the same. (6) Numerous potential agents have been studied including dust, smoke and industrial fumes. NPC incidence in women is still lower than men worldwide despite the growing number of smoking women. (7,8) There has been reported a higher risk of developing NPC in subjects with professional exposure to formaldehyde. (9,10)

Jia et al. (11) analyzed a strong association between NPC and a diet rich in salted fish and poor in vegetables during childhood. Salted fish, which is traditional in southern China contains an important quantity of volatile nitrosamines. These are alkylating agents known to induce malignant tumors in laboratory animals. Dietary carcinogens affect only susceptible populations given the fact that Japan has a low incidence for NPC despite similar consumption of salted fish and canned vegetables.

In Romania, IARC reported an incidence of 1.7% in 100.000 men and 0.85% in 100.000 women for NPC. (12) We cannot attribute these numbers to salted fish consumption, but we can take into consideration the lack of fresh vegetables in basic diet, excessive smoking habits and childhood EBV infection. (13)

The early detection of NPC is almost impossible in our country given the lack of access to the healthcare system; therefore we are still encountering terminal pathologies in other parts of the globe with a poor economy. (14)

In the light of the above, our patients are treated by radiotherapy primarily, other types of treatment being unsuitable for the stage or too expensive. (15-20)

Materials and Methods

We conducted a retrospective descriptive study on 178 patients diagnosed with NPC in the ENT Clinic at Coltea Clinical Hospital Bucharest during 2003-2011.

Our study's objectives are:

1. Descriptive analysis of our study group (gender distribution, age groups distribution, morphological types);
2. Analysis of NPC risk factors impact on the patients (chronic smoking, alcoholism, professional chemical exposure and EBV infection);
3. Immunological features of the biopsy material in order to identify certain molecular characteristics with possible prognostic values.

Inclusion criteria for our study group:

1. histological diagnostic of certainty for NPC;
2. if the histologist requested an immunological differential diagnostic to Victor Babes National Research and Development Institute for Pathology and Biomedical Sciences, Bucharest we included only the cases which received the results back;
- 3) we included only the patients with traceable complete examination charts.

Exclusion criteria:

1. lack of histological diagnostic of certainty for NPC;
2. lack of immunologic analysis for those cases which required differential diagnosis;
3. all the cases without traceable or with incomplete examination charts.

Therefore, from a total of 206 cases of NPC admitted to our hospital 28 cases were excluded: 17 did not meet the inclusion criteria and 11 were subsequent admissions of the same patients to different departments in our hospital.

For statistical analysis we used Microsoft Excel and SPSS. In order to correlate the immunological analysis we used the reference materials available on the website www.vbabes.ro.

Results and Discussions

Our study group included 178 patients diagnosed with NPC during 2003-2011 at Coltea Clinical Hospital Bucharest. Concerning the sex distribution we observed predominance in male sex with 114 (64%) cases, similarly to worldwide statistics, Fig. 1A.

From 2003 to 2011 we recorded a maximum number of 29 patients (16,29%) in 2008 with a fall in numbers in the following years probably due to the general fall in accessibility to the medical system on the background of the economic crises in the EU. A minimum number of 12 (6,74%) patients with NPC was recorded in 2003. The small number of cases analyzed for the period 2003-2007 is due to the failure in meeting the inclusion criteria; Fig. 1B.

We discovered a linear growth in number of cases for both sexes during the study period which confirms the annual growth of cases with NPC worldwide, Fig. 1C.

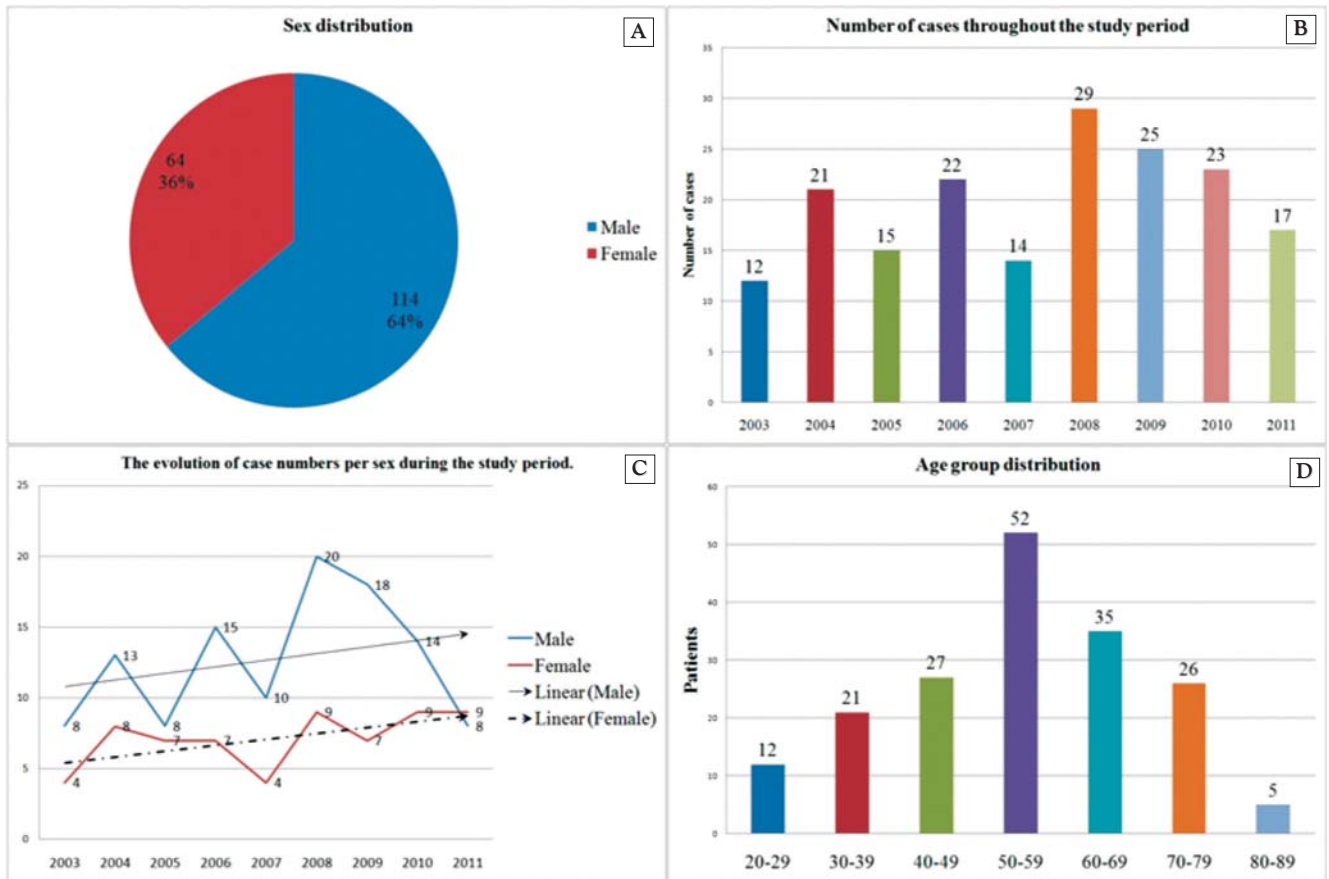


Figure 1. Descriptive statistics of the study group

The age groups distribution records a maximum number of 52 (29,21%) patients between 50-59 years. In the areas with high NPC prevalence the evolution in case numbers has a growth in plateau till the 5th decade of age with a sudden fall in number at a higher ages. On the contrary inside our study group the age curve has a plateau towards the 6th and 7th decades where we record a higher number of cases, Fig. 1D.

Regarding the evolution in number of cases per age group during the analyzed time frame one can notice a constant linear growth. However there are 2 contradictory situations: the linear fall in case numbers for the 30-39 years age group which can be explained by the longer exposure of these individuals to modern prevention campaigns concerning tobacco use and alcohol consumption; the other contradictory situation is given by the 80-89 years age group which has a constant number of cases throughout the study period, Fig. 2A, 2B.

The histological analysis places the undifferentiated forms of NPC on the first place with 96 (54%) cases. Although despite the general epidemiological data which considers lymphomas as a minority, there are 20 (11%) cases in our study group. This aspect is probably influenced by the oncology-hematology specific of our hospital, Fig. 2C.

From the histological point of view the evolution in case numbers shows a linear decrease of the cases diagnosed with

spindle cell NPC in spite of the general pattern growing in numbers for all NPC histological types. Moreover there is a linear constant evolution for the metastasis of other malignancies at nasopharyngeal level. This aspect is influenced by the diagnostic protocols used by the majority of surgeons and physicians which consider metastatic cases as terminal and refer them to oncology departments without consulting an ENT specialist; Fig. 2D.

The prevalence of risk factors in our study group is the following: tobacco use 124 (69,66%) cases; alcohol consumption 67 (37,64%) cases and professional toxic exposure 33 (18,33%) cases; Fig. 3A. The importance of EBV infection was partially quantified because of the positive identification of the virus. It was realized only for the patients with histological samples needing an immunological differential diagnosis which was sent to the Victor Babes Institute. The large number of cases without any of the risk factors is alarming: 53 (29,77%). Although a possible explanation for these cases can be the fact that our unit is specialized in the treatment of this pathology and many difficult cases are sent from other regions, one can notice the growing linear number of such cases throughout the study period, Fig. 3B. Furthermore, there are a constant number of cases associated with toxic professional exposure in spite of the closure of the chemical industry. These cases seem to be part of a reservoir population, which probably will decline in the future.

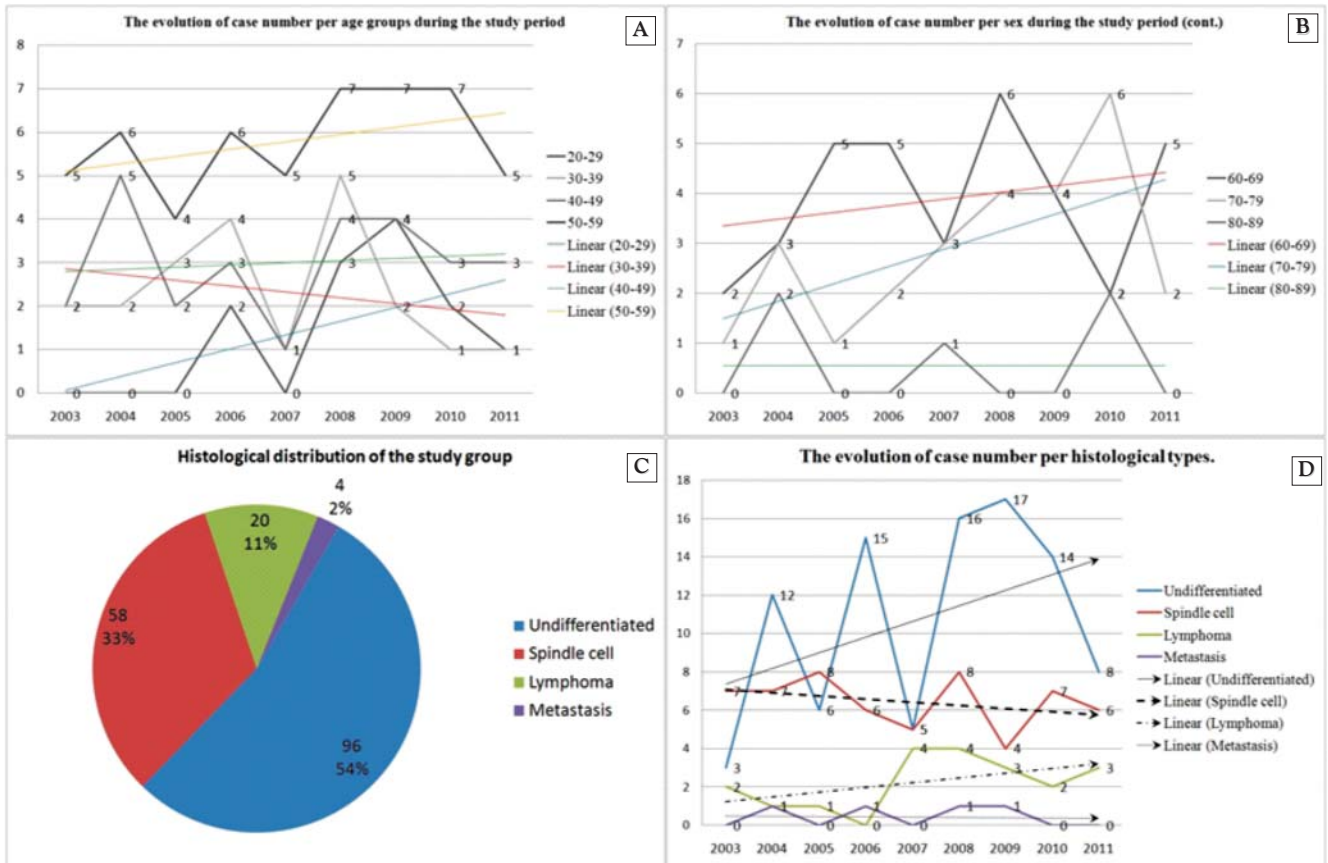


Figure 2. Histological analysis of the study group.

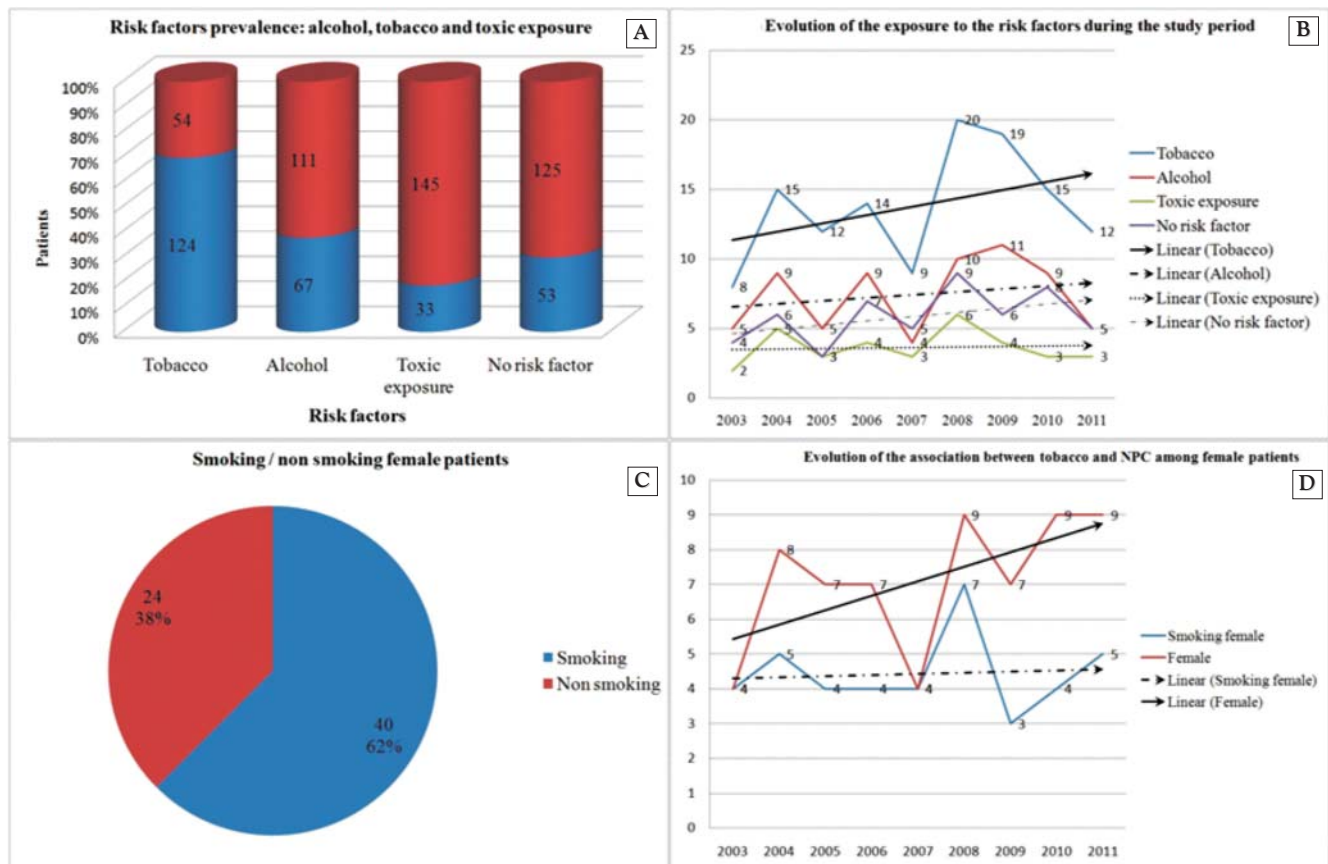


Figure 3. Importance of the risk factors

Numerous recent studies have analyzed the connection between the growing number of smoking women and the number of female patients with NPC. According to these studies the number of women with NPC does not grow exponentially along with the number of smoking women. Data obtained by us sustain this general change of perspective which considers that there is a stronger association between NPC and other risk factors than with tobacco use; Fig. 3 C, D.

30 cases out of the total of 178 (19 cases with undifferentiated NPC and 11 cases of lymphoma) and belonging to all age groups needed immunological investigation for differential diagnosis. There was a slight male predominance. The immunological pattern of our patients presenting with undifferentiated NPC was the following: MNF116, CK19, S100, CD34betaE12, Ki67, EBV positive; the rest of the markers were negative (CerB2, EGFR, COX2, p53, CK7, CD117, VGFR, PCNA, L26/CD20, UHCL1, CD15, CD30, VIM, TTF1, CLA, CK17, CEA, LMP, CD79a, EMA). Concerning the subgroup of patients with lymphoma the immunological pattern included: Ki67, L26/CD20 and EBV positive; other markers were negative (CD79a, Bcl2, CD5, CD10, CLA, UCHL1, MNF116, CD30, VIM, CD23, CyclinD1, Ck34BetaE12, CK19, S100, PAX5, CD3, CD4, CD8). These data support the importance of EBV infection as a risk factor for NPC.

Conclusions

The 178 patients diagnosed with NPC at Coltea Clinical Hospital presented numerous characteristics that sustain the epidemiological data recognized by the international forums such as sex distribution, age groups distribution, histological type distribution and a similar impact of the traditional risk factors.

However there are some specific characteristics for our study group:

- There is a higher number of cases aged over 60 years than younger patients;
- A linear drop in case number for the 30-39 age group;
- A higher number of cases associated with lymphomas;
- A linear drop in case number with spindle cell NPC despite the general rising pattern for all histological types;
- A very large number of cases without any of the traditional risk factors;
- The number of women affected by NPC did not follow the growing number of smoking women;
- The general immunological pattern of our NPC patients was the following: MNF116, CK19, S100, CD34betaE12, Ki67, EBV positive; the rest of the markers were negative (CerB2, EGFR, COX2, p53, CK7, CD117, VGFR, PCNA, L26/CD20, UHCL1, CD15, CD30, VIM, TTF1, CLA, CK17, CEA, LMP, CD79a, EMA).

Due to the fact that NPC does not benefit from a national prevention program we hope that this study will draw

the attention of other ENT clinics in Bucharest in order to study a larger group of patients.

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