Oral Oncology 49 (2013) 237–243

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Lower mortality from nasopharyngeal cancer in The Netherlands since 1970 with differential incidence trends in histopathology

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ARTICLE INFO

Article history:
Received 27 July 2012
Received in revised form 31 August 2012
Accepted 26 September 2012
Available online 22 October 2012

Keywords:
Nasopharyngeal neoplasms
Smoking
Emigration and immigration
Histology
Netherlands
EBV
Cancer registry
Incidence
Mortality

SUMMARY

Objective: Nasopharyngeal carcinoma (NPC) is rare in western countries albeit affected by common and unrelated phenomena: smoking less in men, more in women and immigration from China and North Africa. We studied trends in NPC incidence, tumour morphology, survival and mortality in order to assess progress against this cancer.

Materials and methods: A trend analysis was performed with nationwide incidence and survival data (from The Netherlands Cancer registry in 1989–2009), followed by analysis of mortality (data from Statistics Netherlands) covering the period 1970–2009, and calculating estimated percentages of change (EAPC) in both. According to the WHO classification we distinguished keratinizing SCC (WHO-I), differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma.

Results: NPC incidence significantly decreased since 1989, especially in males (EAPC 1989–2009: −1.3; 95% CI: −2.5, −0.2) and in patients with keratinizing SCC (WHO-I) (EAPC: −3.6; 95% CI: −5.3, −1.8). By contrast, the incidence of differentiated non-keratinizing tumours (WHO-IIA) significantly increased in the same period (EAPC: 9.6; 95% CI: 5.6, 13.5). One- and three-year relative survival, as an indicator of disease-specific survival increased slightly from 79% to 81% and from 57% to 65% since 1989. NPC mortality significantly decreased since 1970 (EAPC: −1.2; 95% CI: −1.8, −0.5) and more pronounced since 1989 (EAPC: −3.0; 95% CI: −4.3, −1.6).

Conclusion: During the past two decades, the incidence of NPC in The Netherlands decreased mainly by less keratinizing, supposedly smoking-related NPC (WHO-I). However, the incidence of non-keratinizing NPC (WHO-IIA, B) increased, most likely due to EBV infection and thus related to higher immigration levels of people from high-incidence areas.

Introduction

Nasopharyngeal carcinoma (NPC) has a substantial geographic and demographic variation. In western countries, NPC is an orphan disease with incidence rates below one per 100,000. NPC is endemic in Southern China and North Africa[1–3] and is thus most prevalent in The Netherlands among immigrants from high incidence countries like China, Indonesia in Southeast Asia and North Africa like Morocco.[4]

The World Health Organization (WHO) distinguishes three major histological forms: keratinizing squamous cell carcinoma (SCC) (WHO-I) – highly differentiated tumours with characteristic epithelial cell shape, growth patterns and keratin filaments – as well as differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma, that retain epithelial cell shape and growth patterns and are distinguished based on light microscopy.[5–7] While WHO-I is more common in low-incidence populations, WHO-IIA and B usually occur more frequently in high-incidence populations.[8,9]

A well-established risk factor for NPC is infection with Epstein-Barr virus (EBV), an ubiquitous herpes virus and confined to non-keratinizing carcinomas (WHO-IIA and B). Tobacco smoking and alcohol consumption are likely to contribute to SCCs of the nasopharynx (WHO-I).[10,11]

Nasopharyngeal carcinoma is highly sensitive to radiotherapy, the standard treatment for NPC patients without distant metastases. Cases with more advanced disease usually receive

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http://dx.doi.org/10.1016/j.oraloncology.2012.09.016

chemo-radiation.[12] Important prognostic factors for survival are stage, WHO type and age at diagnosis. Recently, EBV-related markers for diagnosis and prognosis of NPC became available[13–16] including molecular defined EBV (IgA) serology, which is characteristic for undifferentiated carcinomas (WHO-IIB), detection of EBV DNA load and oncogenic mRNA in nasopharyngeal brushings, reflecting local tumour presence and EBV DNA load in blood reflecting disease activity, clinical response after therapy and predicting distant metastases.[17]

The aim of this study was to assess progress against NPC by investigating population- and behaviour-related trends in incidence and tumour sub-classification, together with survival and mortality since 1970/1989 in The Netherlands, a low incidence country.

Materials and methods

Incidence data on NPC from 1989 to 2009 were extracted from the population-based Netherlands Cancer Registry (NCR). Only malignant tumours were included. Sarcomas in the nasopharynx were excluded. Mortality data from 1970 to 2009 were acquired from Statistics Netherlands which is based on attending doctors filling in cause of death forms.[18] Information on the vital status of newly diagnosed cancer patients during 1989–2009 was initially obtained from municipal registries and from 1995 onward from the nationwide database of all municipal population registries, providing virtually complete coverage of all deceased Dutch citizens. Follow-up was complete until 1 January, 2010. For most analyses, males and females were grouped and stratified into three age groups (<60, 60–74 and $\geqslant$75 years). Three main histological types according to the WHO classification[5] were distinguished: keratinizing SCC (WHO-I) as well as differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma. Neuroendocrine carcinoma, adenocarcinoma and tumours without pathological confirmation were combined as 'other carcinoma'. Stage was registered according to the UICC TNM Classification. Cases diagnosed 1989–1998 were classified according to the 4th TNM edition and diagnosed 1999–2009 according to later editions, as those are equal for NPC. Additional information on country of birth, not included in the original dataset, was provided in hindsight and upon request from the NCR. It thus marginally deviates from the patient group included in the original study but still represents a valid comparison.

Incidence and mortality rates were standardized to the European standard population. Changes in rates were evaluated by calculating the estimated percentage of change (EAPC) and the corresponding 95% Confidence Interval (CI). This was done by performing a linear regression analysis where a regression line is fitted to the natural logarithm of the rates, using calendar year as regressor variable. The trend was considered significant when the *p*-value was below 0.05. Changes in NPC occurrence were identified by performing joinpoint regression analysis (National Cancer Institute, Bethesda, Maryland).[19]

One-, three- and five-year relative survival was used to estimate disease-specific survival. Relative survival reflects the survival of cancer patients, adjusted for competing causes of death in the general population with the same age and gender distribution. Traditional cohort-based relative survival analysis was performed for the period 1989–2009. All statistical analyses were performed using SAS (version 9.2).

Results

The main characteristics of all 1411 patients diagnosed with NPC between 1989 and 2009 are summarized in Table 1. Among the patients were 1005 (71%) males and 406 (29%) females. The male-to-female incidence ratio, being 2.5 during 1989–1993, gradually equalized in more recent years. About 59% of the patients were below age 60 at diagnosis throughout the study period.

During 1989–1998, only 11% of the cases were diagnosed in stage I and II, and 14% in stage III and 69% in stage IV. Stage distribution changed to 25% stage I and II, 29% stage III and 40% stage IV since 1999.

With 621 cases (44%), undifferentiated non-keratinizing carcinoma (WHO-IIB) was the predominant histological type, followed by 555 (39%) keratinizing squamous cell carcinomas (WHO-I) and 115 (8%) differentiated non-keratinizing carcinomas (WHO-IIA). Radiotherapy was most commonly administered to these patients. While 715 patients (51%) received radiotherapy only, another 429 patients (30%) were treated in combination with systemic and/or chemotherapy. Merely 76 patients (5%) received additional surgery and in 99 patients (7%) treatment was abandoned. About 69% of all newly diagnosed NPC patients were born in The Netherlands, 10% in Morocco, 5% in China, 4% in Indonesia and 3% in Turkey.

Histological variation

Patients with WHO-I tumours were on average older, diagnosed at later stages and received surgery more often than patients with other tumour histology. WHO-I was the predominant NPC type in patients born in The Netherlands (47%), whereas in patients born in most non-western countries, WHO-IIB was the most common histological variant (53–66%; Table 1).

Trends in incidence

Among males, the age-standardized incidence rate of NPC significantly decreased over time from 0.8 per 100,000 in 1991 to 0.5 in 2007 (EAPC 1989–2009: −1.3; 95% CI: −2.5, −0.2), whereas the incidence among females remained stable at about 0.2 per 100,000 (Table 2, Fig. 1). The age-specific incidence rose after the age of 30 and peaked at the age 55–65 years, being highest in the period 1989–1991 (Fig. 2). A decline in incidence was observed in almost all age groups, however only significant in patients aged 75 and over (EAPC: −3.5; 95% CI: −6.3, −0.8). The incidence of WHO-I tumours decreased significantly between 1989 and 2009 (EAPC: −3.6; 95% CI: −5.3, −1.8), whereas the incidence of non-keratinizing differentiated tumours significantly increased in males (EAPC: 6.6; 95% CI: 2.5, 10.8) (Table 2).

Trends in survival

One- and three-year relative survival slightly increased and amounted to 81% and 65% in 2009 as compared to 79% and 57% in 1989, respectively (Fig. 3). Five-year relative survival rose from 50% in 1989–1993 to 55% in 2004–2009. No sex-specific differences were found, but relative survival was clearly worse for patients of higher age and stage. Whilst patients with non-keratinizing tumours (WHO-IIA and B) had the highest survival rates which slightly increased over time (1-year relative survival ranging from 91% to 98%), survival of patients with keratinizing SCCs (WHO-I) was lower (1-year relative survival ranging from 65% to 78%) and slightly decreased over time (Fig. 4). Similarly, 3-year relative survival increased in patients with non-keratinizing tumours (ranging from 64% to 78%) and decreased in patients with WHO type I tumours (ranging from 53% to 44%) (data not shown).