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

Melina Arnold [a,*], Maarten A. Wildeman [b], Otto Visser [c], Henrike E. Karim-Kos [a], Jaap M. Middeldorp [d], Renske Fles [b], I. Bing Tan [b], Jan Willem Coebergh [a,e]

[a] Department of Public Health, Erasmus MC, University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands
[b] Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, PO Box 90203, 1006 BE Amsterdam, The Netherlands
[c] Comprehensive Cancer Centre The Netherlands, PO Box 19079, 3501 DB Utrecht, The Netherlands
[d] Department of Pathology, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands
[e] Comprehensive Cancer Centre South, Eindhoven Cancer Registry, PO Box 231, 5600 AE Eindhoven, The Netherlands

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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

* Corresponding author. Tel.: +31 (0)10 70 43112; fax: +31 (0)10 70 38475.
E-mail address: m.arnold.1@erasmusmc.nl (M. Arnold).

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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).

Table 1
Characteristics of incident NPC cases according to WHO histology classification 1989–2009. *Source*: NCR.

	WHO-I Keratinizing squamous cell carcinoma		WHO-IIA Differentiated, non-keratinizing carcinoma		WHO-IIB Undifferentiated, non-keratinizing carcinoma		Other carcinoma		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*
Period of diagnosis									
1989–1993	162	47	13	4	143	41	28	8	346
1994–1998	128	42	10	3	134	44	32	11	304
1999–2003	122	35	29	8	164	47	34	10	349
2004–2009	143	35	63	15	180	44	26	6	412
Age at diagnosis (yrs)									
0–14	3	9	1	3	17	50	13	38	34
15–29	10	14	4	6	50	71	6	9	70
30–44	58	27	23	11	122	56	15	7	218
45–59	218	43	43	8	219	43	27	5	507
60–74	197	45	34	8	164	38	39	9	434
75+	69	47	10	7	49	33	20	14	148
Sex									
Male	412	41	82	8	451	45	60	6	1005
Female	143	35	33	8	170	42	60	15	406
Stage at diagnosis (1989–1999)									
1	20	63	1	3	6	19	5	16	32
2	21	54	3	8	12	31	3	8	39
3	46	52	0	0	39	44	3	3	88
4	190	43	19	4	211	47	27	6	447
Unknown	13	30	0	0	9	20	22	50	44
Stage at diagnosis (1999–2009)									
1	16	41	6	15	12	31	5	13	39
2B	48	32	19	13	78	52	4	3	149
3	69	31	32	14	113	51	7	3	221
4A	78	40	23	12	76	39	16	8	193
4B	31	44	7	10	32	45	1	1	71
4C	14	36	3	8	20	51	2	5	39
Unknown	9	18	2	4	13	27	25	51	49
Country of birth									
Netherlands	444	47	72	8	364	38	70	7	950
Other Western	13	54	0	0	10	42	1	4	24
Indonesia	18	30	9	15	32	53	1	2	60
Suriname/Dutch Antilles	12	35	2	6	18	53	2	6	34
Turkey	17	40	1	2	24	57	0	0	42
Morocco	29	21	17	13	88	65	1	1	135
China	16	25	5	8	43	66	1	2	65
Other non-western	20	31	9	14	35	55	0	0	64

[a] Data on country of birth originate from a separate dataset provided upon request by The Netherlands Cancer Registry.

Table 2
Trends in NPC incidence and mortality according to sex, age group, stage at diagnosis and histology in The Netherlands 1970/1989–2009.[a] *Source*: NCR, Statistics Netherlands

EAPC	Incidence (1989–2009)			Mortality (1970–2009)			Mortality (1989–2009)		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
Overall (95% CI)	**−1.3** (−2.5, −0.2)	−1.0 (−3.2, 1.3)	**−1.2** (−2.3, −0.2)	**−1.5** (−2.2, −0.8)	−0.5 (−1.7, 0.6)	**−1.2** (−1.8, −0.5)	**−3.7** (−5.3, −2.0)	−1.3 (−4.6, 2.1)	**−3.0** (−4.3, −1.6)
Age < 60	−0.9 (−2.2, 0.5)	−1.7 (−4.7, 1.4)	−1.0 (−2.4, 0.3)	**−1.5** (−2.3, −0.6)	−0.4 (−1.8, 1.0)	**−1.1** (−1.8, −0.5)	**−2.2** (−4.1, −0.4)	−2.6 (−6.5, 1.4)	**−2.4** (−3.8, −1.0)
Age 60–74	−1.3 (−3.2, 0.7)	1.1 (−2.8, 5.0)	−0.8 (−2.7, 1.1)	**−1.5** (−2.6, −0.5)	−0.2 (−2.0, 1.6)	**−1.0** (−1.9, −0.1)	**−4.7** (−6.9, −2.4)	0.4 (−4.5, 5.3)	**−3.4** (−5.4, −1.4)
Age ⩾ 75	−3.4 (−8.0, 1.3)	−3.0 (−7.8, 1.7)	**−3.5** (−6.3, −0.8)	**−1.3** (−2.6, −0.1)	**−3.1** (−4.7, −1.5)	**−1.6** (−3.0, −0.2)	−3.0 (−6.3, 0.3)	0.8 (−3.1, 4.7)	**−3.2** (−6.3, −0.2)
WHO-I	**−3.2** (−5.0, −1.3)	−3.7 (−6.7, −0.7)	**−3.6** (−5.3, −1.8)						
WHO-IIA	**6.6** (2.5, 10.8)	3.0 (−8.5, 14.5)	**9.6** (5.6, 13.5)						
WHO-IIB	−0.7 (−2.3, 0.9)	−0.5 (−2.7, 1.8)	−0.7 (−1.8, 0.5)						

EAPC = Estimated Annual Percentage Change; 95% CI = 95% Confidence Interval.
[a] Bold numbers are significant at $p < 0.05$ level.

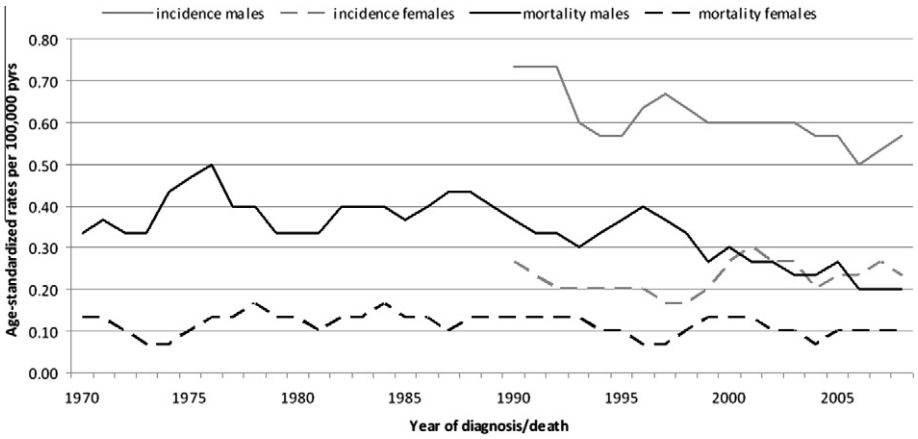

Figure 1 Three-year moving averages of age-standardized NPC incidence and mortality rates per 100,000 person-years (ESR) in The Netherlands 1970/1989–2009. *Source*: NCR, Statistics Netherlands

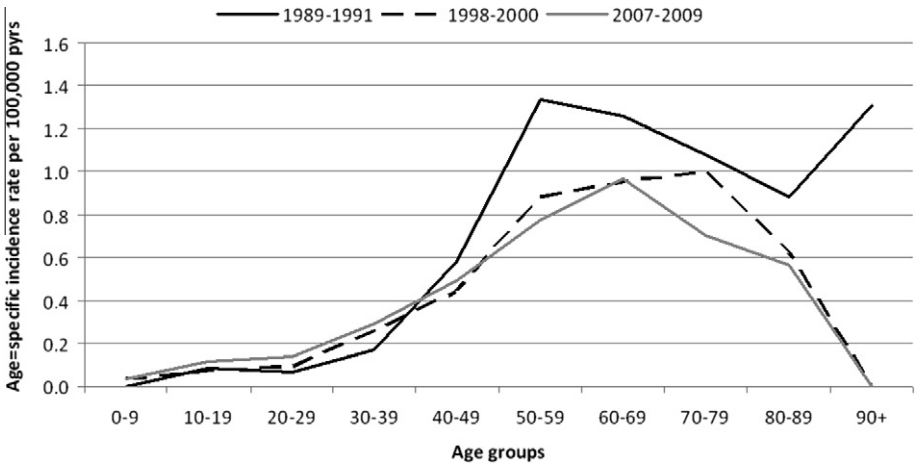

Figure 2 Age-specific NPC incidence per 100,000 person-years, 1989–2009. *Source*: NCR.

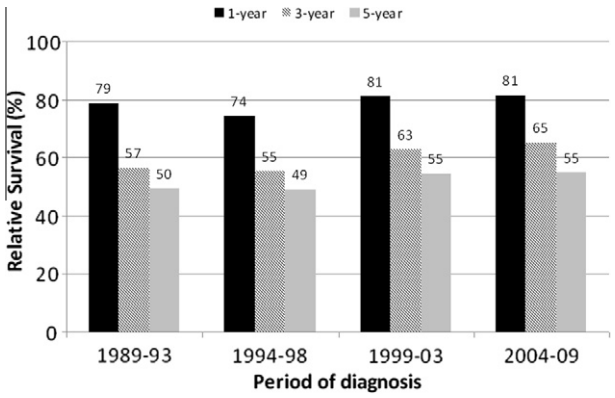

Figure 3 Trends in 1-, 3- and 5-year cohort-based relative survival from NPC, 1989–2009. *Source*: NCR.

Trends in mortality

Between 1970 and 2009, 1275 persons died from NPC in The Netherlands (683 between 1989 and 2009) as recorded by Statistics Netherlands. The mortality-to-incidence ratio, an approximation measure for survival,[20] was thus 0.48 for the period 1989–2009. Most deaths (39%) occurred at age 60–74 years. About 41% of all deaths were younger than age 60 and 21% in patients aged 75 and over.

Overall mortality from NPC significantly decreased between 1970 and 2009 from 0.3 per 100,000 in 1971 to 0.1 per 100,000 in 2008 (EAPC 1970–2009: −1.2; 95% CI: −1.8, −0.5), however even stronger since 1989 (EAPC: −3.0; 95% CI: −4.3, −1.6) (Table 2, Fig. 1). The decrease during the latter period was more pronounced in males than in females and was observed across all age groups, however particularly in females aged 75 and over (Table 1).

Discussion

We found a decrease in NPC incidence, especially in males and of smoking related keratinizing SCC (WHO-I), coinciding with a significant increase of differentiated non-keratinizing NPC (WHO-IIA). The decline of cases with the poorest survival (WHO-I) in combination with slowly improving survival rates led to markedly decreasing mortality from NPC in The Netherlands in recent years, implying real progress.

Between 1989 and 2009, age-standardized incidence of NPC decreased significantly in males and a downward tendency was also observed in females. According to 'Cancer Incidence in Five

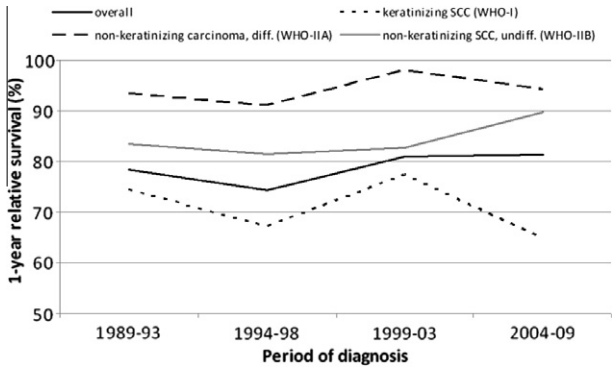

Figure 4 Trends in 1-year cohort-based relative survival from NPC by WHO histology classification, 1989–2009. *Source*: NCR.

Continents – volume VI, VIII and IX' and the literature, NPC risk is slowly decreasing in many European countries.[1,2,21] There is a marked South-North gradient in NPC risk with the highest rates in Malta (Fig. 5). A similar study from Scotland[22] only showed a clear decline in males below age 50 coinciding with increased NPC risks, also of dying, for people from lower socio-economic backgrounds. Studies from China also confirmed an inverse relationship of NPC incidence and social class.[10] Worldwide, a bimodal pattern in age-specific incidence curves of NPC was exhibited in low-risk populations with a first peak in late adolescence/early adulthood (ages 15–24 years), a subsequent decline and a second peak in later life (ages 65–79 years), but this was not evident in high-risk populations.[11] In our data, however, we could not confirm this pattern, possibly due to low numbers.

The observed trends in our study are most likely due to variation over time in exposure to carcinogenic risk factors as well as to increasing immigration from high-incidence regions of NPC. Even though the contribution of environmental, viral and genetic risk factors in the causation of NPC has long been controversial, the role of EBV in the development WHO-IIA and B tumours is clearly established.[23] The association between NPC risk, tobacco smoking and alcohol drinking, however, seems to be confined to SSCs of the nasopharynx (WHO-I).[24] More than two-thirds of differentiated squamous cell NPC cases arising in older persons were due to smoking and, to a lesser degree, to alcohol in a study from the US.[9] However, the role of alcohol in the causation of NPC is considered interactive with smoking.[24] In our study, we found a higher and increasing incidence of non-keratinizing tumours as opposed to a lower and slowly decreasing incidence of (smoking-related) keratinizing SCCs. Smoking in The Netherlands decreased from 59% in 1970 to 28% in 2009.[25] Similarly, a decreasing incidence in WHO-I tumours has been observed in high-incidence areas like Southern China and Hong Kong in recent years and is most probably also due to the decline in smoking.[26] In contrast, the increasing incidence of non-keratinizing tumours suggests a driving role of EBV and other environmental risk factors. The consumption of salted fish and preserved foods may indeed play important etiologic roles.[10]

Earlier studies found that NPC incidence is particularly high in migrants from high-incidence regions. For instance, a recent study from Sweden revealed elevated risks for NPC among immigrants from Former Yugoslavia, Asian Arab countries, Southeast Asia and North Africa, being up to 35-fold the risk of native Swedes.[27] Accordingly, the histological types of NPC varied by patient origin in our study: whereas WHO-I was the predominant NPC type in patients born in The Netherlands, it was WHO-IIB in patients born in most non-western countries. This pattern has also been described previously among Japanese and Chinese in comparison with Caucasian patients with NPC.[28] Thus, the increase in the incidence of EBV-related tumours (WHO-IIA and B) might be explained by recent migration waves to The Netherlands, the number of immigrants from China nearly tripling between 1996 (16,000) and 2011 (45,000).[18] Given the latest immigration figures and assuming that most Chinese, South-East Asian and North-African migrants carry higher NPC risks, especially for WHO-IIA and B tumours, the observed trends in this study are in line with expectations. This also implies that immigrant groups deserve special attention from health care professionals with regard to NPC risk and that EBV-based NPC diagnostics might be considered for risk-assessment and treatment monitoring in this group.[13–15] A recent review on changes in NPC risk in Chinese after migration to a low-risk country indicated decreasing risks the further the population had migrated and the longer they had stayed.[29] In view of these results, it can be expected that NPC risks in migrants in The Netherlands will slowly decrease and converge towards the low rates in the general Dutch population.

In recent years, survival from NPC has increased steadily due to earlier diagnosis and refined staging and treatment in many other countries[30]; more advanced technologies like intensity-modulated radiation therapy (IMRT) have been quite instrumental. In addition, enhanced imaging of the nasopharyngeal region by magnetic resonance imaging (MRI) instead of CT-imaging and adjustment of radiotherapy doses have considerably refined treatment options in recent years. Five-year relative survival increased from 50% in 1989–1993 to 55% in 2004–2009 in our study, which is close to 48% found in 129 NPC patients diagnosed between 1977 and 1993 in The Netherlands.[31] A Europe-wide study found even lower NPC survival; 1- and 5-year relative survival rates were 75% and 34% for males and 72% and 32% for females, respectively.[32] Clearly, stage of disease at diagnosis and tumour histology and, to a lesser extent, age at diagnosis determined the prognosis. As more than two thirds of all newly diagnosed NPC cases are stage 3 or 4 tumours with a reduced chance for cure, this might be due to often non-specific and flu-like symptoms. In addition, low numbers of cases seen by Dutch clinicians per year may limit their familiarity with the diagnosis of NPC. Specialists in non-endemic regions, like The Netherlands, are not very acquainted with the symptoms of NPC and the number of migrants from the especially from North Africa and South East Asia is not rising that rapidly. Substantial doctor's delay is also manifest among in health care workers in high incidence regions like Indonesia where NPC is one of the most common tumours.[33]

We found the poorest survival among patients with keratinizing SCC (WHO-I), reflected by a higher proportional incidence of locally advanced tumours and loco-regional failure, comparing unfavourably with non-keratinizing tumours.[16,34] As migrants of non-western origin more often carry non-keratinizing tumours, they probably have a better survival from NPC than native Dutch patients.

Our results also emphasize the need for more 'tumour-customized' treatment plans for different WHO types of NPC, in particular WHO-I tumours may require a more aggressive or adjusted treatment.

Limitations

We explored the combined picture of NPC incidence, survival and mortality, but the final effect of declining incidence and increasing survival since 1989 will only fully be reflected in mortality in the next few years, even though NPC fatality is rather high and mortality often occurs within few years after diagnosis. However, NPC continues to be a rare disease and trends subject to random variation, entailing difficult interpretations. Besides, changes in pathological practice in the classification of NPC may have contributed to the observed trends and made it impossible

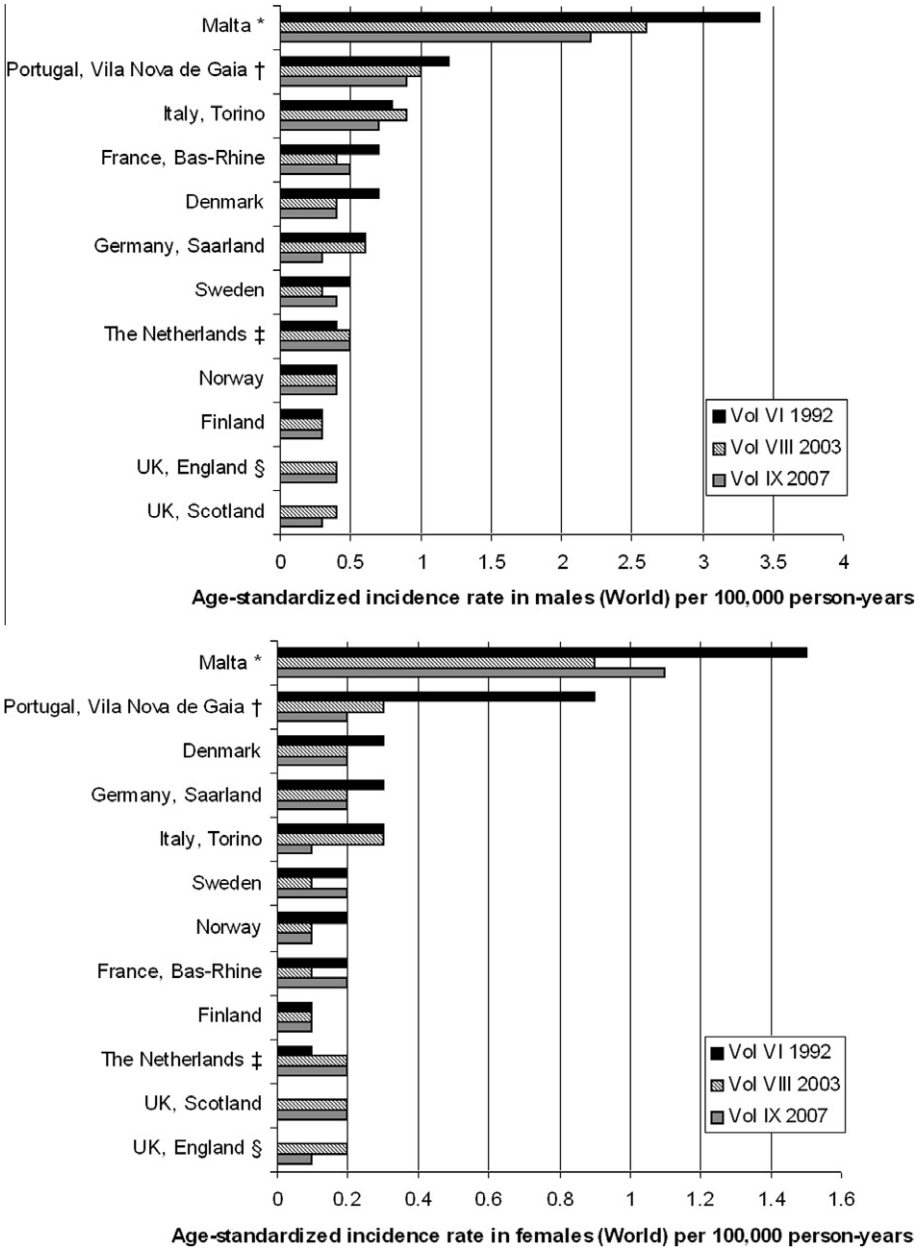

Figure 5 Trends in NPC incidence in males (A) and females (B) in selected European countries according to Cancer Incidence in Five Continents, Volumes VI, VIII and IX (1–2). *For Volume VI, data from Volume III was used as substitute. †For Volume IX, data for Portugal, Porto was used as substitute. ‡For Volume VI, data from The Netherlands, Eindhoven was used as substitute. §For Volume IX, data from the UK, East of England was used as substitute.

to investigate time trends according to stage. Although the correct differentiation of WHO types has advanced in recent years, a small degree of misclassification cannot be ruled out.

Conclusion

Since 1989, the incidence of NPC in The Netherlands decreased, mainly of smoking-related, keratinizing NPC (WHO-I), coinciding with an increase of non-keratinizing NPC (WHO-IIA and B) most likely due to changes in the classification of NPC tumours and immigration of persons from high-incidence countries. The use of EBV-related markers may improve detection of NPC in this group. Mortality clearly decreased over time by the combination of a decrease of the worse prognosis, smoking related WHO-I tumour type and an increase of the better prognostic WHO II type especially in males.

Conflict of interest statement

None declared.

Role of the funding source

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