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ORIGINAL ARTICLE

Incidence and survival of hypopharyngeal cancer: a Danish Nation-Wide Study from 1980 to 2014

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ABSTRACT

Objectives: To evaluate changes in incidence and survival of patients diagnosed with hypopharyngeal cancer (HPC) in Denmark in the period 1980–2014.

Methods: All patients registered with HPC in the Danish Cancer Registry (DCR) in the period 1980–2014 were included. Age-adjusted incidence rates (AAIRs), average annual percentage change in incidence, and overall survival were calculated.

Results: Two thousand and nine patients were included (79.7% men). The overall AAIR increased significantly from 0.3 per 100,000 to 1.1 per 100,000 during the study period, corresponding to an increase of 4.1% per year. The most frequent histology was squamous cell carcinoma (SCC) comprising 90.3%. The overall five-year survival increased with 13.5 percentage points from 13.4% in the period 1980–1985 to 26.9% in the period 2010–2014. Women demonstrated better survival compared to men with a hazard ratio of 0.83, and patients with SCC had better survival compared to the remaining histology groups.

Conclusions: This nation-wide study, covering nearly four decades, showed a significant increase in incidence and survival of HPC in Denmark.

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Introduction

The hypopharynx is a part of the upper aerodigestive tract extending from the pharyngoepiglottic fold inferiorly to the cricoid cartilage [1]. Cancers originating in the hypopharynx comprise less than 5% of all malignant tumors in the head and neck area, and often present at an advanced stage, consequently with a poor prognosis [2,3]. As a consequence of the complex anatomical structures of the hypopharynx, the diagnosis is often delayed and treatment challenging [4]. The lymphatic drainage of the hypopharynx is rich, reflected by 60–80% of hypopharyngeal cancer (HPC) patients, initially present with regional lymph node metastases [5].

Previous studies indicate that 95% of HPCs are squamous cell carcinomas (SCCs) while, e.g., adenocarcinomas and other cancers are rare [6]. The main risk factors for developing HPC are smoking and excessive alcohol intake [7].

The treatment of HPC is complex and requires consideration to several factors including TNM-stage, histology, the patient's comorbidities and performance score. First line of treatment in Denmark is organ preserving radiotherapy (RT) with accelerated and/or hyperfractionated radiation. The goal is 2 Gy fractions, five fractions per week, culminating in a total dose of 66–70 Gy. If tolerated by the patient, Nimorazol, which increases the radiation sensitivity, is recommended alongside the RT. If the patient is in an advanced tumor stage at the time of diagnosis, concomitant chemotherapy (CT) is indicated. Standard concomitant CT consists of cisplatin 40 mg/m^2 once per week. Surgery including transoral robotic surgery (TORS) has in the last couple of years been suggested as treatment for HPC; however, this is not yet standard treatment and is today primarily used as salvage treatment [5,8–10]. Despite the intent to spare surrounding structures, the morbidity following treatments for HPC has to be taken into account and balanced with the prognosis [11,12].

Of all head and neck cancers diagnosed in Denmark, HPCs have the worst 5-year survival, and have been shown to be increasing in incidence [13,14]. The aim of this study was to evaluate incidence and survival trends in a population-based setting, including data on gender, histology and anatomical sublocation in the Danish population from 1980 to 2014.

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Supplemental data for this article can be accessed here.

Material and methods

The data used in this study have been obtained from the Central Population Register (CPR) and from the Danish Cancer Registry (DCR) [15,16]. From 1968 onwards, the CPR registry has provided all Danish residents with an individual identification number (CPR-number), which allows coupling of individual data between registries. Vital status, e.g., date of birth, death, emi- and immigration information, was extracted from the CPR.

In 1987, it became mandatory in Denmark to register all cancer diagnoses to the DCR, but reporting was close to complete from 1980 [16]. In Denmark, cancer patients are only registered and treated at the public hospitals, and therefore no diagnosed cancers are lost to private sectors. Age and date of diagnosis as well as location and histology of the cancer were derived from the DCR.

All patients diagnosed with HPC during the period 1980–2014 were included. Diagnosis codes registered in the DCR during this period changed and were in 2004 converted from the ICD-O (International Classification of Diseases for Oncology) codes to the ICD-10 (10th revision of the International Classification of Diseases) [17]. Based on the ICD-10 codes, six locations were identified, comprising the piriform fossa (ICD-129), the post cricoid region (ICD-130), the aryepiglottic fold (ICD-131), the posterior wall of the hypopharynx (ICD-132), overlapping lesion of the hypopharynx (ICD-138) and hypopharynx unspecified (ICD-139). The codes ICD-130, ICD-131, ICD-132 and ICD-138 were merged with the unspecified hypopharynx group to the category *hypopharynx (general)* due to their relatively rare incidence, resulting in two groups: hypopharynx (general) and piriform fossa. Histological types of HPC were identified via ICD-O-3 based MORPHO3 registrations from the DCR, and the types of histology were categorized into three groups: SCC, adenocarcinoma (salivary gland) and other [17]. Year of diagnosis was categorized in five-year intervals: 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014.

Statistical analysis

Incidence was calculated as age-adjusted incidence rate (AAIR) per 100,000 in R statistics version 3.3.3 [18] using the EpiTools package and WHO standard population as reference [19]. Possible trends in incidence were assessed with the Joinpoint Trend Analysis Software v. 4.2.0.2. The joinpoint regression analysis estimates possible joinpoints, which are significant changes in trends and are also called trend breaks. This is indicated with either a straight line for the whole study period or a segmented line if there are trend breaks during the study period. The joinpoint analysis also identifies increase or decrease in incidence per year in percent for each segment and an average for all segments. We assumed growth to be logarithmic with the formula $\ln(y) = xb$, and allowed up to five joinpoints.

Survival was defined as time from diagnosis to death from any cause and was depicted with five-year survival estimates, Kaplan–Meier plots, and Cox regression. Patients who were alive at the last date of follow-up were censored at this date. The date for the last follow-up was the 31 December 2016. The five-year survival estimate for patients diagnosed in the period 2010–2014 was based on patients diagnosed in 2010 and 2011, since patients diagnosed in the following years were censored at the last date of follow-up. Cox regression was calculated as univariate and multivariate analyses using the survival package. Factors included in the multivariate analysis were as follows: gender, location, histology and year of diagnosis in five-year intervals.

The age-period-cohort (APC) models were estimated with the Epi package using the function 'apc.fit' [20]. This allowed evaluation of the effect of age, calendar period, and birth cohort on incidence. The model gives estimates for age-period effects, age-cohorts effects and age-period-cohort-effect individually. Age and periods were arranged into five-year intervals. For the period effect, the median of the first five-year interval (1981.5) was used as reference, and for the cohort effect we defined the year 1900 as reference. To avoid statistical instability, the analysis was restricted to persons at ages between 30 and 84 years as the number of cases before the age of 30 and after the age of 84 was small. A p value $<.05$ was considered statistically significant.

Results

A total of 2009 patients with HPCs were identified (79.7% men ($n = 1602$)). The overall median age at diagnosis was 62.1 years, for men 61.8 years, and for women 64 years. The most common histology was SCC, comprising 90.3% ($n = 1815$) of all HPCs. The most common registered location was the general hypopharynx group, accounting for 81.3% ($n = 1633$). Cancers originating at the piriform fossa accounted for 18.7% ($n = 376$) (Table 1).

Incidence

The AAIR of HPC increased significantly in the period 1980–2014 from 0.3 per 100,000 in 1980 to 1.1 per 100,000 in 2014, corresponding to a total number of 19 patients in 1980 and 103 patients in 2014 (Figure 1). The annual increase in incidence in the same period was 4.1% (95% CI: 3.6; 4.6). No significant trend breaks were observed. An increase in HPC incidence was observed in both men and women, with an annual increase in incidence of 4.0% (95% CI: 3.5; 4.5) for men and 4.3% (95% CI: 3.0; 5.7) for women (Table 1, Figure 1). Throughout the whole study period, the incidence was higher among men compared to women (Figure 1).

Regarding the anatomical location of HPC, the general hypopharynx group had a significant increase in incidence of 4.7% per year (95% CI: 4.2; 5.3), while cancers in the piriform fossa showed a non-significant increase in incidence at 1.5% per year (95% CI −0.3; 3.3).

When calculating incidence according to histological type, SCC and adenocarcinoma (salivary gland) showed a

Table 1. The average annual percentage change (AAPC) for HPCs in Denmark 1980–2014.

	Cases (%)	AAPC (95% CI)	*p*
Total	2009 (100)	4.1 (3.6; 4.6)	<.05
Male	1602 (79.7)	4.0 (3.5; 4.5)	<.05
Women	407 (20.3)	4.3 (3.0; 5.7)	<.05
Histology			
Squamous cell carcinoma	1815 (90.3)	2.6 (0.1; 5.2)	<.05
Adenocarcinoma (salivary gland)	72 (3.6)	5.4 (1.3; 9.7)	<.05
Other histology[a]	122 (6.1)	4.5 (0.9; 8.2)	<.05
Location			
Piriform fossa	376 (18.7)	1.5 (−0.3; 3.3)	.1
Hypopharynx (general)[b]	1633 (81.3)	4.7 (4.2; 5.3)	<.05

AAPC: average annual percentage change; 95% CI: 95% confidence interval. Significant: $p<.05$.

[a]Comprised of 35 different histology types and includes the following morphology codes: basal cell carcinoma, NOS (1.7%), carcinoma, NOS (1.0%), carcinoma, undifferentiated type, NOS (0.5%), small cell carcinoma, NOS (0.4%), neuroendocrine carcinoma (0.3%), tumor cells, malignant (0.2%), neoplasm, malignant (0.2%), solid carcinoma, NOS (0.1%), non-small cell carcinoma (0.1%), signet ring cell carcinoma (0.1%), carcinosarcoma, NOS (0.1%), large cell carcinoma, NOS (0.05%), giant cell carcinoma (0.05%), spindle cell carcinoma (0.05%), infiltrating basal cell carcinoma, NOS (0.05%), basosquamous carcinoma (0.05%), Schneiderian carcinoma (0.05%), cholangiocarcinoma (0.05%), chromophobe adenoma (0.05%), endometrioid carcinoma (0.05%), serous cystadenoma, borderline malignancy (0.05%), serous surface papillary carcinoma (0.05%), intraductal carcinoma, noninfiltrating, NOS (0.05%), Leydig cell tumor, malignant (0.05%), malignant melanoma, NOS (0.05%), sarcoma, NOS (0.05%), fibrosarcoma, NOS (0.05%), mixed tumor, malignant, NOS (0.05%), serous adenofibroma, borderl. (0.05%), synovial sarcoma, NOS (0.05%), fibrous mesothelioma, malignant (0.05%), epithel. mesothelioma, mal. (0.05%), teratoma, malignant, NOS (0.05%), myxopapillary ependymoma (0.05%) and no morphology (0.05%).

[b]Comprised of post cricoid region (1.6%), Aryepiglottic region (3.2%), posterior wall of hypopharynx (2.1%), overlapping sites of hypopharynx (5.9%) and hypopharynx unspecified (87.2%).

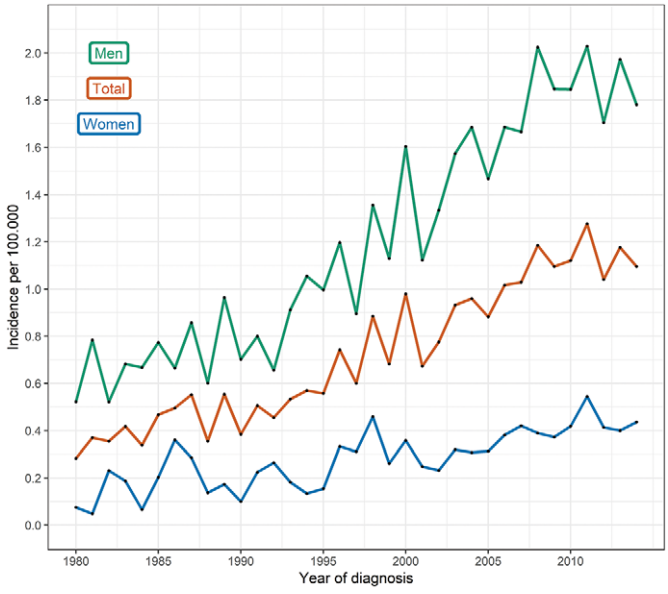

Figure 1. Age-adjusted incidence rates per 100,000 for hypopharyngeal cancer in Denmark in the period 1980–2014.

significant annual increase in incidence of 2.6% (95% CI: 1.9; 5.9) and 5.4% (95% CI: 1.3; 9.7), respectively (Table 1).

To assure that the implementation of the mandatory cancer registration to the DCR did not affect the data, we calculated the annual increase in incidence for the periods 1980–1986 and 1987–2014 specifically. This showed a significant increase in both periods with overlapping confidence intervals (Table S1).

Survival

With a median follow-up of 1.3 years (95% CI: 1.2; 1.4), 1760 patients died during the follow-up period. There was a significant increase in survival during the study period from a 5-year survival of 13.4% (95% CI: 8.6; 20.8) among patients diagnosed in the period 1980–1984 to 26.9% (95% CI: 22.8; 31.6) among patients diagnosed in the period 2010–2014 (Table S2, Figure 2(D)). This corresponds to an increase in survival of 13.5 percentage points with a relative increase of 100.7%. The multivariate Cox-regression analysis also showed an improvement in survival during the study period with a hazard ratio of 0.66 (95% CI: 0.54; 0.82) for the period of 2010–2014 (Table 2).

For men and women, the estimated 5-year survival in percentage showed a significant difference with an estimate of 18.7% (95% CI: 16.8; 20.8) and 27.4% (95% CI: 23.3; 32.2) in men and women, respectively (Table S2, Figure 2(A)). The Cox regression also showed a significantly better survival for female patients with a hazard ratio of 0.82 (95% CI: 0.73; 0.93) (Table 2).

The multivariate Cox-regression analysis showed a better survival for adenocarcinomas and other histologyl types compared with SCC, with hazard ratios of 0.74 (95% CI: 0.57; 0.94) and 0.82 (95%: 0.67; 0.99) (Table 2). Regarding locations, cancers originating in the piriform fossa showed no significant difference in survival compared to the general hypopharynx group (Table 2, Figure 2(B)).

Age-period-cohort model

For the overall APC model, we found an age-cohort deviance of 29.3 ($p < .001$), an age-period deviance of −28.9 ($p < .001$), and an age-period-cohort deviance of 1.4 ($p = .70$), suggesting a significant effect of age on the incidence of HPC, while no significant effect of period or cohort is evident (Figure 3). The same pattern was seen for men, yet for women neither age-cohort deviance, age-period deviance nor age-period-cohort deviance was significant, suggesting no effect of age, period, or cohort (Figure 3).

Discussion

This study investigates incidence and survival of HPC based on gender, histology and location in the Danish population from 1980 to 2014. The study represents the largest Danish registry study on HPC. A total of 2009 cases of HPC were identified and we showed an increase in AAIR from 0.3 per 100,000 in 1980 to 1.1 per 100,000 in 2014, with a corresponding annual increase in incidence of 4.1%.

A similar increase in incidence was also observed in the Netherlands in the period 1989–1997 [21] and in Germany in the period 1996–2005 [22]. Petersen et al. investigated the incidence of HPC in the Netherlands [21] and found a equivalent annual increase in incidence of 4.1% however

Table 2. Univariate and multivariate Cox-regression analyses of survival for patients with hypopharyngeal cancer in Denmark in the period 1980–2014.

			Univariate		Multivariate[a]	
	Cases (%)	Deaths	HR (95% CI)	*p*	HR (95% CI)	*p*
Men	1602 (79.7)	1413	Reference		Reference	
Women	407 (20.3)	347	0.84 (0.74–0.94)	<.01	0.83 (0.73–0.93)	<.01
Histology						
Squamous cell carcinoma	1815 (90.3)	1590	Reference		Reference	
Adenocarcinoma (salivary gland)	72 (3.6)	62	0.74 (0.57–0.94)	.02	0.73 (0.56–0.94)	.02
Other	122 (6.1)	108	0.82 (0.67–0.99)	.04	0.83 (0.68–1.01)	.05
Locations						
Piriform fossa	376 (18.7)	356	Reference		Reference	
Hypopharynx (general)	1633 (81.3)	1404	0.94 (0.84–1.05)	.29	1.02 (0.91–1.15)	.73
Period						
1980–1984	127 (6.3)	127	Reference		Reference	
1985–1989	169 (8.4)	169	1.17 (0.93–1.48)	.18	1.12 (0.89–1.42)	.33
1990–1994	172 (8.6)	169	0.85 (0.67–1.07)	.16	0.81 (0.64–1.02)	.08
1995–1999	252 (12.5)	245	0.86 (0.69–1.06)	.16	0.83 (0.67–1.03)	.09
2000–2004	333 (16.6)	320	0.89 (0.72–1.09)	.26	0.85 (0.69–1.05)	.13
2005–2009	440 (21.9)	372	0.75 (0.61–0.92)	<.01	0.71 (0.58–0.88)	<.01
2010–2014	516 (25.7)	358	0.70 (0.57–0.86)	<.01	0.66 (0.54–0.82)	<.01

HR: hazard ratio; 95% CI: 95% confidence interval.
[a]The multivariate analysis includes all variables listed in this tables.

only applicable until 1997. Hereafter (from 1997 to 2013), the incidence only increased significantly in women. Overall, they found that the incidence increased from 0.81 per 100,000 in 1989 to 0.95 per 100,000 in 2013 [21]. Guntinas-Lichius et al. investigated the incidence in Germany and found a significant increase in HPC throughout the entire study period from 1996 to 2005 accounting for both men and women.

We found an increase in AAIRs for both men and women from 1980 to 2014, with no significant difference in annual increase in incidence between these. In 2014, the incidence in men was, however, significantly higher than the incidence found in women. The known major risk factors for HPC are alcohol consumption and tobacco use. The increased incidence of HPC found in men could be explained by the fact that significantly more men than women consume more than the recommended alcohol amount and until 2010 significantly more men were daily smokers compared to women [23,24].

Interestingly, the percentage of adult smokers in Denmark has been decreasing since 1970 and furthermore the alcohol intake has been decreasing slightly since 1983, which contrasts to our findings of a still increasing incidence of HPC. The direct correlation between the increasing incidence of HPC and the known risk factors is thus difficult to detect. The increase in incidence of HPC is similar to the increased incidence observed for other smoking- and drinking-related head and neck cancers, e.g., oral cavity cancer and oropharyngeal cancer [13]. It has been proposed that the increasing incidence of HPC could be due to HPV [14], a proven risk factor for the development of oropharyngeal cancer [25–27] and a known contributor to the increased incidence of oropharyngeal cancer. HPV has been reported in 3.6–10.9% of cases of SCC in HPCs [28,29]. However, an oncogenic effect of HPV in the hypopharynx has not yet been proven.

The survival rate of HPC was significantly better in the period 2010–2014 compared to 1980–1985. This improvement might be due to improvement in and access to radiation therapy techniques, from two-dimensional treatment planning based on clinical examination alone to modern three-dimensional planning and highly conformal techniques (intensity modulated radiation therapy, volumetric arc therapy, etc.) based on advanced imaging, which were gradually introduced after 2000. Concomitant chemoradiation (CRT) was introduced at the same time and might also have contributed to the improvement in survival, as well as implementation of fast track cancer workup in 2007, resulting in earlier detection and treatment of HPC [5,21,30,31]. The median survival of HPC was 1.0 year after diagnosis, which is far worse than that of other head and neck cancers [13]. This can be explained by the covert anatomical localization causing late diagnosis resulting in debut with an advanced stage. Finally, a rather high incidence of comorbidities including secondary malignancies affecting the survival in HPC is reported [32]. Impaired nutritional status, due to postoperative complications and CRT, might also influence the long-term survival [33]. The poor 5-year survival of HPC in this study is in accordance with other recent reports. Kuo et al. reported an overall 5-year survival of 25.5% in the period 1988–2010 in the US [34], while the 5 year survival was 34% reported by Petersen et al. in the Netherlands in the period 2001–2010 [21].

We evaluated the effect of age, calendar period and birth on incidence and found that there was a significant effect of age on the incidence of HPC for men, thus indicating that increased age resulted in increased risk of HPC in men. This correlates to the fact that cancer of the hypopharynx usually develops over many years and are more common among the elderly [35]. We did interestingly not find an effect of age on incidence in women. This could be due to the fact that only a minor part of the included patients are female, and that no significant correlation could be made due to the small number of cases.

Limitations of our study include the fact that no information on anamnestic or objective measures such as TNM classification, smoking/alcohol status, HPV status and treatment

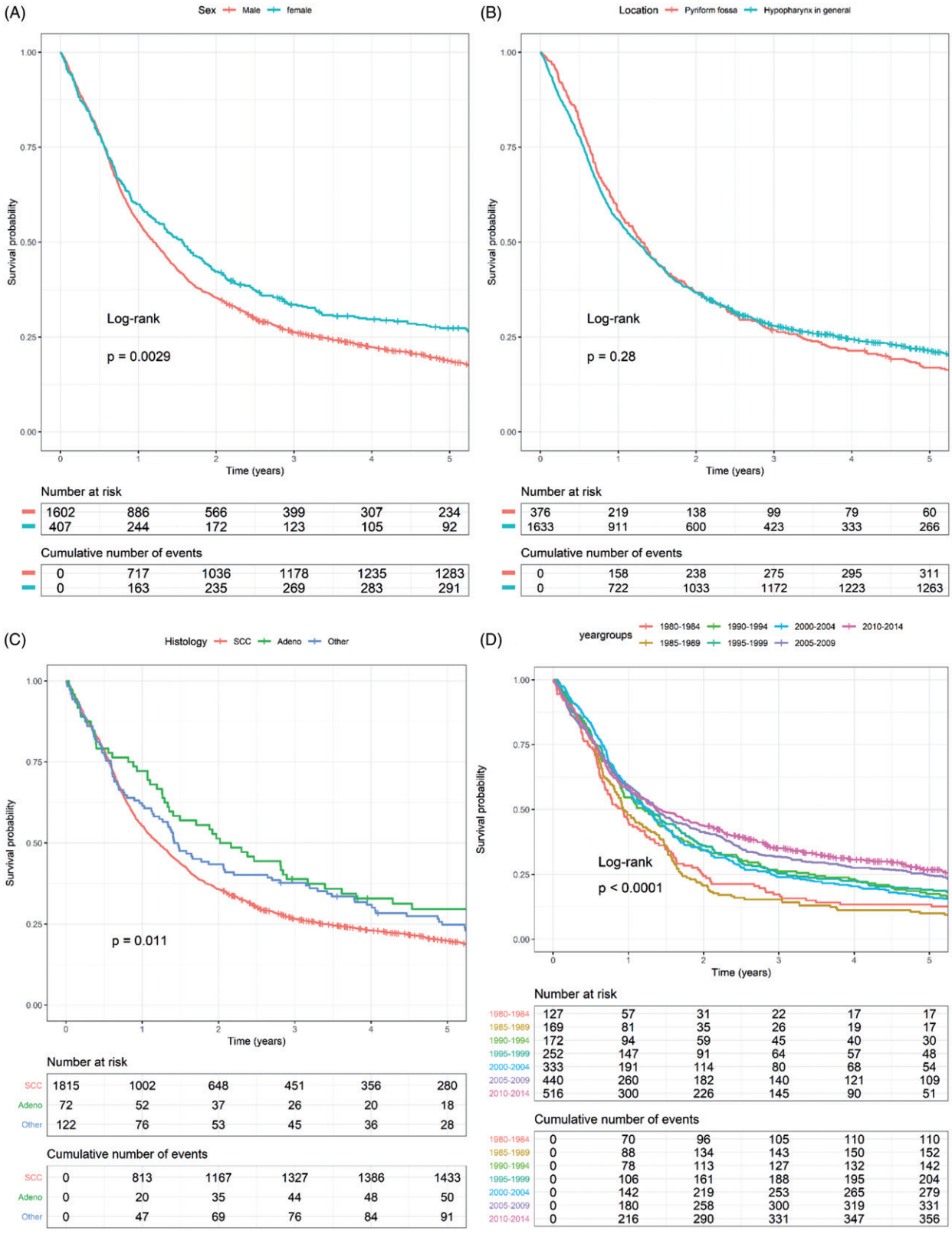

Figure 2. Kaplan–Meier plots depicting overall survival of hypopharyngeal cancer in Denmark stratified by (A) sex, (B) location, (C) histology, and (D) year of diagnosis in five-year intervals. SCC: squamous cell carcinoma; Adeno: adenocarcinoma (salivary gland); other: other histology. Every vertical line on the curves represents a patient being censored at the given point of time.

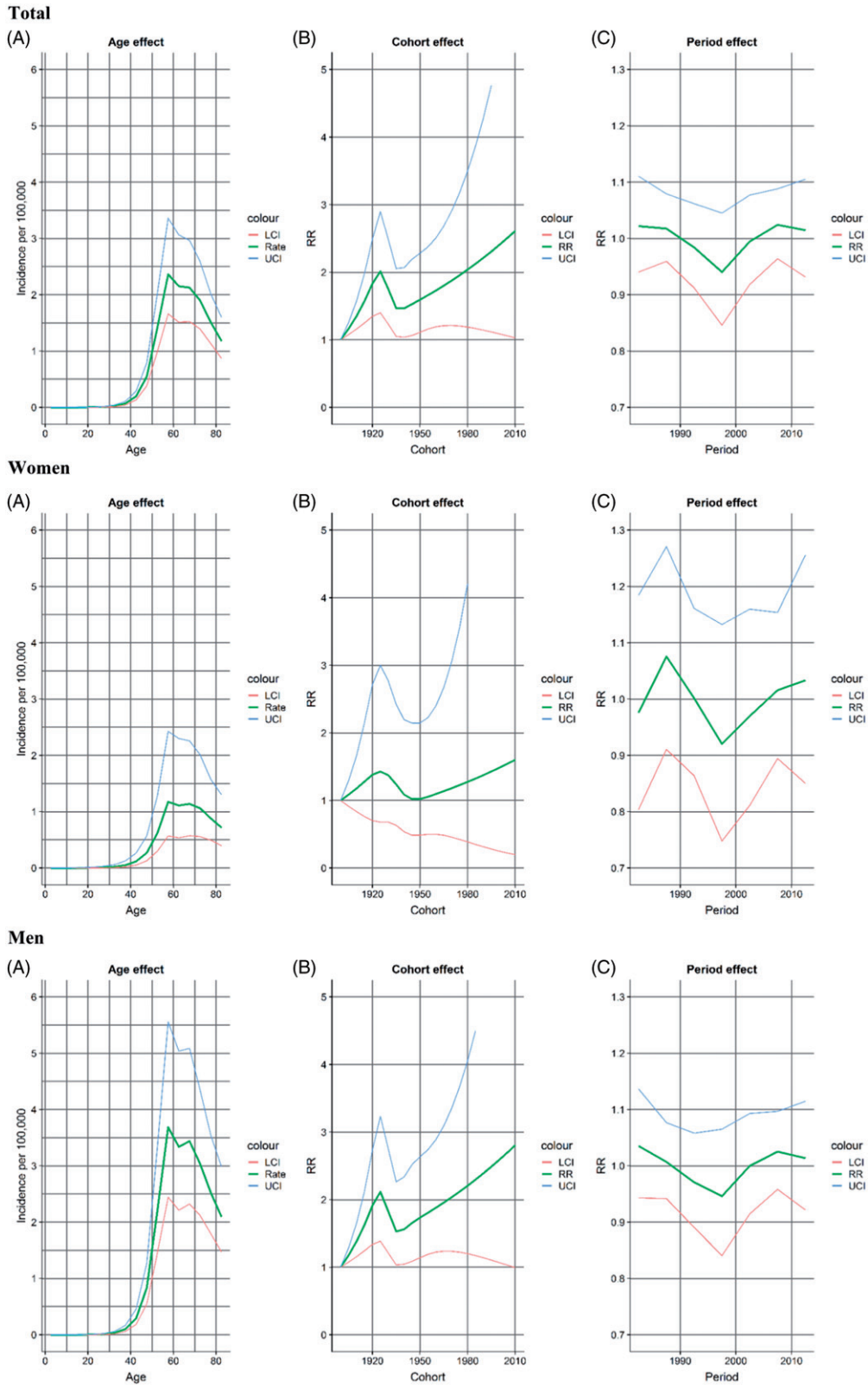

Figure 3. Age-period-cohort model for hypopharyngeal cancer in Denmark in the period 1980–2014. Reference year for cohort effect: 1900, reference year for period effect: 1981.5.

were derived, and as a result a more comprehensive discussion on causality could not be accomplished. Further, there are limited power in the statistical analysis regarding female patients due to few cases.

In conclusion, our study provides a complete presentation of incidence and survival of HPC in Denmark from the period 1980–2014. Hypopharyngeal cancer remains a rare head and neck cancer with a particularly poor prognosis. We report

not only a significant increase in incidence but also results indicating an increase in survival of HPC. Future research is encouraged.

Disclosure statement

No potential conflict of interest was reported by the authors.

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