Incidence and Survival of Head & Neck Cancers in Estonia, 1996–2016

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Abstract

Background and Material

Changing patterns of alcohol and tobacco consumption and human papillomavirus (HPV) infection have affected the epidemiology of head & neck cancers. The aim of the study was to examine 20-year trends in the incidence and survival of head & neck cancers in Estonia by site, sex, morphology and stage.

Methods

Data on all adult cases of invasive head & neck cancers diagnosed in Estonia in 1996–2016 were obtained from the population-based cancer registry. TNM stage was available for 2010–2016. Incidence trends were modelled with *joinpoint* regression and five-year relative survival ratios (RSR) were calculated.

Results

A total of 6769 cases were included, 64% among men. We observed significant decline in the incidence of lip and laryngeal cancer and significant increase in the incidence of hypopharyngeal and oropharyngeal cancers. Over 60% of mouth & pharyngeal cancers were diagnosed at stage IV.

Age-standardized five-year RSR for mouth & pharyngeal cancer increased significantly over the study period, from 21% in 1996–2002 to 33% in 2010–2016. The largest survival increases were seen for cancers of oral cavity (44% in 2010–2016), tongue (41%) and larynx (63%), while modest changes were seen for oropharynx (24%) and hypopharynx (17%). The latest five-year RSR was 90% for thyroid cancers (99% for papillary carcinoma). Large female survival advantage was seen for most sites.

Conclusions

The observed trends suggest an emerging role of HPV infection in combination with traditional risk factors in the development of head & neck cancers in Estonia. Efforts targeting health behavior, HPV vaccination and earlier diagnosis are crucial for reducing mortality from these cancers.

Background

Head & neck cancers (including cancers of lip, mouth & pharynx, salivary glands, nasal cavity and sinuses, larynx, and thyroid) comprise around 8% of all incident cancers diagnosed in the world each year [1]. The etiology of these cancers varies and globally, the incidence and mortality trends of head & neck cancers observed recently are rather diverse, due to differences in the prevalence of risk factors and diagnostic activities. Decreasing use of tobacco has brought along declining trends of oral and laryngeal cancer, whereas growing burden of HPV infection has caused increasing rates of oropharyngeal cancers [2, 3]. Furthermore, there have been reports of rising incidence of late-stage oral and pharyngeal cancers [4]. Thyroid cancer trends are deeply affected by wide-spread diagnostic activities and the detection of indolent tumors in many highly developed countries [5–7].

According to GLOBOCAN 2018 [1], the incidence of head & neck cancers in Estonia is not high, lower than the very high rates of several Eastern European countries. However, the survival of these tumors has been among the lowest in Europe both in EUROCARE-3 [8] and in EUROCARE-5 [9], particularly in men.

A detailed examination of incidence and survival of head & neck cancers in Estonia was thus warranted, in view of the decreasing burden of smoking-related cancers in Estonia [10] but the very high incidence of cervical cancer [11], which suggests high prevalence of HPV infection in the population. Also, previous studies have shown a large effect of diagnostic activities on cancer incidence during the transition of the health-care system and increasing availability of modern diagnostic methods [12, 13].

The aim of the study was to examine 20-year trends in the incidence and survival of head & neck cancers in Estonia by site; separate analyses were done by sex, morphology and stage.

Methods

The Estonian Cancer Registry provided data on all adult (age ≥ 15 years) cases of invasive head & neck cancers diagnosed in Estonia in 1996–2016, regardless of cancer sequence. The sites were categorized based on the ICD-O-3 topography codes: lip (ICD-O-3 code C00); tongue (C02, excl. C02.4); oral cavity (C03–06, excl. C05.1–2); salivary glands (C07–08); oropharynx (C01, C02.4, C05.1–2, C09–10); nasopharynx (C11); hypopharynx (C12–13); nasal cavity and sinuses (C31–32); larynx (C32); thyroid (C73); other (C14). Site group “mouth & pharynx” included tongue, oral cavity, oropharynx, nasopharynx, hypopharynx, other.

Percentage of microscopic verification, percentage of death certificate only cases and percentage of cases diagnosed at autopsy were used as data quality indicators.

The study period was divided into three seven-year periods: 1996–2002, 2003–2009, 2010–2016. For mouth & pharyngeal cancers and laryngeal cancers, morphology was divided into squamous cell carcinoma (ICD-O-3 morphology codes 8070–8076); other and not otherwise specified (NOS). For thyroid cancer, morphology was divided into papillary (8050, 8260, 8340–8344, 8350, 8350, 8450, 8452, 8453, 8460); follicular (8290, 8330–8333, 8335); medullary (8345, 8510, 8512, 8513); anaplastic (8020–8022, 8030–8035); other and NOS. Stage was available for cases diagnosed in 2010–2016; stage was grouped according to UICC version 7 of the TNM Classification.

Death certificate only and autopsy cases were excluded from survival analyses. Patients who were diagnosed and died on the same day were included with one day of survival time. Relative survival ratio (RSR) with 95% confidence interval (CI) was calculated by dividing the observed survival in the study cohort by the expected survival, derived from age-, sex- and calendar-period-specific life tables of the Estonian general population, using the Ederer II method [14]. Cohort method was used to calculate RSRs for cases diagnosed in 1996–2002 and 2003–2009, and period method for 2010–2016. For stage-specific survival analysis for 2010–2016, complete method was used. International standards were used for age-standardization of RSRs [15].

Two-sided p-values were used to compare proportions. Survival analyses were done with *strs* algorithm in STATA 14 [16].

Joinpoint analysis with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/) was used to model the rates and calculate the estimated annual percent change (APC) with 95% CI. Permutation test was used to assess the statistical significance of the APCs, where APC is significantly different from zero at alpha = 0.05.

The study protocol was approved by the Tallinn Medical Research Ethics Committee.

Results

Overall, 6769 cases of head & neck cancers were diagnosed in Estonia in 1996–2016. The most common site was thyroid, followed by larynx and oropharynx (Table 1). In general, %MV was high and %DCO and %Autopsy were low. The proportion of women was 36% among all incident cases, while it ranged from 4% for hypopharynx to 82% for thyroid. In site group mouth & pharynx, women comprised 21% of the cases. Median age of all patients was 62 years; it was the lowest for thyroid and nasopharynx (59 years) and the highest for lip cancer (73 years). The age distribution shifted significantly towards older age groups as the proportion of cases age 70 years and over increased from 23–31% from 1996–2002 to 2010–2016 ($p < 0.001$).

Incidence

A significant decline was seen in the incidence of lip and laryngeal cancer (Fig. 1). Starting from early 2000s, a significant increase was seen for oropharyngeal and hypopharyngeal cancer. For tongue cancer, an increase started in 2010. A slight but nonsignificant increase was seen for thyroid cancer. The incidence of papillary thyroid cancers increased significantly at a rate of 4.9% (95% CI 2.5; 7.4) per year until 2007 and levelled off thereafter. The incidence of follicular thyroid cancer decreased significantly throughout the study period (APC − 5.3, 95% CI -8.4;-2.0).

The incidence increases of oropharyngeal and hypopharyngeal cancer were significant only for ages 60 years and over, while the modest increases seen for younger people were not significant. Similar findings were observed for thyroid cancer.

Within the group of mouth & pharyngeal cancers, the proportion of oropharyngeal and hypopharyngeal cancers increased significantly over the study period, in parallel with the significant drop in the proportion of oral cavity cancers (Supplementary Table 1).

The majority of cases among mouth & pharyngeal cancers were histologically squamous cell carcinomas and this proportion did not change over the study period (Supplementary Table 2). The proportion of squamous cell carcinomas among laryngeal cancers increased significantly on the account of other and

NOS tumors. For thyroid, there was a significant increase in the proportion of papillary cancers, while the proportion of follicular tumors and medullary tumors decreased.

Stage was available for cases diagnosed from 2010. For mouth & pharyngeal cancers, the majority of cases (62%) were diagnosed at stage IV (Fig. 2). For hypopharynx, the proportion of stage IV tumors was close to 80%. Thyroid and laryngeal cancer had the lowest proportion of stage IV cancers. Over 40% of thyroid cancer cases were diagnosed at stage I.

Survival

Overall, the age-standardized five-year RSR for mouth & pharyngeal cancer increased significantly over the study period, from 21% to 33% (Table 2). An even larger increase (from 20–35%) was seen for squamous cell carcinomas of the same site group. By site, the largest survival increases were seen for oral cavity, tongue and laryngeal cancers, while modest changes were seen for oropharyngeal and hypopharyngeal cancers. The RSR for thyroid cancer increased by 7 percentage units. The highest survival was seen for papillary thyroid cancers, approaching 100% in 2010–2016.

The difference between female and male RSRs in 2010–2016 was 35 percentage units for salivary gland cancers and 20 percentage units for mouth & pharyngeal cancers, while there was no difference for laryngeal cancer (Table 3).

Stage-specific survival rates for selected cancers in 2010–2016 are shown in Supplementary Table 3. For mouth & pharyngeal and laryngeal cancers, the five-year RSR was around 80% for stage I while it remained around 30% for stage IV. The RSR was close to 100% in stages I–III for both papillary and follicular thyroid cancers, while survival differed between histological types in stage IV.

Discussion

In this population-based study of 20-year trends in the incidence and survival of head & neck cancer patients in Estonia, we found that the incidence has significantly increased for hypopharyngeal and oropharyngeal cancers and decreased for lip and laryngeal cancer. More than 60% of head & neck cancers in Estonia are diagnosed at stage IV, except for thyroid, salivary and laryngeal cancers. Survival increased for most sites, but the prognosis remained poor for mouth & pharyngeal cancers with a large disadvantage of male patients. The increase in thyroid cancers was driven by papillary cancers that demonstrated excellent survival.

Incidence

The slightly declining trend in oral cavity cancer rate, together with the steep decrease in lip and laryngeal cancer incidence is in concordance with previously observed decreasing rates of lung cancer in Estonia [10]. Smoking is one of the strongest risk factors for most head & neck cancers. Daily smoking prevalence among working-age men in Estonia has dropped from 45% in 1996 to 23% in 2018; the respective change among women was from 21–13%; however, the change in women has been too recent

to influence cancer occurrence [17]. There have been no particular changes in alcohol consumption as the proportion of men and women who consumed alcohol at least a few times a week fluctuated from 20% in 1996 to 27% in 2008 and to 24% in 2018 [17]. As only 4–6% of oral cancers are known to be HPV-positive, papillomavirus is not expected to play important role in oral cavity cancer pathogenesis [18]. Inconsistent patterns in the incidence of oral cavity cancers has been observed worldwide with trends in some countries contrasting those of lung cancer, suggesting the role of other factors or their interaction [3]. The recent significant increase of tongue cancer incidence in Estonia since 2010 needs further monitoring to confirm. Laryngeal cancer, also mainly caused by smoking and alcohol consumption [19], demonstrated a significant decline, which correlates with prior research from other European countries [20–22].

The oropharyngeal cancer trend has turned into a steep rise since 2004, which is consistent with similar trends in Europe, US and South-East Asia [2, 3, 20]. These trends have been driven by increasing incidence of HPV-positive cancers, and the role of HPV infection has been confirmed by the increase in the proportion of HPV-positive tumors, shown to reach 70% in the US and Sweden [23, 24]. In the US, the rise in HPV-positive tumors was accompanied by a decrease in HPV-negative tumors [23]. HPV-infections play higher role in economically more-developed countries, whilst in economically less-developed countries, the disease is still mainly caused by tobacco [25–27]. Worldwide, approximately 30% of oropharyngeal cancers are due to HPV infection [28]. Testing for p16 in Estonia started only from 2014 and the expression of p16 in formalin fixed paraffin embedded (FFPE) tissue blocks has been consistently evaluated starting from 2018. Based on unpublished data from the cancer center where most of Estonian head & neck cancer patients are managed, 45% of oropharyngeal cancer cases in 2018–2019 were p16-positive. The trends observed in this study regarding HPV-related cancer sites, together with the continuously increasing risk of cervical cancer in successive birth cohorts [11] and rising incidence of anal cancer among younger women in Estonia [29] suggest an important role of HPV infection. Recent studies have also shown an increase in the prevalence of genital warts in Estonia [30]. HPV vaccination, expected to have a protective role against HPV-associated cancers, is available for girls in the national immunization program in Estonia only since 2018. The vaccination coverage reached 61% for the first birth cohort in 2019. Even so, vaccination is unlikely to play a role in incidence rates anytime soon, and unfortunately, boys are not covered by HPV vaccinations in Estonia.

The incidence for hypopharyngeal cancers has shown a significant increase since 2002. Similar trends have been observed in other European countries [2, 20, 21], regardless of decreases in alcohol consumption, the main known risk factor for hypopharyngeal cancer. Alcohol consumption is also not a likely explanation for our findings as the trend resembled that of oropharyngeal cancer rather than that of oral cavity cancer, and therefore partial role of HPV can be suggested. The predominance of men was particularly evident for hypopharyngeal cancer as only 4% of the cases were seen in women, while a fifth of all mouth & pharyngeal cancers were diagnosed in women. The overall proportion of women was similar to that seen in other countries [31]. The excess of men is probably explained by differences in health behavior.

Thyroid cancer was the most common head & neck tumor in females, who constituted 82% of the cases. Recent studies from Europe, USA, Canada, and Australia have reported a steady increase in thyroid cancer incidence over time with a particular increase in papillary thyroid cancer [7, 32]. These trends may be explained by increases in diagnostic activity and changed histological criteria [33] or linked to changes in risk factors such as iodine supplementation, radiation exposure, Hashimoto thyroiditis, and hormonal or reproductive factors [34–36]. In addition, a link between obesity and thyroid malignancies has been demonstrated [37]. The latter explanations are supported by reports of increasing incidence of advanced-stage thyroid cancers [5]. At the same time, other countries have not reproduced these findings [38]. A recent report suggested a substantial contribution of overdiagnosis to the rising incidence in high-income, but also in less affluent countries [39]. The rise in thyroid cancer incidence in Estonia was significant only in women age 60 years and over (data not shown). A larger increase may have occurred before the start of our study as the availability of new diagnostic procedures increased rapidly in the beginning of the 1990s. According to Cancer in Five Continents, the ASR for women increased from 2.8 to 5.5 from 1983–1987 to 1998–2002 and from 0.6 to 1.2 in men [40] and stabilized thereafter. Trends in thyroid cancer warrant further monitoring, particularly among younger age groups, as there have been reports of increasing incidence of papillary tumors among young adults [41].

Survival

The survival of mouth & pharyngeal cancer has increased in Estonia, but a large deficit compared to other European countries persists. For these sites, the RS estimates for Estonia in 2010–2016 have not yet reached those observed in Europe in 2000–2007 [9]. The largest survival increase was seen for oral cavity cancers, but the latest estimates for both men and women still remain well below those observed for the Nordic countries [42]. Relative survival of oropharyngeal cancers was 58% in Denmark in 2010–2014 [21] and only 24% in our study. Stage at presentation is the most important prognostic factor for squamous cell head & neck cancers [43] and patients with advanced tumors show the shortest survival [44]. The majority (62%) of mouth & pharyngeal cancers in Estonia in 2010–2016 presented in stage IV. Roughly, only ¼ of the patients in Estonia presented with an early disease, which is similar to United States, where approximately 29% of head & neck tumors were diagnosed as localized [45]. We observed a huge gender gap in survival for all mouth & pharyngeal cancers, but particularly for oropharyngeal and salivary gland cancers. Significantly later stage at diagnosis for mouth & pharyngeal cancers among men compared to women (proportion of stage IV tumors 65% in men and 52% in women, $p < 0.001$, data not shown) is one potential explanation. Male sex has been found to be a predictor of late-stage head & neck cancer, together with increased age, black race, absence of health insurance and tumor site [4]. A significant female survival advantage was found in Estonia for five of the nine studied common solid tumors, including mouth & pharyngeal tumors, even after adjusting for age, stage and subsite, suggesting the role of less co-morbidities, higher treatment compliance and better health behavior among women [46]. Smoking status has an impact on survival even in long-term [47, 48], and differences in smoking prevalence and intensity (both before and after diagnosis) might partially explain sex differences. Recent studies elsewhere have shown a change in the profile of oropharyngeal cancer patients towards non-smokers, younger age at diagnosis with better performance status, less co-morbidities and HPV-positivity

[49–51]. HPV-positive patients have displayed better overall survival and progression-free survival in comparison to HPV-negative cancer patients indicating separate risk factors, treatment response and prognosis for the disease [48, 50]. The persistently low survival observed in our study, however, suggests the predominance of tobacco- and alcohol-related cancers in Estonia.

Patients with head & neck cancer are known to have a higher comorbidity burden in comparison to general population [52], which may influence the choice of treatment modality and has a significant negative impact on their survival outcome [53, 54]. Estonian cancer patients have been shown to have more comorbidities than their European counterparts [55] and this may be particularly true for patients with health behavior-related cancers. Moreover, we also observed a large age difference in mouth & pharyngeal cancer survival, over 20 percentage points in favor of the youngest age group (49% for age < 50, 27% for age ≥ 70 years, data not shown).

Treatment possibilities in terms of timely access to radiotherapy, use of concomitant chemoradiation, adequate palliative care, social support and rehabilitation, utilization of PET-scan for better diagnostics, and centralization of head and neck cancer patients into specialized units are key clinical factors for ensuring the best possible outcomes. Head & neck cancers are mainly treated at one comprehensive cancer center in Estonia. However, the availability of radiotherapy has been severely hindered due to low number of radiotherapy treatment machines up until 2012 [56]. This deficit has caused prolonged waiting times, which have been shown to cause progress of head & neck cancers to next stage [57]. In 2012, less than 60% of patients in Estonia who would have required at least one radiotherapy course were actually treated [58]. The total number of linear accelerators per million inhabitants increased to 4.6 only in 2016, and this recent improvement had no effect on our results.

In EUROCARE-5, the survival deficit of Estonian laryngeal cancer patients compared to those in Central or Northern Europe exceeded 10 percent units [9]. There has been a steady increase and the most recent survival estimates in this study for both men and women are close to those observed in Finland for 2012–2016 [42]. In contrast to Estonia and Finland, men have higher survival for laryngeal cancer than women in other Nordic countries [42].

Thyroid cancer survival in Estonia is good and higher than in Denmark in 2010–2014, where the five-year RS estimates were 82% in women and 74% in men, and 91% for papillary and 80% for follicular cancer [6]. Our results for both sexes are well comparable with NORDCAN estimates for all Nordic countries [42]. Nevertheless, the gender survival gap of 12 percentage units was larger in Estonia than in the Nordic countries. One possible explanation for women's survival advantage is that they have higher proportion of papillary tumors than men (67% vs 55%, data not shown), and women have their tumors diagnosed at a significantly earlier stage (stage I proportion 44% for women, 26% for men, data not shown). Also, overdiagnosis may be more common among women, inflating survival estimates [39].

The main strength of our study was the use of high-quality population-based cancer registry data over a 20-year period. Another strength was the availability of relatively complete TNM-stage information for recent years, as the proportion of unknown stage did not exceed 11% for any site.

The main limitations of the current study were the lack of individual data on major behavioral, socioeconomic and other risk factors, most importantly HPV-status, smoking and alcohol consumption habits, and comorbidities, as well as data on diagnostic and treatment delays and treatment compliance. Small numbers prevented more specific analysis of incidence and survival trends (e.g. by site/morphology and age).

Conclusions

Discordant trends were observed in the incidence of head & neck cancers in Estonia, with declines seen for oral and laryngeal cancers, but recent sharp increases for sites with persistently dismal prognosis, such as oropharyngeal and hypopharyngeal cancers. Primary prevention targeting health behavior but also HPV vaccination have a central role in reducing mortality from these cancers. A shift in the diagnosis towards earlier stage is crucial for improving the survival and the quality of life of head & neck cancer patients. Increasing awareness of these cancers and educating the public, as well as physicians, are critical in achieving this goal. Further analyses should focus on ascertaining the effect of HPV-infection on the incidence and survival trends, examining the availability of optimal treatment for all patient groups and identifying factors that affect treatment choice and survival outcome.

Declarations

Ethics approval and consent to participate:

Ethical approval for the research has been confirmed.

Availability of data and materials:

All data generated or analysed during this study are included in this published article and its supplementary files.

Authors' contributions:

Study concepts: K.I, M.K

Study design: K.I; A.B

Data acquisition: K.I; A.B

Quality control of data and algorithms: K.I; A.B

Data analysis and interpretation: K.I; A.B ; M.K, S. K

Statistical analysis: K.I; A.B

Manuscript preparation: S.K

Manuscript editing: K.I, M.K; S. K

Manuscript review: K.I; A.B, M.K, S.K

All authors read and approved the final manuscript

Competing interests:

The authors declare that they have no competing interests

Consent for publication:

Not applicable

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Tables

Table 1
Incident cases of head & neck cancers in Estonia, 1996–2016

Site	ICD-10	No	%	%MV	%DCO	%Autopsy	Median age	%Female
Total		6769	100	96	0.6	0.8	62	36
Lip	C00	355	5	94	0.6	0.3	73	36
Tongue	C02 (excl. C02.4)	567	8	96	0.7	0.2	62	29
Oral cavity	C03–06 (excl. C05.1–2)	673	10	97	0.3	0.2	62	30
Salivary glands	C07–08	345	5	97	0.6	0.3	65	53
Oropharynx	C01, C02.4, C05.1–2, C09–10	861	13	96	0.6	0.5	60	17
Nasopharynx	C11	111	2	92	0.9	0.0	59	37
Hypopharynx	C12–13	446	7	95	0.5	0.5	61	4
Nasal cavity and sinuses	C30–31	254	4	95	2.0	0.0	65	36
Larynx	C32	1497	22	95	0.4	1.1	63	8
Thyroid	C73	1616	24	97	0.6	1.7	59	82
Other	C14	44	1	80	6.8	4.6	61	20

Table 2
Age-standardized five-year relative survival ratio (RSR) of head & neck cancers by site and histology in Estonia, 1996–2016

	RSR (95% CI)			
Site	1996–2002	2003–2009	2010–2016	Change [a]
Mouth & pharynx	21 (16–25)	28 (23–32)	33 (29–38)	**12**
Squamous cell carcinoma	20 (16–25)	27 (22–31)	35 (30–40)	**15**
Tongue	22 (14–32)	28 (20–35)	41 (32–50)	19
Squamous cell carcinoma	24 (15–34)	29 (21–37)	41 (32–51)	17
Oral cavity	23 (16–30)	38 (30–46)	44 (34–53)	**21**
Squamous cell carcinoma	20 (14–27)	36 (27–45)	50 (38–62)	**30**
Oropharynx	20 (11–30)	19 (13–29)	24 (19–29)	4
Squamous cell carcinoma	23 (10–38)	18 (12–25)	26 (20–31)	3
Hypopharynx	12 (6–19)	15 (8–25)	17 (9–28)	5
Squamous cell carcinoma	12 (6–21)	19 (10–30)	18 (9–28)	6
Larynx	51 (43–59)	57 (50–64)	63 (56–69)	12
Squamous cell carcinoma	58 (47–68)	60 (53–67)	67 (60–74)	9
Salivary glands	-	42 (20–63)	52 (41–62)	10
Thyroid	83 (79–87)	86 (82–89)	90 (87–92)	7
Papillary	97 (72–100)	97 (90–99)	99 (86–100)	2
Follicular	93 (80–98)	89 (74–95)	90 (78–95)	-3
Medullary	-	85 (62–95)	88 (73–95)	3

[a] Comparing first and last period; statistically significant findings in bold

Table 3
Age-standardized five-year relative survival ratio (RSR) of head & neck cancers by sex and histology in Estonia, 2010–2016

Site	Men	Women	Difference (female-male) [a]
Mouth & pharynx	28 (24–33)	49 (40–57)	**21**
Squamous cell carcinoma	30 (24–35)	50 (40–59)	**20**
Tongue	37 (26–47)	49 (32–64)	12
Squamous cell carcinoma	36 (25–47)	50 (33–65)	14
Oral cavity	39 (25–53)	54 (39–67)	15
Squamous cell carcinoma	47 (26–65)	58 (40–73)	11
Oropharynx	25 (19–31) [b]	45 (30–59) [b]	20
Squamous cell carcinoma	28 (22–35) [b]	48 (32–63) [b]	20
Larynx	62 (55–69)	65 (44–79)	3
Squamous cell carcinoma	67 (59–74)	69 (45–84)	2
Salivary	35 (20–50)	70 (55–81)	**35**
Thyroid	80 (68–88)	92 (89–95)	**12**

[a] Statistically significant findings in bold

[b] Not age-standardized due to small numbers

Figures

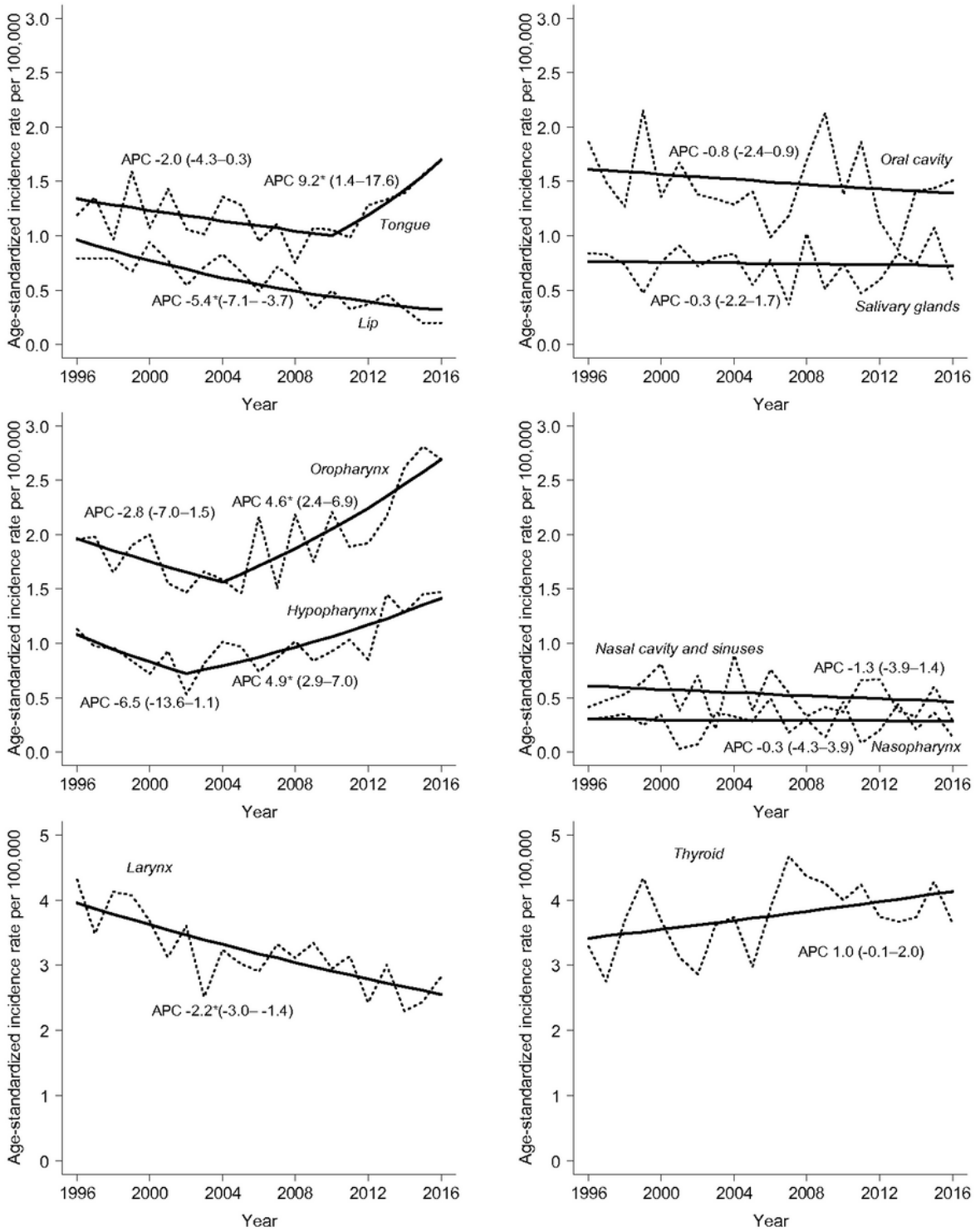
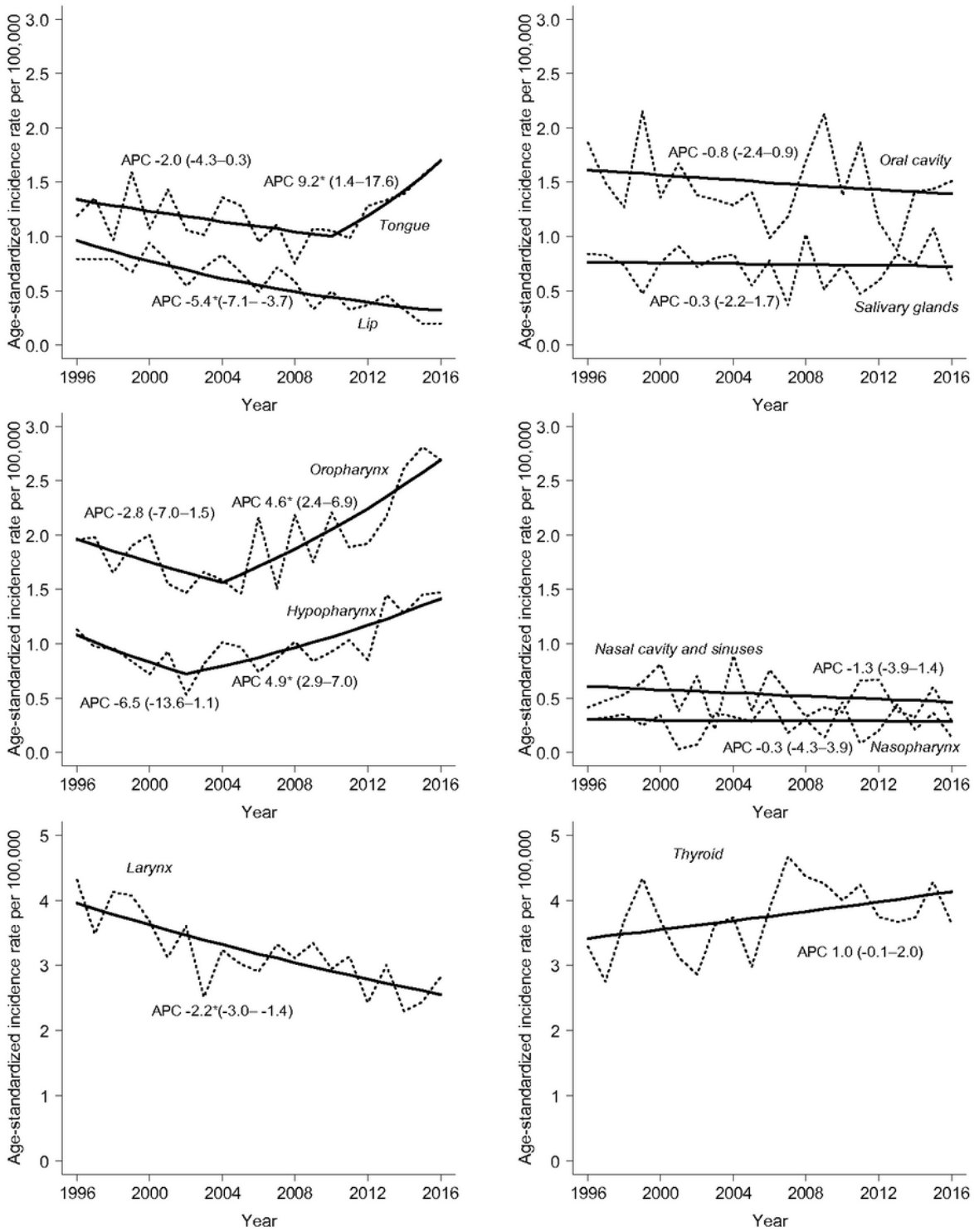


Figure 1

Observed (dashed line) and modelled (solid line) age-standardised (world) incidence rates and annual percentage change (APC) with 95% confidence intervals for trends in head & neck cancer incidence in Estonia, 1996–2016. *The APC is significantly different from zero at alpha=0.05.



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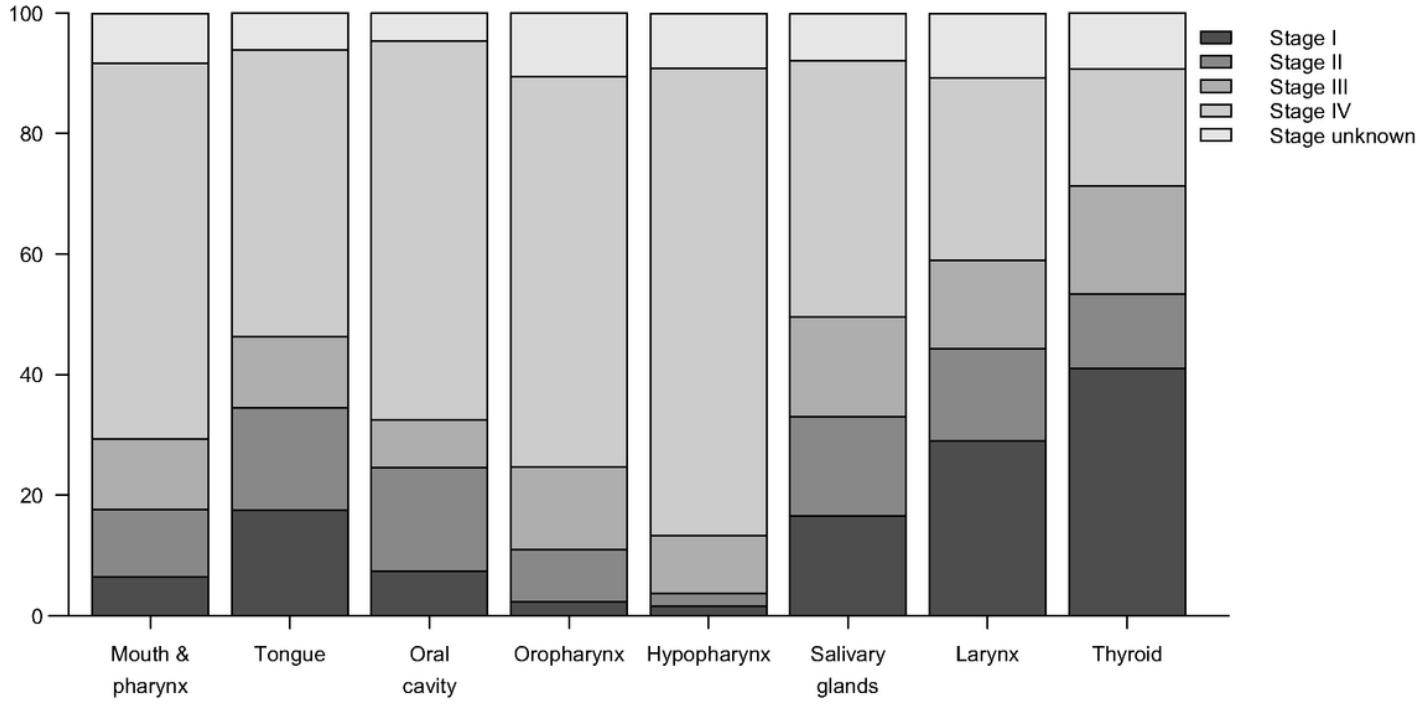

Figure 2

Stage distribution (%) of head & neck cancers in Estonia, 2010–2016.

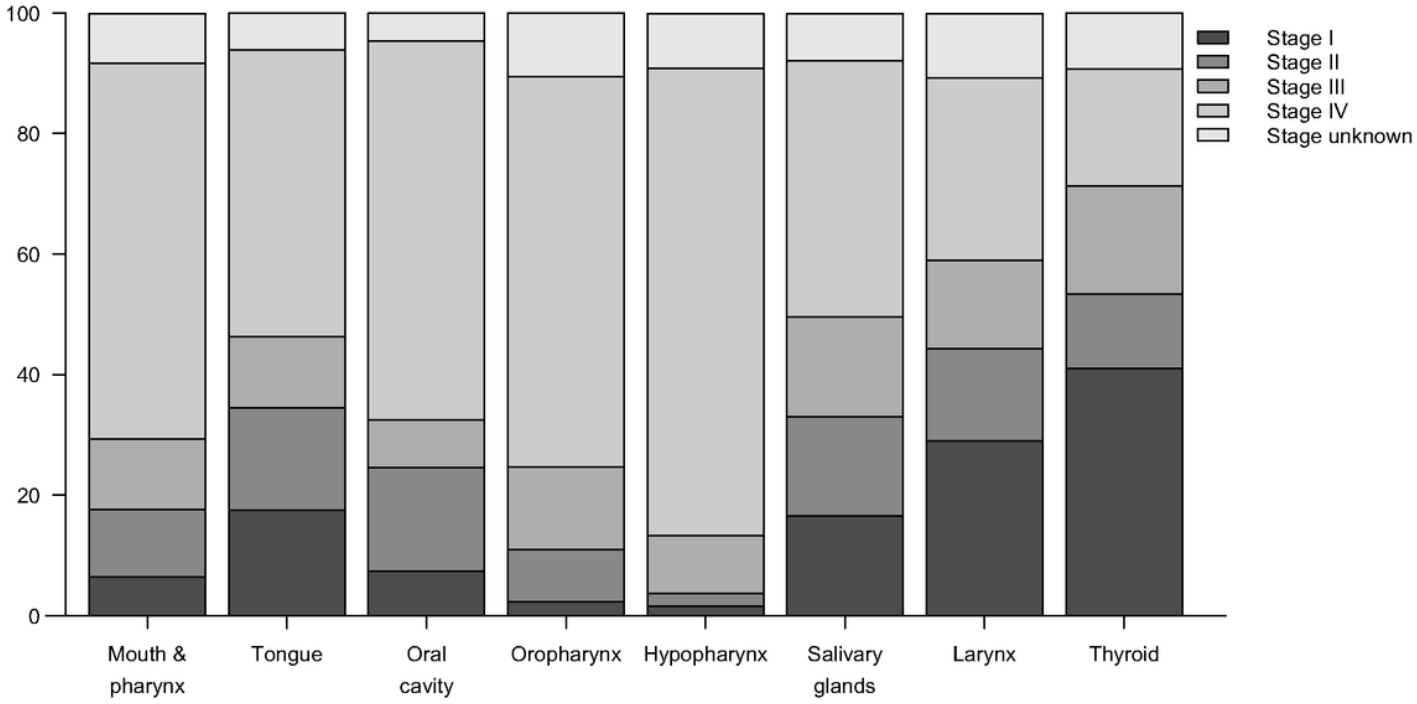

Figure 2

Stage distribution (%) of head & neck cancers in Estonia, 2010–2016.

Supplementary Files

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