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Incidence and Survival for Head and Neck Cancers in Estonia, 1996–2016: A Population-Based Study

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

Methods: Data on all adult cases of invasive head and neck cancers diagnosed in Estonia in 1996–2016 were obtained from a population-based cancer registry. TNM stage was available for 2010–2016. Incidence trends were modeled with join-point regression, and five-year relative survival ratios (RSRs) were calculated.

Results: A total of 6,769 cases were included, 64% men. We observed declining incidence of lip and laryngeal cancer and substantial increases in the incidence of hypopharyngeal and oropharyngeal cancers. Over 60% of mouth and pharyngeal cancers were diagnosed at stage IV. Age-standardized 5-year RSR for mouth and pharyngeal cancer increased substantially over the study period, from 21% (95% CI 16%–25%) in 1996–2002 to 33% (29%–38%) in 2010–2016. The largest survival increases were seen for cancers of the oral cavity (reaching 44% in 2010–2016), tongue (41%), and larynx (63%), while modest changes were seen for the oropharynx (24%) and hypopharynx (17%). The latest 5-year RSR was 90% for thyroid cancers (99% for papillary carcinoma). Large female survival advantage was seen for most sites.

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

Keywords: head and neck cancer, oral cancer, pharyngeal cancer, laryngeal cancer, relative survival, stage

Background

Head and neck cancers (including cancers of the lip, mouth and 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 and 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 a 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 widespread diagnostic activity and detection of indolent tumors in many highly developed countries.[5–7]

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

A detailed examination of incidence and survival of head and 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 human papillomavirus (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 and neck cancers in Estonia by site. Separate analyses were done by sex, morphology, and stage.

Methods

The Estonian Cancer Registry (ECR) provided data on all adult (age ≥15 years) cases of invasive head and neck cancers diagnosed in Estonia in 1996–2016, regardless of cancer sequence. Reporting to the ECR is mandatory for all physicians and pathologists. Multiple sources are used for case ascertainment, including linkages with patient files of two cancer centers and trace-back of cases first identified from death certificates. The ECR uses the ICD-O-3 for coding topography and morphology, and adheres to international definitions and rules issued by the International Association of Cancer Registries and European Network of Cancer Registries for reporting incidence and survival.[14]

Sites were categorized based on ICD-O-3 topography codes: lip (C00), tongue (C02, excluding C02.4), oral cavity (C03–06, excluding 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), and other (C14). The group "mouth and pharynx" included tongue, oral cavity, oropharynx, nasopharynx, hypopharynx, other.

Percentage of microscopic verification (%MV), percentage of death certificate–only cases (%DCO; cases for which no information source other than a death certificate mentioning cancer can be found), and percentage of cases diagnosed at autopsy were used as data-quality indicators.

The study was divided into three 7-year periods: 1996–2002, 2003–2009, and 2010–2016. For mouth and pharyngeal cancers and laryngeal cancers, morphology was divided into squamous-cell carcinoma (ICD-O-3 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, and was grouped according to version 7 of the Union for International Cancer Control TNM classification.

DCO cases (n=42) and autopsy cases (n=56) were excluded from survival analyses. Patients who had been diagnosed and died on the same day were included as one day's survival. Relative survival ratio (RSR) with 95% 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.[15] The cohort method was used to calculate RSRs for cases diagnosed in 1996–2002 and 2003–2009, and the period method for 2010–2016. For stage-specific survival analysis for 2010–2016, the complete method was used. International standards were used for age standardization of RSRs.[16]

Differences in proportions are presented with 95% CIs and two-sided *p*-values. Survival analyses were done with the "strs" algorithm in Stata 14.[17]

Join-point analysis with the 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 percentage change (APC) with 95% CI. Join-point regression analysis identifies the best-fitting points (join points) where a significant change in the linear slope (on a log scale) of the trend is detected. The default maximum number of join points recommended by the program for the number of data points available in our study was five. Permutation tests were used to assess the statistical significance of the APCs, where APC was significantly different from zero at α=0.05.

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

Results

Patients

Overall, 6,769 cases of head and neck cancer were diagnosed in Estonia in 1996–2016. The most common site was the thyroid, followed by the larynx and oropharynx (Table 1). In general, %MV was high and %DCO and % Autopsy low. The proportion of women was 36% among all incident cases, while it ranged from 4% for the hypopharynx to 82% for the thyroid. Median age of all patients was 62 years: it was lowest for the thyroid and nasopharynx (59 years) and highest for lip cancer (73 years). Age distribution shifted markedly toward older age groups: the proportion of cases aged ≥70 years increased from 23% to 31% from 1996–2002 to 2010–2016 ($p<0.001$).

In the mouth and pharynx group, women comprised 21% of cases. An increase of 5% was seen in the proportion of oropharyngeal and hypopharyngeal cancers over the study period, in parallel with an 8% drop in the proportion of oral cavity cancers (Supplementary Table 1).

The majority of cases among mouth and 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 on account of other and NOS tumors. For the thyroid group, there was a 10% 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 and pharyngeal cancers, the majority of cases (62%) were diagnosed at stage IV (Figure 1). For the 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.

Incidence Trends

A consistent decline was seen in the incidence of lip (APC −5.4, 95% CI −7.1 to −3.7) and laryngeal cancer (APC −2.2, 95% CI −3.0 to −1.4; Figure 2). Starting from early the 2000s, a marked increase of 5% per year 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 at a rate of 4.9% (95% CI 2.5%,–7.4%) per year until 2007 and leveled off thereafter. The incidence of follicular thyroid cancer decreased throughout the study period (APC −5.3, 95% CI −8.4 to -2.0).

The increases in oropharyngeal and hypopharyngeal cancer were largely limited to ages ≥60 years, with only modest increases seen for younger people (data not shown). Similar findings were observed for thyroid cancer.

Survival Trends

After the exclusion of 42 DCO and 56 autopsy cases, the total number of cases available for survival analysis was 6,671.

Overall, the age-standardized 5-year RSR for mouth and pharyngeal cancers combined increased markedly over the study period: from 21% to 33% (Table 2). An even larger increase (from 20% to 35%) was seen for squamous-cell carcinomas for the same group. By site, the largest survival increases were seen for the oral cavity, tongue, and laryngeal cancers, while modest changes were

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

Site	ICD10	n	%	%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 (excluding C02.4)	567	8	96	0.7	0.2	62	29
Oral cavity	C03–06 (excluding 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

Abbreviations: ICD, International Classification of Diseases, %DCO, proportion of death certificate–only cases, %MV, proportion of microscopically verified cases.

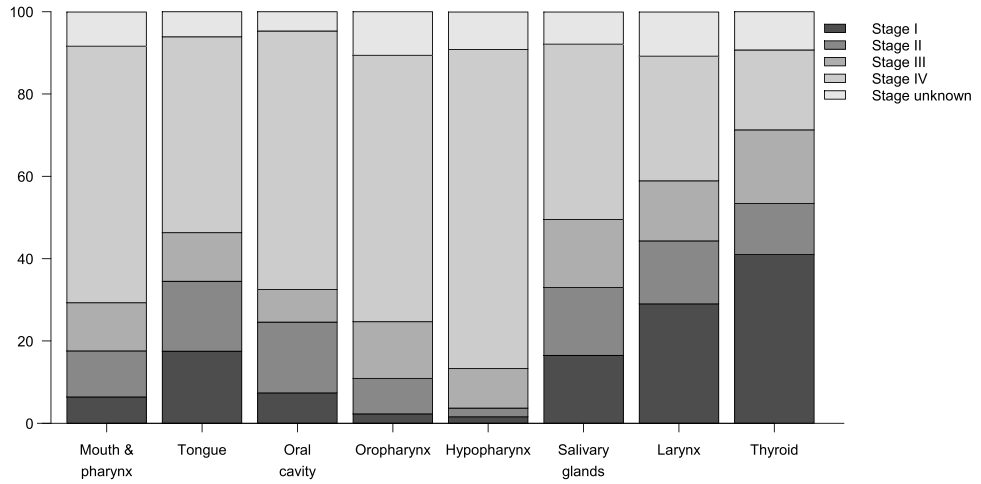

Figure 1 Stage distribution (%) of head and neck cancers in Estonia, 2010–2016.

seen for oropharyngeal and hypopharyngeal cancers. The RSR for thyroid cancer increased by 7%. 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% for salivary gland cancers and 20% for mouth and 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 5-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 among histological types in stage IV.

Discussion

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

Incidence

The slightly declining trend in oral cavity cancer, together with the steep decrease in lip and laryngeal cancer incidence, is in acordance with previously observed decreasing rates of lung cancer in Estonia.[10] Smoking is one of the strongest risk factors of most head and neck cancers. Daily smoking prevalence among working-age men in Estonia dropped from 45% in 1996 to 23% in 2018 the among women from 21% to 13%; however, the change in women has been too recent to influence cancer occurrence.[18] There were 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.[18] As only 4%–6% of oral cancers are known to be HPV-positive, HPV is not expected to play an important role in oral cavity cancer pathogenesis.[19] 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 decrease in lip cancer incidence is in contrast to recent rapid increases observed in the incidence of skin melanoma,[20] another cancer associated with excessive sun exposure, suggesting a larger role of declining smoking rates or increasing use of lip protection as a result of better awareness, and follows patterns similar to Portugal and Denmark.[21,22]

The recent increase in tongue cancer incidence in Estonia since 2010 needs further monitoring to confirm. Laryngeal cancer, also mainly caused by smoking and alcohol consumption,[23] demonstrated a substantial decline, which correlates with research from other European countries and Canada.[24–27]

The oropharyngeal cancer trend has demonstrated a steep rise since 2004, consistent with similar trends in

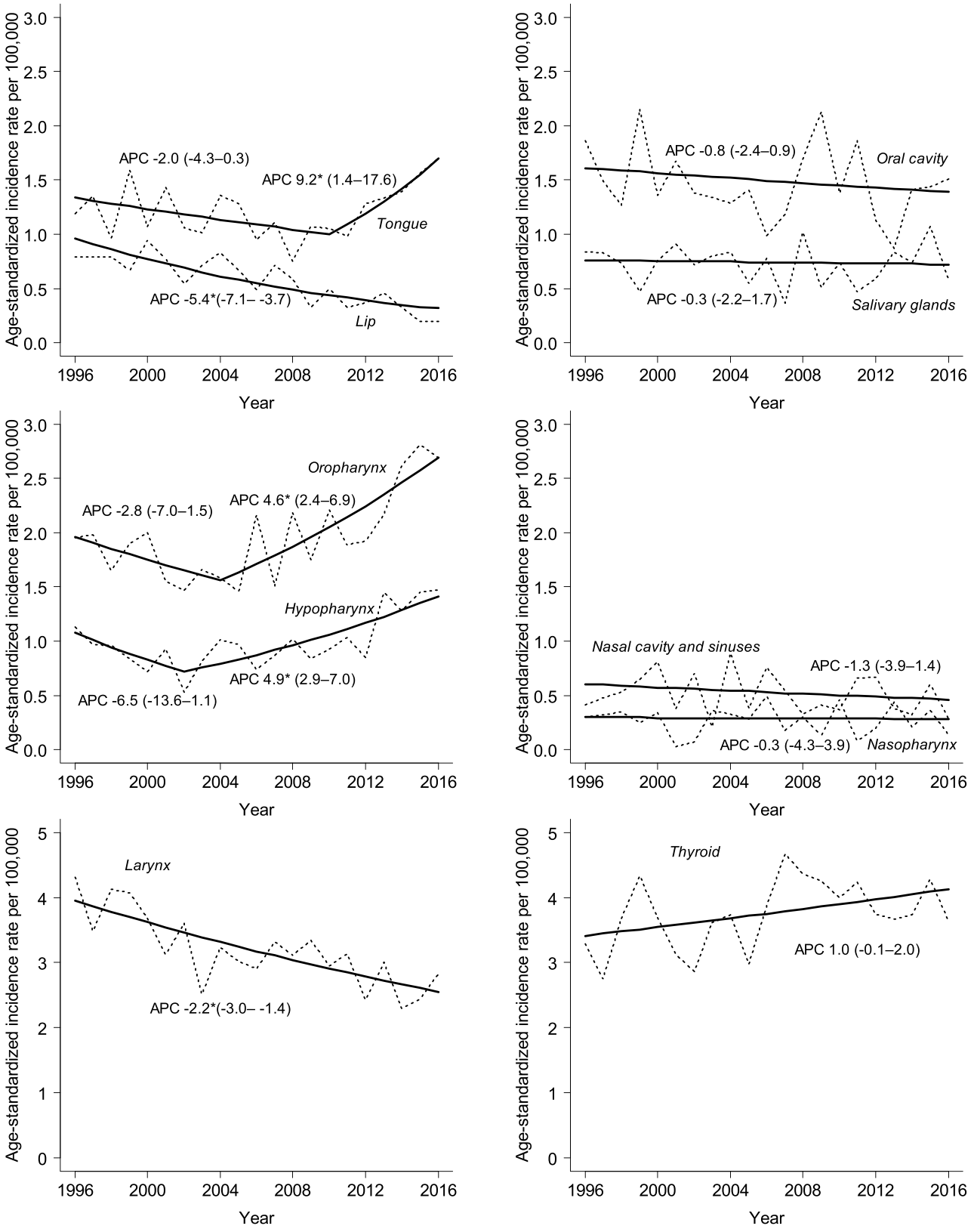

Figure 2 Observed (dashed line) and modeled (solid line) age-standardized (world) incidence rates and annual percentage change (APC) with 95% confidence intervals for trends in head and neck cancer incidence in Estonia, 1996–2016. *APC is significantly different from zero at α=0.05.

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

	RSR (95% CI)			
Site	**1996–2002**	**2003–2009**	**2010–2016**	**Change[a]**
Mouth and 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

Note: [a]Comparing first and last period.

Europe, the US, Canada, and Southeast Asia.[2,3,24,27] 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 proportion of HPV-positive tumors, shown to reach 70% in the US and Sweden.[28,29] In the US, the rise in HPV-positive tumors was accompanied by a decrease in HPV-negative tumors.[28] HPV infections play a higher role in economically more developed countries, while in economically less developed countries, the disease is still mainly caused by tobacco.[22,30,31] Worldwide, approximately 30% of oropharyngeal cancers are due to chronic HPV infection, reaching nearly 50% in Europe recently.[32,33] Testing for p16 in Estonia started only from 2014, and the expression of p16 in formalin-fixed paraffin-embedded tissue has been consistently evaluated since 2018. Based on unpublished data from the cancer center, where most Estonian head and 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,[34] suggest an important role of HPV infection in current and future cancer burden. Recent studies have also shown an increase in the prevalence of genital warts in Estonia.[35] HPV vaccination, expected to have a protective role against HPV-associated cancers, has been available for girls in the national immunization program in Estonia only since 2018. 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 yet covered by HPV vaccinations in Estonia.

The incidence of hypopharyngeal cancers has shown an increase since 2002. Similar trends have been observed in other European countries,[2,24,25] regardless of decreases in alcohol consumption and smoking, the main known risk factors for hypopharyngeal cancer. Decreasing smoking or alcohol consumption is not a likely explanation for our findings, as the trend resembled that of oropharyngeal cancer, rather than that of oral cavity or laryngeal cancer, and thus a partial role of HPV can be suggested. The predominance of men was particularly evident for hypopharyngeal cancer, as only 4% of cases were seen in women, while a fifth of all mouth and pharyngeal cancers were diagnosed in women. The overall proportion of women was similar to that seen in other countries.[36] The excess of men is probably explained by differences in health behavior.

Thyroid cancer was the most common head and neck tumor in females, who constituted 82% of cases. Recent studies from Europe, the US, Canada, and Australia have reported a steady increase in thyroid cancer incidence

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

Site	Men	Women	Difference (femalevs male)
Mouth and 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)[a]	45 (30–59)[a]	20
Squamous-cell carcinoma	28 (22–35)[a]	48 (32–63)[a]	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

Note: [a]Not age-standardized, due to small numbers.

over time, with a particular increase in papillary thyroid cancer.[37] These trends may be explained by increases in diagnostic activity and changed histological criteria[38] or linked to changes in risk factors, such as iodine supplementation, radiation exposure, Hashimoto thyroiditis, and hormonal or reproductive factors.[39–41] In addition, a link between obesity and thyroid malignancies has been demonstrated.[42] 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.[43] A recent report suggested a substantial contribution of overdiagnosis to the rising incidence in high-income countries, but also in less affluent ones.[44] A substantial rise in thyroid cancer incidence in Estonia was seen only in women aged ≥60 years (data not shown). A larger increase may have occurred before the start of our study, as the availability of new diagnostic procedures increased rapidly at the beginning of the 1990s. According to *Cancer in Five Continents*, the age-standardized rate for women increased from 2.8 to 5.5 from 1983–1987 to 1998–2002 and from 0.6 to 1.2 in men[45] 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.[46]

Survival

Survival from mouth and pharyngeal cancer has increased in Estonia, but a large deficit compared to other European countries persists. For these sites, 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 remain well below those observed for the Nordic countries.[47] RS from oropharyngeal cancers was 58% in Denmark in 2010–2014[25] and only 24% in our study. Stage at presentation is the most important prognostic factor for squamous-cell head and neck cancers,[48] and patients with advanced tumors show the shortest survival.[49] The majority (62%) of mouth and pharyngeal cancers in Estonia in 2010–2016 presented at stage IV (69% of cases with known stage). Roughly, only a quarter of the patients in Estonia presented with early-stage disease,similar to the US, where approximately 29% of head and neck tumors were diagnosed as localized,[50] but lower than in Germany, where close to 40% of mouth and pharyngeal cancer cases with known stage were diagnosed at stages I–III.[51]

We observed a huge sex gap in survival for all mouth and pharyngeal cancers, but particularly for oropharyngeal and salivary gland cancers. Later stage at diagnosis for mouth and 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 and 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 common solid tumors studied, including mouth and pharyngeal tumors, even after adjusting for age, stage, and subsite, suggesting the role of fewer comorbidities, higher treatment compliance, and better health behavior among women.[52] Smoking status has an impact on survival, even in the long term,[53,54] 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 toward non-smokers and younger age at diagnosis, with better performance status, fewer comorbidities, and HPV positivity.[55–57] HPV-positive patients have displayed better overall survival and progression-free survival than HPV-negative cancer patients, indicating separate risk factors, treatment response, and prognosis for the disease.[54,56] The persistently low survival observed in our study, however, suggests the predominance of tobacco- and alcohol-related cancers in Estonia.

Patients with head and neck cancer are known to have a higher comorbidity burden than the general population,[58] which may influence the choice of treatment modality and has a significant negative impact on their survival outcome.[59,60] Estonian cancer patients have been shown to have more comorbidities than their European counterparts,[61] and this may be particularly true for patients with health behavior–related cancers. Moreover, we also observed a large age difference in mouth and pharyngeal cancer survival: over 20% in favor of the youngest age-group (49% for age <50 and 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 scans 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 and neck cancers are mainly treated at one comprehensive cancer center in Estonia. However, the availability of radiotherapy was severely hindered, due to the low number of radiotherapy treatment machines until 2012.[62] This deficit caused prolonged waiting times, which have been shown to cause progress of head and neck cancers to the next stage.[63] In 2012, <60% of patients in Estonia who would have required at least one radiotherapy course were actually treated.[64] 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 exceeds 10%.[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.[47] In contrast to Estonia and Finland, men have higher survival rates for laryngeal cancer than women in other Nordic countries.[47]

Thyroid cancer survival in Estonia is good and higher than in Denmark in 2010–2014, where 5-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.[47] Nevertheless, the survival gap between the sexes of 12% was larger in Estonia than in the Nordic countries. One possible explanation for women's survival advantage is that they have a higher proportion of papillary tumors than men (67% vs 55%, data not shown) and 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.[44]

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 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 (eg, by site/morphology and age).

Conclusion

Discordant trends were observed in the incidence of head and 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 and HPV vaccination have a central role in reducing mortality from these cancers. A shift in the diagnosis toward early stages is crucial for improving the survival and quality of life of head and 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 incidence and survival trends, examining the availability of optimal treatment for all patient groups, and identifying factors that affect treatment choice and survival outcomes.

Data Sharing Statement

Data can be made available upon reasonable request from the last author (KI).

Ethics Approval and Consent to Participate

The study protocol was approved by the Tallinn Medical Research Ethics Committee (decision 2636, February 14, 2019). Informed consent to participate was not required, as

registry data with no personal identifiers were used and no subjects were contacted in person. All data were either public or available for research upon request without permission.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

References

1. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory. international agency for research on cancer. cancer today multibars; 2018. Available from: https://gco.iarc.fr/today/online-analysis-multi-bars. Accessed May 22, 2020.
2. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol*. 2014;50(5):387–403. doi:10.1016/j.oraloncology.2014.01.016.
3. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol*. 2013;31(36):4550–4559. doi:10.1200/JCO.2013.50.3870.
4. Thompson-Harvey A, Yetukuri M, Hansen AR, et al. Rising incidence of late-stage head and neck cancer in the United States. *Cancer*. 2020;126(5):1090–1101. doi:10.1002/cncr.32583.
5. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *JAMA*. 2017;317(13):1338–1348. doi:10.1001/jama.2017.2719.
6. Mirian C, Grønhøj C, Jensen DH, et al. Trends in thyroid cancer: retrospective analysis of incidence and survival in Denmark 1980–2014. *Cancer Epidemiol*. 2018;55:81–87. doi:10.1016/j.canep.2018.05.009.
7. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer*. 2015;136(9):2187–2195. doi:10.1002/ijc.29251.
8. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94 - results and commentary. *Ann Oncol*. 2003;14:61–118. doi:10.1093/annonc/mdg754.
9. Gatta G, Botta L, Sánchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. *Eur J Cancer*. 2015;51(15):2130–2143. doi:10.1016/j.ejca.2015.07.043.
10. Aareleid T, Zimmermann ML, Baburin A, Innos K. Divergent trends in lung cancer incidence by gender, age and histological type in Estonia: a nationwide population-based study. *BMC Cancer*. 2017;17(1):1–10. doi:10.1186/s12885-017-3605-x.
11. Ojamaa K, Innos K, Baburin A, Everaus H, Veerus P. Trends in cervical cancer incidence and survival in Estonia from 1995 to 2014. *BMC Cancer*. 2018;18(1):1–9. doi:10.1186/s12885-018-5006-1.
12. Innos K, Baburin A, Kotsar A, Eiche IE, Lang K. Prostate cancer incidence, mortality and survival trends in Estonia, 1995–2014. *Scand J Urol*. 2017;51(6):442–449. doi:10.1080/21681805.2017.1392600.
13. Innos K, Sepp T, Baburin A, et al. Increasing kidney cancer incidence and survival in Estonia: role of age and stage. *Acta Oncol (Madr)*. 2019;58(1):21–28. doi:10.1080/0284186X.2018.1512158.
14. International Agency for Research on Cancer, World Health Organization, International Association of Cancer Registries, et al. *International Rules for Multiple Primary Cancers (ICD-O)*. 3rd ed. Lyon: International Agency for Research on Cancer; 2004.
15. Ederer F, Heise H. *Instructions to IBM 650 Programmers in Processing Survival Computations. Methodological Note No. 10*. Bethesda, MD, USA: National Cancer Institute, End Results Evaluation Section; 1959.
16. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40(15):2307–2316. doi:10.1016/j.ejca.2004.07.002.
17. Dickman PW, Coviello E. Estimating and modeling relative survival. *Stata J*. 2015;15(1):186–215. doi:10.1177/1536867X1501500112
18. National Institute for Health Development. Health statistics and health research database. Available from: http://pxweb.tai.ee/PXWeb2015/index_en.html. Accessed May 22, 2020.
19. Zafereo ME, Xu L, Dahlstrom KR, et al. Squamous cell carcinoma of the oral cavity often overexpresses p16 but is rarely driven by human papillomavirus. *Oral Oncol*. 2016;56:47–53. doi:10.1016/j.oraloncology.2016.03.003.
20. Padrik P, Valter A, Valter E, Baburin A, Innos K. Trends in incidence and survival of cutaneous malignant melanoma in Estonia: a population-based study. *Acta Oncol (Madr)*. 2017;56(1):52–58. doi:10.1080/0284186X.2016.1243804.
21. Monteiro LS, Antunes L, Bento MJ, Warnakulasuriya S. Incidence rates and trends of lip, oral and oro-pharyngeal cancers in Portugal. *J Oral Pathol Med*. 2013;42(4):345–351. doi:10.1111/jop.12010.
22. Blomberg M, Nielsen A, Munk C, Kjaer SK. Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites. *Int J Cancer*. 2011;129(3):733–741. doi:10.1002/ijc.25699.
23. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol*. 2006;7(2):149–156. doi:10.1016/S1470-2045(06)70577-0.
24. Braakhuis BJM, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. *Oral Oncol*. 2014;50(7):670–675. doi:10.1016/j.oraloncology.2014.03.008.
25. Jakobsen KK, Grønhøj C, Jensen DH, et al. Increasing incidence and survival of head and neck cancers in Denmark: a nation-wide study from 1980 to 2014. *Acta Oncol (Madr)*. 2018;57(9):1143–1151. doi:10.1080/0284186X.2018.1438657.
26. Peller M, Katalinic A, Wollenberg B, Teudt IU, Meyer JE. Epidemiology of laryngeal carcinoma in Germany, 1998–2011. *Eur Arch Otorhinolaryngol*. 2016;273(6):1481–1487. doi:10.1007/s00405-016-3922-8.

27. Mifsud M, Eskander A, Irish J, et al. Evolving trends in head and neck cancer epidemiology: Ontario, Canada 1993–2010. *Head Neck*. 2017;39(9):1770–1778. doi:10.1002/hed.24829.
28. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294–4301. doi:10.1200/JCO.2011.36.4596.
29. Haeggblom L, Attoff T, Yu J, et al. Changes in incidence and prevalence of human papillomavirus in tonsillar and base of tongue cancer during 2000–2016 in the Stockholm region and Sweden. *Head Neck*. 2019;41(6):1583–1590. doi:10.1002/hed.25585.
30. Ramqvist T, Dalianis T. An epidemic of oropharyngeal squamous cell carcinoma (OSCC) due to human papillomavirus (HPV) infection and aspects of treatment and prevention. *Anticancer Res*. 2011;31:1515–1519.
31. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. *Vaccine*. 2006;24:11–25. doi:10.1016/j.vaccine.2006.05.111.
32. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664–670. doi:10.1002/ijc.30716.
33. Stein AP, Saha S, Kraninger JL, et al. Prevalence of human papillomavirus in oropharyngeal cancer: a systematic review. *Cancer J*. 2015;21(3):138–146. doi:10.1097/PPO.0000000000000115
34. Innos K, Reima H, Baburin A, Paapsi K, Aareleid T, Soplepmann J. Subsite- and stage-specific colorectal cancer trends in Estonia prior to implementation of screening. *Cancer Epidemiol*. 2018;52:112–119. doi:10.1016/j.canep.2017.12.016.
35. Uusküla A, Reile R, Rezeberga D, et al. The prevalence of genital warts in the baltic countries: findings from national cross-sectional surveys in Estonia, Latvia and Lithuania. *Sex Transm Infect*. 2015;91(1):55–60. doi:10.1136/sextrans-2014-051540.
36. Hertrampf K, Wiltfang J, Katalinic A, Timm O, Wenz HJ. Trends in incidence, tumour sites and tumour stages of oral and pharyngeal cancer in Northern Germany. *J Cancer Res Clin Oncol*. 2012;138(3):431–437. doi:10.1007/s00432-011-1118-6.
37. Reynolds RM, Weir J, Stockton DL, Brewster DH, Sandeep TC, Strachan MWJ. Changing trends in incidence and mortality of thyroid cancer in Scotland. *Clin Endocrinol (Oxf)*. 2005;62(2):156–162. doi:10.1111/j.1365-2265.2004.02187.x.
38. Verkooijen HM, Fioretta G, Pache JC, et al. Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. *Cancer Causes Control*. 2003;14(1):13–17. doi:10.1023/A:1022593923603.
39. Larson SD, Jackson LN, Riall TS, et al. Increased incidence of well-differentiated thyroid cancer associated with hashimoto thyroiditis and the role of the PI3k/Akt pathway. *J Am Coll Surg*. 2007;204(5):764–773. doi:10.1016/j.jamcollsurg.2006.12.037.
40. Dijkstra B, Prichard RS, Lee A, et al. Changing patterns of thyroid carcinoma. *Ir J Med Sci*. 2007;176(2):87–90. doi:10.1007/s11845-007-0041-y.
41. Mack WJ, Preston-Martin S, Bernstein L, Qian D. Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. *Ann Epidemiol*. 2002;12(6):395–401. doi:10.1016/S1047-2797(01)00281-2.
42. Kitahara CM, Platz EA, Beane Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev*. 2011;20(3):464–472. doi:10.1158/1055-9965.EPI-10-1220.
43. Dyntar D, Lorez M, Diebold J. Incidence-based mortality trends for thyroid cancer: is there a « true » increase in incidence of thyroid cancer in Switzerland ? *Schweizer Krebsbulletin*. 2018;3/2018:281–288.
44. Li M, Maso LD, Vaccarella S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. *Lancet Diabetes Endocrinol*. 2020;8(6):468–470. doi:10.1016/S2213-8587(20)30115-7.
45. Ferlay J, Bray F, Steliarova-Foucher E, Forman D. CI5 I-X: cancer incidence in five continents, volumes I to X 2014. Available from: https://ci5.iarc.fr/CI5I-X/Default.aspx. Accessed May 22, 2020.
46. Schmidt Jensen J, Grønhøj C, Mirian C, et al. Incidence and survival of thyroid cancer in children, adolescents, and young adults in Denmark: a nationwide study from 1980 to 2014. *Thyroid*. 2018;28(9):1128–1133. doi:10.1089/thy.2018.0067.
47. Danckert B, Ferlay J, Engholm G, et al. NORDCAN: cancer incidence, mortality, prevalence and survival in the nordic countries, version 8.2 (26.03.2019). *Assoc Nord Cancer Regist Danish Cancer Soc*. 2019.
48. Kowalski LP, Carvalho AL. Influence of time delay and clinical upstaging in the prognosis of head and neck cancer. *Oral Oncol*. 2001;37(1):94–98. doi:10.1016/S1368-8375(00)00066-X.
49. Talani C, Mäkitie A, Beran M, Holmberg E, Laurell G, Farnebo L. Early mortality after diagnosis of cancer of the head and neck – a population-based nationwide study. *PLoS One*. 2019;14(10):1–18. doi:10.1371/journal.pone.0223154.
50. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7–34. doi:10.3322/caac.21551.
51. Dittberner A, Friedl B, Wittig A, et al. Gender disparities in epidemiology, treatment, and outcome for head and neck cancer in germany: a population-based long-term analysis from 1996 to 2016 of the thuringian cancer registry. *Cancers (Basel)*. 2020;12(11):1–14. doi:10.3390/cancers12113418.
52. Innos K, Padrik P, Valvere V, Aareleid T. Sex differences in cancer survival in Estonia: a population-based study. *BMC Cancer*. 2015;15(1):1–9. doi:10.1186/s12885-015-1080-9.
53. Beynon RA, Lang S, Schimansky S, et al. Tobacco smoking and alcohol drinking at diagnosis of head and neck cancer and all-cause mortality: results from head and neck 5000, a prospective observational cohort of people with head and neck cancer. *Int J Cancer*. 2018;143(5):1114–1127. doi:10.1002/ijc.31416.
54. Du E, Mazul AL, Farquhar D, et al. Long-term survival in head and neck cancer: impact of site, stage, smoking, and human papillomavirus status. *Laryngoscope*. 2019;129(11):2506–2513. doi:10.1002/lary.27807.
55. Bøje CR, Dalton SO, Primdahl H, et al. Evaluation of comorbidity in 9388 head and neck cancer patients: a national cohort study from the DAHANCA database. *Radiother Oncol*. 2014;110(1):91–97. doi:10.1016/j.radonc.2013.11.009.
56. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24–35. doi:10.1056/NEJMoa0912217.
57. Schimansky S, Lang S, Beynon R, et al. Association between comorbidity and survival in head and neck cancer: results from head and neck 5000. *Head Neck*. 2019;41(4):1053–1062. doi:10.1002/hed.25543.
58. Paleri V, Wight RG, Silver CE, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. *Oral Oncol*. 2010;46(10):712–719. doi:10.1016/j.oraloncology.2010.07.008.
59. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL. Prognostic importance of comorbidity in a hospital-based cancer registry. *J Am Med Assoc*. 2004;291(20):2441–2447. doi:10.1001/jama.291.20.2441.
60. Leoncini E, Ricciardi W, Cadoni G, et al. Adult height and head and neck cancer: a pooled analysis within the INHANCE consortium. *Head Neck*. 2014;36:1391. doi:10.1002/HED.
61. Minicozzi P, Van Eycken L, Molinie F, et al. Comorbidities, age and period of diagnosis influence treatment and outcomes in early breast cancer. *Int J Cancer*. 2019;144(9):2118–2127. doi:10.1002/ijc.31974.
62. Grau C, Defourny N, Malicki J, et al. Radiotherapy equipment and departments in the European countries: final results from the ESTRO-HERO survey. *Radiother Oncol*. 2014;112(2):155–164. doi:10.1016/j.radonc.2014.08.029.

63. Graboyes EM, Kompelli AR, Neskey DM, et al. Association of treatment delays with survival for patients with head and neck cancer: a systematic review. *JAMA Otolaryngol Head Neck Surg*. 2019;145 (2):166–177. doi:10.1001/jamaoto.2018.2716.

64. Borras JM, Lievens Y, Dunscombe P, et al. The optimal utilization proportion of external beam radiotherapy in European countries: an ESTRO-HERO analysis. *Radiother Oncol*. 2015;116(1):38–44. doi:10.1016/j.radonc.2015.04.018.