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Differences in incidence and survival of oral cavity and pharyngeal cancers between Germany and the United States depend on the HPV-association of the cancer site

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ABSTRACT

Introduction: The epidemiology of squamous cell oral cavity and pharyngeal cancers (OCPC) has changed rapidly during the last years, possibly due to an increase of human papilloma virus (HPV) positive tumors and successes in tobacco prevention. Here, we compare incidence and survival of OCPC by HPV-relation of the site in Germany and the United States (US).

Materials and methods: Age-standardized and age-specific incidence and 5-year relative survival was estimated using data from population-based cancer registries in Germany and the US Surveillance Epidemiology and End Results (SEER) 13 database. Incidence was estimated for each year between 1999 and 2013. Relative survival for 2002–2005, 2006–2009, and 2010–2013 was estimated using period analysis.

Results: The datasets included 52,787 and 48,861 cases with OCPC diagnosis between 1997 and 2013 in Germany and the US. Incidence was much higher in Germany compared to the US for HPV-unrelated OCPC and more recently also for HPV-related OCPC in women. Five-year relative survival differences between Germany and the US were small for HPV-unrelated OCPC. For HPV-related OCPC, men had higher survival in the US (62.1%) than in Germany (45.4%) in 2010–2013. These differences increased over time and were largest in younger patients and stage IV disease without metastasis. In contrast, women had comparable survival for HPV-related OCPC in both countries.

Conclusions: Strong survival differences between Germany and the US were observed for HPV-related OCPC in men, which might be explained by differences in HPV-attributable proportions. Close monitoring of the epidemiology of OCPC in each country is needed.

Introduction

Oral cavity and pharyngeal cancers (OCPC) include cancers of the lip, oral cavity, and pharynx. Together, this group of cancers accounts for over 500,000 new cancer cases per year worldwide [1]. In 2007, the WHO concluded that human papillomavirus (HPV) type 16 is a cause of some subtypes of OCPC [2]. Many epidemiological and molecular studies have meanwhile provided evidence for this causal link, particularly

Abbreviations: OCPC, squamous cell oral cavity and pharyngeal cancers; HPV, human papillomavirus; US, United States; SEER, Surveillance, Epidemiology, and End Results; DCO, death certificate only; AAPC, average annual percentage changes; 95% CI, 95% confidence interval

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for squamous cell cancers of the oropharynx, the tonsils and parts of the tongue [3]. Consequently, a paradigm shift in the understanding of OCPC has occurred.

HPV-positive and HPV-negative OCPCs have different risk factor profiles [4]. Tobacco use and alcohol consumption are considered the primary risk factors for HPV-negative OCPCs. In contrast, HPV-positive OCPCs are associated with several measures of sexual behavior and marijuana use, which have not been found to be associated with HPV-negative OCPCs. It has been estimated that the combined effects of tobacco use and alcohol consumption are responsible for 70–80% of OCPCs in the United States (US) [5], while HPV was reported to be associated with 46% of oropharyngeal carcinomas [6]. However, the attributable fractions vary strongly by geographical location and calendar time due to changes in the prevalence of HPV-infection, tobacco use and alcohol consumption.

In many high-income countries, the incidence of OCPC at HPV-unrelated sites has declined, presumably because of reduced tobacco and alcohol use. In contrast, incidence for HPV-related oropharyngeal cancers has risen strongly, specifically among males [7]. While in earlier studies increases in incidence for HPV-related sites were mainly observed among ages 40–59 years [8], they have recently also been observed in patients aged 65+ years with similar magnitude [9], highlighting the rapidly changing epidemiology of OCPC.

Changes in survival patterns after OCPC have also been reported in various countries. In Europe, 5-year relative survival increased between 1999–2001 and 2005–2007 from 42.3 to 47.4 for tongue and lingual tonsil and from 36.7 to 40.1 for oropharynx and tonsil cancer. For oral cavity cancer, the improvement in survival was less pronounced (45.6–48.1) [10]. In the US, survival for oropharyngeal cancer rose considerably in the last years, while it was stable over time for HPV-unrelated OCPC sites [8]. These differences have been explained by the increasing proportion of HPV-positive OCPCs together with the more favorable prognosis of HPV-positive OCPC [11].

Thus, the epidemiology of OCPC is changing strongly over time and will lead to modifications in OCPC management [12]. The magnitude of these changes will depend on changes in the prevalence of the main risk factors tobacco use and HPV. Here, we provide a comprehensive comparison of incidence and survival of OCPC at HPV-related and non-related sites in Germany and the US. These countries differ largely in their risk factors distribution, with a higher smoking prevalence [13–15] and an presumably lower proportion of HPV-positive OCPCs [16] in Germany. Thus, a comparison of these countries will provide further insights about reasons for the strong changes in the epidemiology of OCPC.

Patients and methods

Data bases

For survival analysis, a pooled national dataset from the German cancer survival project was used [17,18]. Briefly, the survival-dataset comprises data from 12 population-based cancer registries encompassing 12 of the 16 federal states and covering 28.3 million inhabitants in 2013 (approx. 35% of the total German population). Regions were selected by their data quality assessed by the proportion of death certificate only (DCO) and autopsy only cases among all registered malignant cancers (Supplementary Table 1). Regions were included if the proportion of DCO cases in the period 2002–2013 was below 13%. Patients age 15 or older diagnosed with a first OCPC tumor in 1997–2013 with a passive mortality follow-up to December 2013 were included in this analysis. Incidence was calculated for the same regions, with the exception of Lower Saxony, where state wide cancer registration did not start before 2003, and which was therefore excluded from incidence analysis. We also restricted the incidence analysis to the period 1999–2013 as three registers started in 1998/99. Patients notified by DCO or autopsy only were excluded.

We selected and classified OCPC cancers based on the anatomic site and etiologic relationship with HPV following two publications [8,19]. The classification was based on the International Classification of Disease for Oncology version-3 (ICD-0-3) [20]. Cancer with morphology codes 8050–8076, 8078, 8083, 8084 and 8094 (squamous cell carcinoma) with malignant behavior (behavior code 3) of the oral cavity (topography codes C01.9-C06.9) and pharynx (codes C09.0-C10.9, C12.9-C14.8) (excluding lip, salivary glands, and nasopharynx) were included and further classified in three groups: HPV-related OCPC, HPV-unrelated OCPC, and HPV-unrelated oral tongue (C02.0-C02.3, C02.8-C02.9) (Supplementary Material).

Data from the Surveillance, Epidemiology, and End Results (SEER) 13 database was used to estimate incidence and survival for the US [21]. SEER-13 covers about 41 million inhabitants (13.4% of the total US population). The same selection and classification criteria as for the German dataset were applied for the US. In sensitivity analyses, analyses were conducted after restricting the US data to Whites.

Statistical methods – incidence

Age standardized incidence rates according to the Segi standard world population were calculated [22]. Rates (per 100,000 persons) for HPV-related OCPC, HPV-unrelated OCPC and HPV-unrelated oral tongue cancer were estimated for Germany and the US for each calendar year between 1999 and 2013. We used “Joinpoint” software for calculation of average annual percentage changes (AAPC) and corresponding 95% confidence intervals as a summary measure for the trend over the whole study period (1999–2013). It is computed as a weighted average of the annual percentage changes (APC) for each segment from the final joinpoint model. We assumed the random errors in the regression model to have constant variance. The regression coefficients were estimated by ordinary least squares [23]. Incidence rates for Germany were calculated using the software CARESS [24]. The US incidence rates were calculated using the software SEER*Stat [21].

Statistical methods – survival

Period analysis [25] was used to derive 5-year relative survival estimates for the time periods 2002–2005, 2006–2009, and 2010–2013 in Germany and the US. Relative survival was calculated as the ratio of the observed survival in the group of OCPC patients divided by the expected survival of a comparable group in the general population. Expected survival was derived according to the Ederer II method [26] from life tables, stratified by age, sex, calendar year, and, in the US, race, as obtained from the German Federal Statistical Office and the Center for Disease Control and Prevention in the US [27]. Age-standardization was performed using weights defined by the International Cancer Survival Standard (age-groups: 15–54, 55–64, 65–74, 75–84, and 85+ years) [28].

Model-based period analysis [29] was employed to test for differences between 5-year relative survival in Germany and US, including adjustment or stratification by age, sex and stage. In the model, the numbers of deaths were modeled as a function of the year of follow-up, country and the adjustment factors by Poisson regression with the logarithm of the person-years at risk as offset. Patients with missing information on stage were excluded in model-based analyses (Germany: 9172 (26%), US: 4235 (14%)). Survival estimates were derived from the models by using standard weights for age-standardization and weights derived from the distribution among all included patients for stage and sex.

For subgroups analysis by stage and for stage adjustment, tumors were classified using the TNM Classification of Malignant Tumors (6th and 7th edition) [30,31]. Stage IV tumors were additionally subdivided in stage IV with (M1) and without metastasis (M0). Comparative stage analyses were restricted to the time period 2004–2013, as only for these years TNM information based on the 6th or 7th edition was available in