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Oropharyngeal cancer survivorship in Denmark, 1977–2012

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SUMMARY

Objectives: Incidence rates for human papillomavirus positive oropharyngeal cancer (HPV-positive OPC) have significantly increased in numerous developed countries in recent decades. Fortunately, HPV-positive OPC has improved survival relative to HPV-negative OPC. Given these incidence trends and survival differences, we hypothesized that OPC survivorship has increased in affected populations over time.

Materials and Methods: Poisson and Cox regression models were used to examine incidence and OPC survivorship trends in a population-based prospective registry, the Danish Cancer Registry.

Results: In Denmark, OPC incidence ($p < 0.001$) and median survival ($p < 0.001$) significantly increased from 1977 to 2012. Consequently, the number of 5-year OPC survivors in the Danish population increased from 72 in 1980 to 1311 in 2010.

Conclusions: The long-term sequelae of curative therapy in the growing number of OPC survivors will need to be evaluated to address their unique survivorship needs.

Introduction

Incidence rates for oropharyngeal squamous cell carcinoma (OPC) have significantly increased in numerous countries around the world [1]. These trends have been attributed to an increasing risk for human papillomavirus (HPV)-positive OPC in the last several decades, predominantly among young men [2–5]. HPV-positive OPC is associated with a favorable response to therapy [6], and therefore the majority of patients with HPV-positive OPC are cured [7]. Consequently, young survivors of HPV-positive OPC have decades to potentially experience the long-term sequelae of cancer therapy, which can confer significant morbidity [8].

Recent recognition of this phenomenon has been the impetus to critically examine therapeutic strategies for HPV-positive OPC with a goal of improving long-term quality of life. Current clinical trials are investigating whether a reduced intensity of therapy (e.g. lower cumulative doses of radiotherapy) will improve quality of life measures while maintaining high survival rates for HPV-positive OPC [9]. A recent Institute of Medicine report highlighted the importance of addressing cancer survivorship issues, especially for "rare" malignancies such as OPC, including an accurate assessments of the number of cancer survivors in a population [10]. Such estimates are paramount to cancer survivorship planning.

The Danish Cancer Registry (DCR) affords a unique opportunity to elucidate population-level trends in OPC survivorship elicited by incidence trends for HPV-positive OPC. The rising risk of OPC experienced by the Danish population subsequent to 1978 [11] is attributed to an ~5% increase per year in incidence rates for HPV-positive tonsillar cancer [5]. Within a decade (2000–2010), the proportion of HPV-positive tonsillar cancers in Denmark increased from 68% to 82% [5]. Therefore, we utilized data from the DCR to evaluate trends in incidence, survival and prevalence of OPC in the Danish population from 1977 through 2012.

Material and methods

The DCR is a prospective, population-based program of the National Board of Health that has estimated the incidence and prevalence of malignant neoplasms in the Danish population since 1943 [12]. Vital status and dates of emigration or immigration are maintained separately by the Central Population Register, which is linked to the Danish Cancer Registry. All Danish residents who contributed person-time between 1977 and 2012 were eligible for analysis. For cancer incidence, follow-up began on January 1, 1977 and ended on date of OPC diagnosis, death, emigration or December 31, 2012. Cancer outcomes included a diagnosis of

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squamous cell carcinoma of the base of tongue, tonsil, oropharynx, pharynx, Waldeyers' ring and branchial cleft (ICD0 codes C01, C09, C10, C14, C02.4, C02.8, C9.0, C09.1, C09.8, C09.9, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2, and C14.8).

OPC incidence rates were estimated by age, calendar period, cohort, and gender by use of Poisson regression models. Survival after OPC diagnosis was defined from date of diagnosis to death or censored at the date of emigration or December 31, 2012, whichever came first. Overall survival was estimated by Cox regression models and illustrated by Kaplan–Meier curves. Consistent with the Institute of Medicine, National Coalition for Cancer Survivorship and the National Cancer Institute Office of Cancer Survivorship definition of cancer survivor, an individual is considered an OPC survivor from the time of diagnosis until death [13]. Based upon this, OPC survivors were defined as individuals with a prevalent diagnosis (i.e. ever had a diagnosis) of OPC. All statistical tests were two-sided and a significance level of 5% was applied. Analyses were conducted using R statistical software [14].

Results

Data were available for 8,271,409 Danish civilians who contributed 186,085,701 person-years of follow-up time. From 1977 to 2012, 5673 individuals were diagnosed with incident OPC. During this period, incidence rates for OPC significantly increased from 1.35 to 5.87 per 100,000 person-years ($p < 0.001$; Fig. 1). This corresponds to a 48% increase in incidence of OPC per decade (IRR 1.48, 95% CI 1.44–1.52, $p < 0.001$; Fig. 2). Additionally, risk of OPC increased significantly with age (Fig. 2, $p < 0.001$) and plateaued after 60 years.

Given the improved survival for HPV-positive relative to HPV-negative OPC observed in Denmark [15], and the increased incidence rates of HPV-positive OPC [5], all-cause mortality rates due to OPC significantly increased in the Danish population over time although not as steeply as incidence (Fig. 1; $p < 0.001$). This was attributable to a significant improvement in median survival after an OPC diagnosis from 1.81 years during the period from 1977 to 1995 to 5.45 years after 2005 ($p < 0.001$). Median age at diagnosis also significantly declined from 64.1 to 58.6 years in 1977 and 2012, respectively ($p < 0.001$; average decline of 0.16 years per calendar-year).

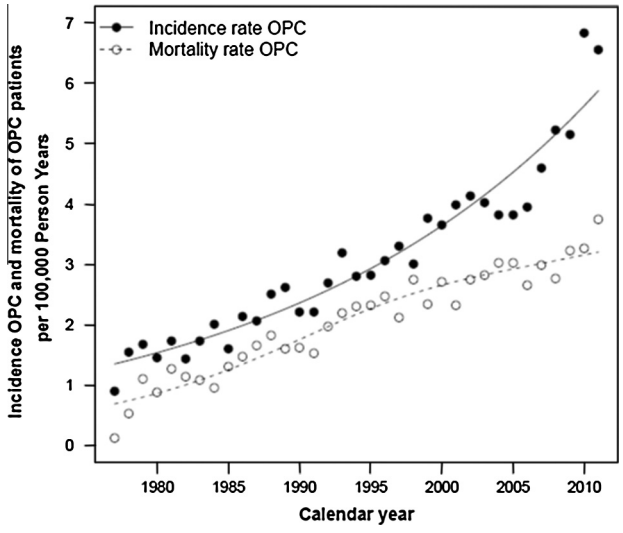

Fig. 1. Incidence and all-cause mortality rates of oropharyngeal squamous cell cancer in Denmark (1977–2012). Incidence and all-cause mortality rates of oropharyngeal squamous cell cancer (OPC) in Denmark are depicted on the *y*-axis per 100,000 person years, by calendar year (*x*-axis).

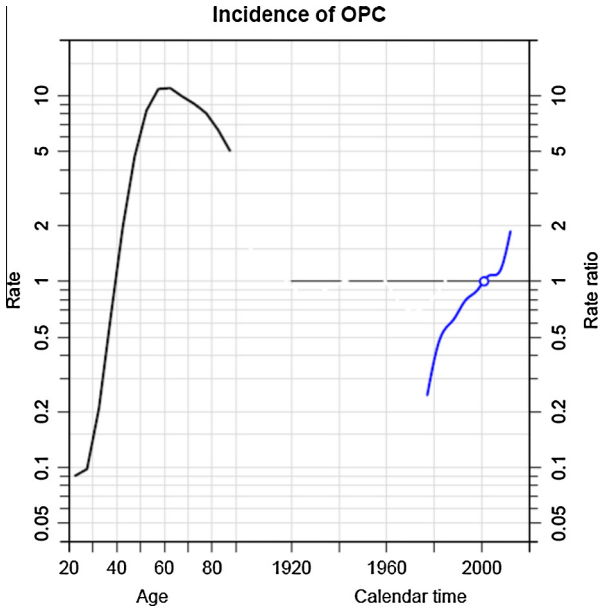

Fig. 2. Incidence trends of oropharyngeal cancer by age and calendar time. Age-related rate of oropharyngeal cancer is represented by incidence per 100,000 person years. The period effect is depicted by incidence rate ratio (incidence rate relative to the calendar year 2000).

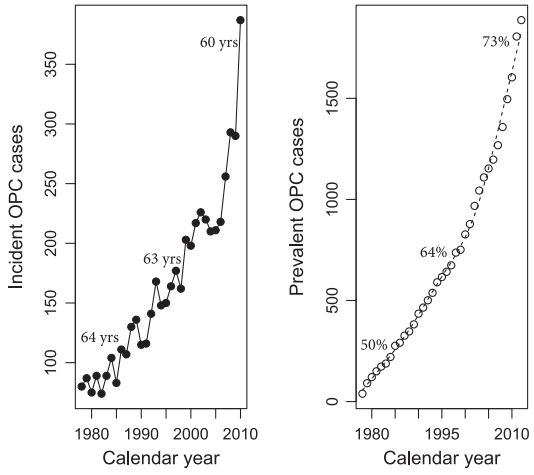

Fig. 3. Increased number of oropharyngeal cancer survivors from 1977 to 2012. Left panel: The number of individuals with incident oropharyngeal squamous cell cancer diagnosis is shown on the *y*-axis by calendar year. Mean age for incident cases is displayed above the curve. Right panel: The number of prevalent cases with oropharyngeal squamous cell cancer diagnosis is depicted on the *y*-axis. The proportion of prevalent cases who are five-year survivors is shown above the curve.

As a consequence of increased incidence and improved survival for OPC in the Danish population over time, the number of individuals surviving after an OPC diagnosis significantly increased from 1977 to 2012 (Fig. 3; $p < 0.001$). In 1980, there were only 72 five-year OPC survivors in the Danish population, but by 2010 that had increased to 1311.

Discussion

These data reveal a significant growth of OPC survivors in Denmark in recent decades and underscore the need to ascertain analogous estimates in countries like the United States, where the number of individuals diagnosed with OPC each year is expected to continue to increase [3].

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Prior studies have described the increasing incidence of HPV-related OPCs, the unique clinicodemographic characteristics of this patient population and their improved survival relative to HPV-unrelated OPC. In the context of increasing incidence, optimizing survival outcomes after primary therapy for OPC is paramount. However, when considering that the majority of individuals with OPC in the Danish population are 5-year OPC survivors, not newly diagnosed, the priority broadens to understanding the issues of importance to survivors and improving their health outcomes. Indeed, when accounting for the number of individuals in a population with incident and prevalent diagnosis, the scope of disease burden and the epidemiologic significance broadens. Of note, these changes have quickly evolved; the proportion of OPC survivors who were 5-year survivors increased from 50% to 73% from 1980 to 2010. This population-level demographic shift in OPC patients highlights the need to focus upon the growing population of survivors.

Additionally, these trends emphasize the need to identify the unique health and psychosocial needs of the growing number of OPC survivors. Recent studies have called for particular attention to the health maintenance and psychosocial needs specific to young breast and prostate cancer survivors [16–18]. Whether OPC survivors have analogous or additional needs is presently unknown.

Current oropharynx cancer clinical trials are motivated by a growing concern to reduce long-term sequelae of therapy, improve health-related quality of life and maintain the survival benefit afforded by the current clinical standard of care. Necessary first steps for improving health-related quality of life and health outcomes of this emerging population include determining the magnitude of this population. In this analysis, such estimates are elucidated for Danish citizens and provide a glimpse of the importance of acknowledging OPC survivors on both ends of the spectrum, at diagnosis and long-term survivor. While there is literature describing potential long-term morbidities of therapy including osteoradionecrosis, xerostomia, dysphagia, and depression, the actual disease burden among OPC survivors remains unknown. Within the context of these estimates, such knowledge will become important.

This report highlights the growing importance of OPC survivors in populations with rising incidence of OPC and the need to rigorously evaluate the long-term sequelae of curative therapy, as well as the unique needs of this survivor population. Such efforts are necessary to inform practice guidelines for OPC survivors (e.g. surveillance for treatment related cardiovascular or dental toxicities), budget plans (e.g. allocation of resources to OPC survivors' care) and research agendas (e.g. the success of treatment de-intensification protocols).

Conflict of interest statement

None declared.

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