Comparison of oropharyngeal and oral cavity squamous cell cancer incidence and trends in New Zealand and Queensland, Australia.

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Abstract

Background: Increases in the incidence of squamous cell oropharyngeal cancer (OPC) have been reported from some countries, but have not been assessed in Australia or New Zealand. This study examines trends for squamous cell OPC and squamous cell oral cavity cancer (OCC) in two similarly sized populations, New Zealand and Queensland, Australia.

Methods: Incidence data for 1982 to 2010 were obtained from the respective population-based cancer registries for squamous cell OPC and OCC, by subsite, sex, and age. Time trends and annual percentage changes (APCs) were assessed by joinpoint regression.

Results: The incidence rates of squamous cell OPC in males in New Zealand since 2005 and Queensland since 2006 have increased rapidly, with APCs of 11.9% and 10.6% respectively. The trends were greatest at ages 50-69 and followed more gradual increases previously. In females, rates increased by 2.1% per year in New Zealand from 1982, but by only 0.9% (not significant) in Queensland. In contrast, incidence rates for OCC decreased by 1.2% per year in males in Queensland since 1982, but remained stable for females in Queensland and for both sexes in New Zealand. Overall, incidence rates for both OCC and OPC were substantially higher in Queensland than in New Zealand. In males in both areas, OPC incidence is now higher than that of OCC.

Conclusions: Incidence rates of squamous cell OPC have increased rapidly in men, while rates of OCC have been stable or reducing, showing distinct etiologies. This has both clinical and public health importance, including implications for the extension of human papilloma virus (HPV) vaccination to males.

Keywords: HPV; oral cancer; oropharyngeal cancer; epidemiology; trends; incidence.

Background

With the advent of human papillomavirus (HPV) vaccines which target HPV strains associated with cervical cancer, there has been increasing interest in the role of HPV in other cancers (1-4). These DNA viruses are epitheliotropic, that is, they generate productive infections within epithelial tissue; about 40 types can infect the genital tract (5). Recent studies have suggested a heterogeneous association between HPV and cancers of the head and neck (1). In particular, among oral and pharyngeal squamous cell tumors, a stronger relationship with HPV has been reported for oropharyngeal cancer (OPC) than for other sites such as oral cavity cancer (OCC) (6, 7).

There have been several contemporary studies documenting increasing incidence rates of squamous cell OPC, while rates of OCC have been found to be generally stable or decreasing (1, 6, 8-11). Since comparisons of incidence trends across time and geographical areas can provide important insights into the relative burden and etiology of these cancers, we undertook this study to compare the trends and distribution of squamous cell OPC and OCC between two similar sized populations of New Zealand and the Australian state of Queensland.

Methods

Data sources

De-identified data on incident cases of OPC and OCC for the period 1982-2010 were obtained from the New Zealand and Queensland Cancer Registries. Both are population-based registries to which relevant health providers are required by law to provide pathology reports of all new malignant cancers (excluding non-melanoma skin cancers) (12, 13). Year of diagnosis, age at diagnosis, sex, site code and morphology were included in the data.

The study cohort was restricted to invasive squamous cell carcinomas (SCC) based on the 4-digit morphology codes 8050-8076, 8078 and 8083. Most (over 70%) primary cancers in these sites are SCC, the others including a large number of diverse histological types. Tumors were further classified into the following subsites: base of the tongue, the tonsils, and the oropharynx for OPC; and other parts of the tongue, gum and cheek, floor of the mouth, palate and other parts of the mouth, and the internal mucosa of the lip for OCC. The codes from the International Classification of Diseases in Oncology, 3rd edition (ICD-O-3) (14) used to define these subsites are shown in Table 1. Both the New Zealand and Queensland Cancer Registries back-coded all data from the study period to the ICD-O-3 classification.

We based our subsite classification on two major studies by Chaturvedi et al. (10), and Auluck et al. (1), but these differ in some ways. In agreement with the Chaturvedi study (10), we included C100, C101, C104, and C142 within OPC. In contrast Auluck at al. (1) excluded these, although they included adjacent sites as OPC. We grouped C050 and C051 within OCC (1), while Chaturvedi et al. (10) included them as OPC, although they say that these sites are not HPV-related. We excluded C000-002 and C006-009, external and unspecified lip cancers, as did Auluck et al. (1). Chaturvedi et al. (10) grouped these cancers with OCC, although external lip cancers are exposed to other factors such as ultraviolet light. For all other subsites, our classifications were the same as those of both the other studies. Cancers of the salivary glands, nasopharynx, hypopharynx, and ill-defined sites of the oral cavity were excluded.

Population data required to form the denominators for calculating rates (stratified by year, sex and 5-year age groups) were obtained from Statistics New Zealand (15) and the Australian Bureau of Statistics (16).

Statistical analyses

Incidence rates were directly age-standardized to the 2000 World Health Organization standard population (17) using the distrate command in Stata (© StataCorp LP), and expressed per 100,000 population along with the corresponding 95% confidence interval (95% CI).

For the most recent decade (2001-2010), average annual incidence rates for each site and subsite were calculated for all persons and by sex. The incidence rate ratios (IRRs) for males compared to females and for Queensland compared to New Zealand were then assessed using either a Poisson or negative binomial regression model (depending on model fit and convergence), where the response variable was the number of cases in each cell offset by the log of the accompanying population. All models were also adjusted for age in 5-year groups, except that those under 30 years of age were aggregated into a single group due to the small numbers of cases.

Trends in the incidence of OPCs and OCCs over the entire study period by sex and broad age group (defined as less than 50 years, 50-69 years, and 70 years and over) were calculated from annual rates using joinpoint regression (18, 19). This method uses Monte Carlo permutation tests to determine whether changes in the magnitude or direction of the trend would improve the fit of the initial model, in which constant change over time is assumed (i.e. no joinpoints). The option with the fewest joinpoints that provides the best fit to the observed data is chosen as the final model. For the purposes of this study, a maximum of three joinpoints were specified with a minimum of 5 years of data in each segment. Trends were expressed in terms of an annual percentage change (APC) along with the 95% CI.

Due to the relatively small number of cases, it was not feasible to calculate incidence rate trends by subsite based on annual data. However, average annual rates were calculated by subsite for each decade, and either Poisson or negative binomial regression was then used to compare the incidence rate ratio for 2001-2010 to 1982-1990, similar to the approach described earlier.

Results for all analyses were deemed to be statistically significant if the associated p-value was less than 0.05.

Results

In the overall study period 1982-2010, 3,975 eligible incident cases were identified in New Zealand and 6,559 in Queensland. Approximately two-thirds were OCCs (66% in New Zealand and 63% in Queensland) and males outnumbered females (66% and 71%, respectively). The median age at diagnosis was higher for OCCs (63 years for both areas combined) compared to OPCs (59 years). The most common subsites for OCC and OPC were the tongue (excluding the base of the tongue) and tonsils, respectively.

Between 2001 and 2010, the average annual age-standardized incidence rate of OPCs was 70% higher (IRR=1.7, 95% CI = 1.5-1.9; $p < 0.001$) in Queensland (2.4/100,000) than New Zealand (1.4/100,000 - Table 2). A similar degree of variation was seen for OCCs, with the incidence rate of 3.2/100,000 per year in Queensland being 50% higher than the rate of 2.0/100,000 in New Zealand (IRR=1.5, 95% CI = 1.3-1.7; $p < 0.001$).

Despite these differences in incidence rates, the distribution by cancer site and sex appeared to be generally similar; for example, in both areas the ratio of the incidence rates of OPC for males compared to females was greater than 4:1, while for OCC it was under 2:1 (Table 2). Furthermore, incidence rate ratios by cancer subsite for Queensland compared to New Zealand were largely consistent by sex (Supplementary table 1).

Some variation was, however, apparent in the incidence distribution by age at diagnosis (Supplementary Table 2). The IRR for Queensland relative to New Zealand for OPCs was similar in each age group; however, for OCCs it was significantly higher in the 50-69 age group (IRR = 1.9,

95% CI = 1.7-2.1) than for either the under 50 (IRR = 1.3, 95% CI = 1.1-1.6) or over 70 age groups (IRR = 1.3, 95% CI = 1.1-1.5). This difference was mainly driven by tongue cancers. There was also a marked decrease in the Queensland: New Zealand IRR by age for cancers on the floor of the mouth, falling from 4.2 (95% CI = 2.1-8.4) in the under 50 age group to 1.1 (95% CI = 0.8-1.6) among persons aged 70 years and over.

Rapid increases in the incidence of OPCs among males in recent years were evident for both New Zealand (APC = +11.9% from 2005-2010) and Queensland (APC = +10.6% from 2006-2010; Figure 1). These large rises followed smaller increases since 1982 in Queensland and from 1991 in New Zealand. A more gradual, but statistically significant, increase of 2.1% per year from 1982 to 2010 was also seen for OPCs among females in New Zealand, compared with a smaller and non-significant increase (APC = +0.9% per year) among females in Queensland.

For OCCs, incidence rates remained stable for both sexes in New Zealand and for females in Queensland. A significant decrease of 1.2% per year over the entire study period was observed among Queensland males, although this occurred from a much higher baseline rate compared to males in New Zealand.

Ongoing increases in the incidence of OPCs were found for persons under 50 years of age in both areas for the whole time period (APC = +5.7% in New Zealand, +3.1% in Queensland), as well as for those aged 70 years and over in New Zealand (APC = +2.1%; Figure 2). Further analysis by age group and sex revealed that the latter trend (those aged 70 years and over in New Zealand) was only significant for males, among whom the incidence rates of OPC increased by 10.4% (95% CI = +1.4%, +20.1%) from 2003-2010. Large increases for OPCs were also seen within the 50-69 year age group from 1997 onwards in New Zealand (APC = +8.0%), and from 2005 in Queensland (APC = +10.8%), and again were predominantly driven by males of this age in both areas (results not shown). The only significant trends for OCCs by age at diagnosis were an increase of 1.6% per year among the under 50s in New Zealand, contrasting with a 1.1% decrease per year for those aged 50-69 years in

Queensland. When stratified by sex, the corresponding trends were also found to be significant for males but not for females (results not shown).

When the annual average age-standardized incidence rates by subsite were compared by decade of diagnosis (Table 3), significant increases were observed between the 1980s and 2001-2010 for the base of the tongue and tonsil for both areas, and for the mucosa of the lip in New Zealand. This contrasts with the significant decreases that were seen for cancers on the floor of the mouth in both areas, as well as on the palate and other mouth and mucosa of the lip in Queensland only.

Discussion

New Zealand is geographically separated from the state of Queensland in Australia by more than 2,000 km of ocean. Both have universal public health care systems, generally similar social patterns, and well established cancer registries. Despite these similarities, this study has shown that Queensland had a 50 to 70% greater incidence of both OPCs and OCCs than New Zealand during the period 2001 to 2010.

Our analysis also shows the very different time trends for OPC compared to OCC in Queensland and New Zealand. This clearly indicates that the etiology of these two sets of cancers is different, despite their similar histology and adjacent anatomical distribution. It is already known that one important difference is infection with HPV; in studies using HPV assays on stored tissue from 3 population-based registries in the US, the increase in OPC was restricted to HPV-associated cancers (10). Other studies have also shown increases in HPV-associated OPC tumors (7-9). However, the subsite distinction is not absolute: HPV is found in other oral and pharyngeal cancers (20), and also adjacent areas such as laryngeal and nasal sinus tumors (21, 22), but less frequently than it is found in the subsites grouped here as OPC.

The trends in OPC incidence in New Zealand and Queensland are very similar, with a striking difference in trends between males and females. In both places (although not significantly in Queensland), incidence rates in females have risen slowly and consistently over the 30 year period. However, in males, the rates have increased sharply by over 10% per year since 2005 in New Zealand and from 2006 in Queensland. Consequently, the incidence of OPCs now exceeds that of OCCs in males in both areas.

This is in clear contrast with the incidence of OCC, which has shown no significant trend in New Zealand for either sex or for females in Queensland. The trend for males in Queensland was different, with a significant decrease from rates in the 1980s which were initially high in comparison to males in New Zealand and to females in both areas.

The results of this study are comparable to previous Australian studies. Between 1982 and 2005, significant annual increases in the incidence of tonsil and base of tongue squamous cell cancers in males and base of tongue cancers in females have been shown, with concurrent significant decreases in oral cavity cancers (9). A study of mortality trends in oral, pharyngeal and oesophageal cancer in Australia likewise showed divergent trends in death rates in oropharyngeal cancers versus oral cavity cancers of all histological types over the last half century (23).

This change in the distribution of squamous cell carcinomas within the oral cavity and pharynx is important clinically in terms of awareness, diagnosis, and management. Tumors which are associated with HPV have a better prognosis and are more sensitive to radiotherapy (24-26). This implies that overall survival rates for tumors located in the oral cavity and pharynx will probably increase due to this change in the mix of cancer types within this category.

It seems unlikely that any substantial part of the increase in OPCs is due to changes in surveillance or clinical awareness. There is very little screening activity in New Zealand or Queensland for OCCs or OPCs, and in any case, screening would mainly affect the more visible tongue and mouth tumors

rather than the subsites for OPCs (27). With the incidence of OCC being mostly related to alcohol and tobacco consumption (6), it is possible that the decreasing trends of OCC among males in Queensland, also reported in the United States (6), reflect the decreasing smoking prevalence in Queensland (28). However this decreasing trend has not been observed in New Zealand, even though the incidence rate of lung cancer, an indicator of previous smoking prevalence, is also decreasing among males in that country (29).

Free HPV immunization, primarily to prevent cervical cancer, was introduced in Queensland as elsewhere in Australia in 2007 as a catch-up program for girls aged 13 to 18, with rollout to younger age groups from 2008 (30, 31). A similar program was commenced in New Zealand in 2008 for girls born in 1990 and 1991, and from 2009 for younger age groups (32). The immunization program for HPV was extended to boys aged 12-13 in Australia in 2013 (33). The New Zealand program has not been extended to boys. While these programs will in the medium to long-term have an impact on the incidence of all HPV-associated cancers, their introduction is too recent to contribute to the trends reported here. However, with the incidence of OPC in males growing dramatically, it will be important to monitor trends in OPC in the cohort of Australian boys who have received the vaccination, and the growing evidence suggesting a link between HPV and OPC supports the argument for HPV vaccination of boys in New Zealand. The first study showing a reduction in oral prevalent HPV infections, in a randomized trial in Costa Rica of women given HPV 16/18 vaccine at ages 18-25, has been reported, although based on small numbers (34).

The increase in HPV-related OPC has been linked to changing population behaviors including an increased number of sexual partners (35), and of lifetime oral sexual partners and open-mouthed kissing partners (35, 36) . Research in Australia has shown an increase in HPV-positivity in oropharyngeal squamous cell carcinomas (SCC), increasing from 19% in 1987 -1990 to 47% in 2001-2005 (8). Further, whilst there is only limited data on changing trends in sexual behavior in New Zealand, an Australian survey in 2001-2002 showed a decline in age at first intercourse from 18 years for men and 19 years for women aged 50-59 to 16 years for both men and women aged 16-19 (37). A

higher proportion of younger age groups also reported having had initiated first intercourse before the age of 16 (37). The study showed a significant association between first intercourse before age 16 and a greater number of lifetime sexual partners (37), which in turn has been linked to an increased risk of HPV-related OPC (35).

A major survey report showed that the frequency of premarital sex in the US increased from 12.3% to 62.9% in women and from 61% to 89.5% in men between birth cohorts born before 1910 and those born in 1940-49 (38, 39); if valid, this suggests much earlier increases in this indicator in men than in women. However, a 2010 review of studies of oral HPV in surveyed healthy individuals showed a similar prevalence in men and in women (40). It therefore remains unclear whether HPV can explain why the male: female IRR is more than double for OPC compared to OCC, or why there has been a recent, sudden increase in the incidence of OPCs among men and within the 50-69 age bracket.

HPV-related oropharyngeal squamous cell carcinomas in the U.S. are more likely to be in diagnosed in young men and in African American populations compared to other ethnicities (10). While both Queensland and New Zealand have majority populations of European origin (New Zealand: 68% in 2006, Queensland: 63% in 2011) (41, 42), both areas have substantial immigration from Asian and/or Pacific countries (in Queensland, approximately 30% of immigrants are from Asian countries and in New Zealand, approximately 20% are from Asian countries and 15% from Pacific countries) (43, 44) and Indigenous populations (15% Maori in New Zealand in 2006, and 4% Aboriginal/Torres Strait Islander in Queensland in 2011). Further analysis will be undertaken to explore whether ethnicity has any effect on the observed trends for OPC and OCC.

This descriptive study confirms a substantial increase in OPC in two countries while rates of OCC were stable or reducing. Further investigation of the reasons for the significantly higher incidence of OPC among the Queensland population and the striking increase in incidence of OPC among males in both regions is warranted, with the potential for important clinical and public health implications.

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