HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2486768
https://doi.org/10.1080/21645515.2025.2486768

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Human papillomavirus (HPV) related oropharyngeal cancers in Canada: A multicenter retrospective cohort study

Voica Racovitan[a], Elizabeth Goodman[b], Winson Y. Cheung[c], Anthony C. Nichols[d], Lisa Caulley[e], and Sabrina Wurzba[f]

[a]Global Marketing HPV Strategy, Merck & Co. Inc ., North Wales, PA, USA; [b]Vaccine Outcomes Research, Value and Implementation, Merck and Co., Inc ., North Wales, PA, USA; [c]Departments of Medicine and Oncology, University of Calgary and the Charbonneau Cancer Institute, Calgary, AB, Canada; [d]Department of Otolaryngology – Head and Neck Surgery, University of Western Ontario, London, ON, Canada; [e]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [f]Department of Otolaryngology – Head and Neck Surgery, McGill University and the Jewish General Hospital, Montreal, QC, Canada

ABSTRACT

Oral human papillomavirus (HPV) infection is a risk for oropharyngeal cancer (OPC), now the leading HPV-related cancer in males in Canada. P16 positivity is a marker of HPV positivity. Since 2015, all major Canadian cancer centers perform routine p16 tumor marker testing of OPCs to define their HPV status but recent data on the HPV-attributable fraction for OPC in Canada do not exist. A retrospective chart review was conducted of all squamous cell OPC cases in patients 18 years and older diagnosed from 2016 to 2020 in 4 major Canadian hospital-based regional oncology centers to determine the HPV attributable fraction for OPC in Canada using p16 as a surrogate marker for HPV. 1154 OPC cases were identified. Most patients (85.4%) were male; about one-third 26 (31.4%) had never smoked. Most OPC (80.6%) were P16 positive. p16 positivity was 27 associated with younger age (mean age p16+ 61.6 vs. p16- 66.5 years, $p < 0.0001$), male sex 28 (p16+ males 84.0% vs p16+ females 60.9%, $p < 0.0001$), lower tumor stage (Stage 1 p16+ 29 88.1% vs Stage 4 p16+ 69.4%, $p < 0.001$), and non-smoking (never smoked 92.3% vs past 30 smoker 82.8% vs current smoker 65.0%, $p < 0.001$). Logistic regression confirmed these 31 associations. This study, the largest cohort of Canadian patients with OPC yet reported, demonstrates the high attributable fraction for HPV-related OPC. HPV-related OPC was more likely in men, younger individuals, and never smokers. These findings highlight the burden of HPV-related OPC in Canada and support gender-neutral HPV vaccination as an important public health strategy to prevent head and neck cancer.

ARTICLE HISTORY
Received 17 January 2025
Revised 13 March 2025
Accepted 27 March 2025

KEYWORDS
Human papillomavirus; oropharyngeal cancer; p16; risk factors; Canada

Introduction

Head and neck squamous cell carcinomas (HNSCCs) are the sixth most common global cancer.[1,2] Their incidence, currently estimated at 890,000 new cases with 450,000 deaths per year, has risen substantially during the past two decades and is predicted to exceed 1 million new cases annually by 2030.[3,4] Age-standardized rates are highest in high-income countries, including Canada, the USA and Oceana, and remain high due primarily to increasing oropharyngeal cancers (OPC), which arise from progenitor cells in the oropharynx, soft palate, tonsils and posterior one-third of the tongue.[3,5] Age-standardized incidence rates of OPC are up to 5 times higher in males than in females, and Canadian cancer statistics indicate that the incidence of OPC in males is rapidly approaching, and will exceed, the rate of cervical cancer in females.[6–9] Despite advances in therapy, including minimally invasive or transoral robotic resection, combinatorial radiotherapy and multidrug chemotherapy, and the emerging use of immunotherapy for checkpoint inhibition,[10] OPC imposes a high disease burden and outcomes are poor. Swallowing and speech impairment occur in approximately half of survivors, quality of life is often seriously diminished, and suicide is common.[11]

Epidemiological studies document multiple risk factors including genetic disorders resulting in impaired DNA repair or delayed carcinogen metabolism, tobacco and alcohol consumption, exposure to environmental pollutants and oral carcinogens, and viral infections including Epstein-Barr virus (EBV) and human papillomavirus (HPV).[3,5] More than 200 subtypes of HPV are known to infect humans, principally by cutaneous or mucosal routes during sexual contact.[12,13] HPV is now the most common sexually transmitted infection with a worldwide infection risk of approximately 50%, and more than 70% of sexually active individuals will have an HPV infection during their lifetime.[14] Over 90% of infections resolve spontaneously with no physical symptoms,[15] while persistent HPV infection in others results in disease, including anogenital warts, precancerous lesions or cancer of the anogenital tract and throat.[16] HPV-related malignancies are now believed to comprise approximately 5% of all cancers worldwide.[17]

The PROGRESs study examining oropharyngeal HPV in healthy adult subjects in the U.S.A and Europe reported an overall prevalence of 6.6% to 15.0% in males and 3.6% to 6.8% in females, with 1.8%–4.5% and 0.2%–2.1%, respectively, carrying high-risk viral subtypes.[18] HPV strains exhibit variable

CONTACT Elizabeth Goodman elizabeth.goodman@merck.com Vaccine Outcomes Research, Value and Implementation, Merck and Co., Inc., 351 N. Sumneytown Pike, North Wales, PA 19454-2505, USA.

oncogenic potential.[19] HPV-16 is the primary causal type in OPC though other high-risk HPV types may include HPV-18, HPV-31, HPV-333 and HPV-52.[20] The p16 protein is used as a surrogate marker HPV, and all major cancer centers in Canada have routinely tested for this since 2015. The sensitivity and specificity of p16 to detect 16 hPV in OPC have been reported from a meta-analysis to be 94.6% and 83.2%, respectively.[21] Despite the robust evidence linking OPC with HPV and concerns of increasing rates of HPV related OPC, current Canadian data on the attributable fraction of OPC are lacking. The study objective was to determine the proportion of recent OPC cases in Canada attributable to HPV in order to fill the current knowledge gap. The results reported here confirm the continuing rise in disease incidence and support the policy discussion for the broader use of gender-free HPV vaccination in an additional at-risk population.[22,23]

Material and methods

Study design

This was a retrospective review of data from OPC patients receiving care at four major Canadian regional cancer centers: the Jewish General Hospital, Montreal; the Ottawa Hospital, Ottawa, Ontario; the London Health Sciences Centre, London, Ontario; and the Tom Baker Cancer Centre, Calgary, Alberta. Participating sites identified all sequential patients seen in a 5-year period between January 1, 2016, and December 31, 2020, who were diagnosed with squamous cell OPC (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10], codes C01, C05.1, C05.2 and C10), were 18 years of age or older at the time of diagnosis and in whom p16 status was confirmed and recorded. Patient data were obtained from the hospital record by the study team in each institution as approved by the respective Research Ethics Board from each institution which imposed specific guidelines to safeguard confidentiality. Data variables extracted from the charts included age, sex, marital status, smoking history and alcohol consumption. Tumor data included the date of OPC diagnosis, the tumor subsite (base of tongue, tonsil, other), and clinical staging (tumor stage T1-T4; nodal stage N0-N3; metastatic stage M0-M1). HPV status was defined by standardized automated monoclonal p16 protein immunohistochemical staining methods and was reported as negative or positive based on strong and diffuse staining according to the College of American Pathologists guidelines.[19,24,25] No patient identifiers were collected or reported in order to protect patient confidentiality.

Statistical analysis

Data management, integration and analysis were conducted according to a detailed statistical plan, and statistical analysis was performed using SAS version 9.4. Data screening was performed prior to analysis to detect missingness, implausible values and outliers. Missing values were noted but were not imputed. Implausible values were queried and excluded if they could not be corrected. Outliers (which were possible for a defined variable but appeared extreme) were identified using conventional measures of visualization, distribution and consistency. Data were summarized by presenting the numbers of subjects, Descriptive statistics (N, %, mean, standard deviation (SD), minimum, median, and maximum values) were generated. Associations with p16 positivity were assessed using the Wilcoxon rank test for continuous variables due to skewness and Chi-square tests for categorical variables. The relationship between sociodemographic and tumor characteristics and p16 positivity were further explored using multiple logistic regression in separate logistic regression models.

Results

A total of 1,154 adult patients were identified during the 5-year period of observation. Table 1 describes sociodemographic and tumor characteristics of these OPC cases. Patients were primarily male (85.4%). Smoking was fairly evenly distributed between past (39.3%), current (28.9%) and never (31.4%) smokers. Nearly all (91.1%) of the tumors were at the base of the tongue or tonsil and were metastasis stage 0 (95.3%); over half (60.2%) were tumor stages 1–2. Of the 1,154 OPC cases, 930 (80.6%) were p16+. As shown in Figure 1, annual prevalence rates of p16 positivity ranged from 77.3% to 86.8% per year. There was no significant change in the p16 positivity rates across the period of observation.

Table 1. Description of OPC Cases from 4 regional cancer centers in Canada, 2016–2020.

	Mean	SD
Age at diagnosis (years)	62.5	9.4
	N	**%**
Sex		
Male	985	85.4
Female	169	14.6
Smoking status		
Current	334	28.9
Past	454	39.3
Never	362	31.4
Missing	4	0.3
Alcohol use		
Current	629	54.5
Past	97	8.4
Never	412	35.7
Missing	16	1.4
Cancer subsite		
Base of tongue	536	46.4
Tonsil	516	44.7
Other	102	8.8
Tumor stage		
1	253	21.9
2	442	38.3
3	207	17.9
4	252	21.8
Nodal stage		
0	142	12.3
1	396	34.3
2	531	46.0
3	79	6.8
Unknown	6	0.5
Metastasis stage		
0	1100	95.3
1	34	2.9
Unknown	20	1.7
P16 Positive	930	80.6

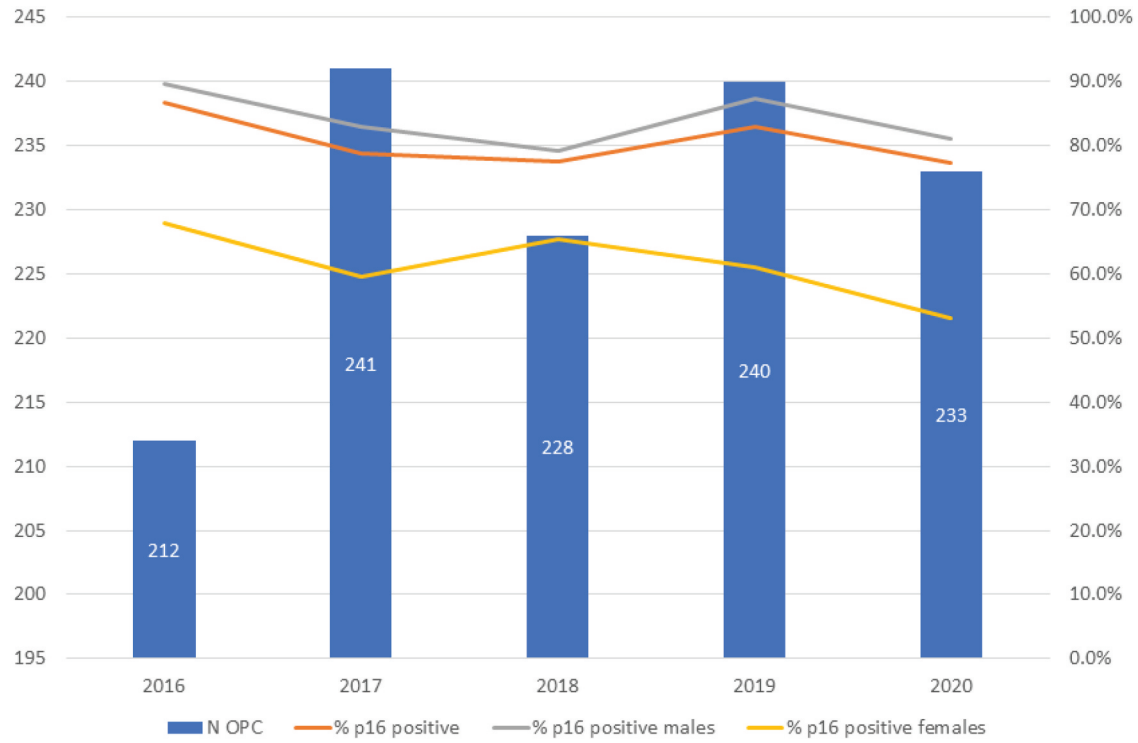

Figure 1. Number of OPC cases identified at 4 regional Canadian cancer centers by year during the observation period of 2016–2020 as well as proportion who were p16 +by year overall and stratified by sex.

Correlates of p16 positivity are shown in Table 2. p16 +patients were, on average, younger than p16 negative patients (p16+ mean age = 61.6 ± 8.9 years [CI 65.1–67.9] vs p16- mean age = 66.5 ± 10.5 years [CI: 61.0–62.1]). Males were more likely to have p16+ OPC (84.0% males vs 60.9% females, $p < .0001$) and this sex difference was consistent across years. p16+ OPC patients were more likely to be never smokers: 75.2% current or prior smokers were p16 +compared with 92.3% nonsmokers, (CI: −0.210 – −0/128, $p < .0001$), but there was no significant association of alcohol consumption to p16 positivity. Among tumors arising in the base of the tongue or tonsil, 82.6% and 84.9% (CI: 81.5%–86.0%], respectively, were p16 +compared with 48.0% (38.3%–57.7%) at other sites ($p < .0001$) and over 80% of stage 1 or stage 2 tumors were p16 +(CI: 82.2%–87.5%). Of 1,148 patients with data on nodal stage, over 80% were nodal stage 1 or 2 (91.9 and 80.6%), while fewer were nodal stage 3 (65,8%) ($p < .0001$). Of 1,134 patients with data on metastasis stage, more than 80% who were metastasis stage 0 (81.1%) at the time of diagnosis were p16 +, while a minority was more advanced.

Multivariable analyses

Multiple logistic regression of sociodemographic characteristics (Table 3) and tumor characteristics (Table 4) confirmed these bivariate associations. As shown in Table 3, p16 +patients were more likely to be male (OR: 3.703, CI: 2.50–5.49) ($p < .0001$), younger (OR: 0.940, CI: 0.92–0.96) and nonsmokers (current smoker OR: 0.139, CI: 0.09–0.22); past smoker OR 0.452, CI: 0.28–0.73). With regard to tumor characteristics (Table 4), p16 positivity was associated with tumor origin in the tonsil or at the base of the tongue (OR: 5.256, 95% CI: 3.249–8.501 and 5.603, 95% CI: 3.432–9.150, respectively) compared with other sites and with early tumor stages compared with stage 4 (stage 1 OR: 2.617, 95% CI: 1.569–4.363 and stage 2 OR: 1.922, 95% CI: 1.288–2.869). Nodal stage 1 was associated with increased odds for p16+.

Discussion

This study presents current data from four large regional Canadian cancer centers representative of the structured national framework for cancer management. It describes the largest cohort to date of Canadian OPC cases, demonstrates that four out of five cases of OPC in adults are now attributable to HPV; 80.6% of squamous cell OPC diagnosed during the 5-year period from 2016 to 2020 were p16+. These findings confirm the current phenotype of this cancer in which patients with HPV positive tumors were more commonly male, younger in age, and were more likely to never have smoked. These findings are also consistent with prior reports that HPV-related OPC occurred more commonly at the base of tongue or tonsil and were generally diagnosed at an early stage.[5] Alcohol consumption was not a statistically significant contributor in either univariable or multivariable analyses. While there is some debate in the literature, our findings align with several studies reporting no statistically significant correlation between p16 overexpression and alcohol consumption. This supports the notion that HPV-driven carcinogenesis may follow a distinct molecular pathway, independent of the carcinogenic effects of alcohol.[26,27] It is unlikely that the disease rates or attributable fraction reported here were influenced by the Canadian HPV vaccination programs which commenced between 2008 and 2016.[28]

Table 2. Sociodemographic and tumor correlates of P16 positivity among OPC cases from Canada 2016–2020.

	P16 Positive (N = 930)	P16 Negative (N = 224)	*p* value[a]
Mean age at diagnosis (SD)	61.6 (8.9) (9.4)	66.5 (10.5)	<.0001
	N (%)	N (%)	
Sex			
Male	827 (84.0%)	158 (16.0%)	<.0001
Female	103 (60.9%)	66 (39.1%)	
Smoking status			
Current	217 (65.0%)	117 (35.0%)	<.0001
Past	376 (82.8%)	78 (17.2%)	
Never	334 (92.3%)	28 (7.7%)	
Missing	3 (30%)	7 (70%)	
Alcohol use			
Current	497 (79.0%)	132 (21.0%)	.0753
Past	74 (76.3%)	23 (23.7%)	
Never	346 (84.0%)	66 (16.0%)	
Missing	13 (81.2%)	3 (18.8%)	
Cancer subsite			
Base of tongue	443 (82.6%)	93 (17.4%)	<.0001
Tonsil	438 (84.9%)	78 (15.1%)	
Other	49 (48.0%)	53 (52.0%)	
Tumor stage			
1	223 (88.1%)	30 (11.9%)	<.0001
2	367 (83.0%)	75 (17.0%)	
3	165 (79.7%)	42 (20.3%)	
4	175 (69.4%)	77 (30.6%)	
Nodal stage			
0	84 (59.2%)	58 (40.8%)	<.0001
1	364 (91.9%)	32 (8.1%)	
2	428 (80.6%)	103 (19.4%)	
3	52 (65.8%)	27 (34.2%)	
Unknown	2 (33.3%)	4 (66.7%)	
Metastasis stage			
0	892 (81.1%)	208 (18.9%)	.1126
1	25 (73.5%)	9 (26.5%)	
Unknown	13 (65.0%)	7 (35.0%)	

[a]Chi square test for significance for categorical variables, Mann-Whitney U for continuous. Statistical testing did not include missing category.

Table 3. Multiple logistic regression analysis: relationship of sociodemographic characteristics and p16 positivity.

	Odds Ratio	95% CI for OR	P-value
Age (years)	0.94	(0.923, 0.957)	<.0001
Male Sex	3.703	(2.499, 5.488)	<.0001
Alcohol (Reference = never drinker)			
Current drinker	0.719	(0.5, 1.035)	0.076
Past drinker	0.787	(0.434, 1.428)	0.4308
Smoking (Reference = never smoker)			
Current Smoker	0.139	(0.086, 0.225)	<.0001
Past Smoker	0.452	(0.279, 0.732)	0.0013

The HPV-attributable fraction of OPC demonstrated herein is notably higher compared with Canadian rates of 25% to 71% noted in earlier studies[8,9,29] and with international reports over the prior decade which indicated a frequency of 52% to 71% in the UK and USA, respectively.[5] The frequency of OPC attributed to high-risk HPV types has risen sharply in the past decades in Canada – continuing the increasing trend observed by Habbous et al. - and other advanced economies such as the USA and Australia/New Zealand, as well as in many other regions around the world.[4,8,18,30 – 33] The 2016 Canadian Cancer Statistics Report documented an increase in annual percentage change of incidence from 1.4% to 3.1% over 2 decades.[7] These increases likely reflect several factors, including increasing awareness, the evolution in diagnostic methods, and the change in screening practices to include p16 screening.[20,34,35]

In 2012, 35% of new HPV-attributable cancers in Canada were OPC, the same proportion as cervical cancer.[7] Canada has a well-established screening program for cervical cancer. However, despite the strong association reinforced here, there are no formal screening programs for HPV-associated OPC, or screening program for HPV in men.[36] The success of cervical screening programs provides promise for the development of screening programs for HPV-associated OPC.[37] Primary prevention of HPV-associated OPC can also be affected through HPV vaccination. Since 2007, all Canadian provinces and territories have had a publicly funded HPV vaccination program in girls. Vaccination for boys was added some 10 years later although uptake rates have been below 70% and catch-up vaccination policies and uptake rates still vary greatly between regions.[38] While the benefit of vaccination in prevention of OPC remains to be formally established,[39] evidence suggests that HPV vaccination is associated with a reduction in HPV-16 exposure in the oropharyngeal cavity.[40] This study provides important data on the HPV attributable fraction of OPC, data which can inform the current discussion regarding the burden of disease and the potential for primary prevention by vaccination.

The study was designed to ensure maximum rigor and objectivity and to avoid the potential of funder bias. The protocol was based on robust scientific rationale, guided by established epidemiological methods, and in consultation with independent academic experts in the field. The statistical plan was defined prior to data collection, minimizing the potential for post-hoc bias. Data were analyzed by an expert team external to the study sponsor and interpretation of the results followed rigorous internal and external scrutiny by the authors. Despite these cautions, there are several limitations that should be noted with this study. While the study included a large pragmatic sample from 4 major Canadian referral centers, data were not available from all provinces. Caution is therefore required in generalizing the findings to the entire Canadian population. However, inclusion of patients from Canadian cancer centers not included

Table 4. Multiple logistic regression analysis: relationship of tumor characteristics to p16 positivity.

Parameters	Odds Ratio	95% CI for OR	*p*-value
Metastasis Stage (M0 = reference)			
Metastasis Stage M1	1.084	(0.458, 2.569)	.674
Metastasis Stage Unknown	0.565	(0.177, 1.798)	.8544
Nodal Stage (N1 = reference)			
Nodal Stage N0	7.313	(4.384, 12.198)	<.0001
Nodal Stage N2	2.420	(1.560, 3.753)	<.0001
Nodal Stage N3	4.996	(2.670, 9.347)	<.0001
Nodal Stage (Unknown vs. N0)	11.164	(1.563, 79.757)	.0162
Cancer Subsite (Other = reference)			
Cancer subsite Base of Tongue	5.256	(3.249, 8.501)	<.0001
Cancer subsite Tonsil	5.603	(3.432, 9.150)	<.0001
Tumor State (T4 = reference)			
Tumor State T1	2.617	(1.569, 4.363)	.0002
Tumor Stage T2	1.922	(1.288, 2.869)	.0014
Tumor Stage T3	1.527	(0.961, 2.427)	.0732

in prior reports[9] increased the representativeness of the Canadian OPC population in this study and strengthens the generalizability of its findings. While information bias due to missingness or misclassification cannot be entirely excluded, strict data extraction protocols and data screening were employed to minimize any such bias. Finally, we must recognize that p16 immunohistochemistry testing varied slightly between sites and is not a perfect surrogate marker for HPV-driven oropharyngeal carcinoma, with a reported sensitivity of 90–95% and specificity of 80–90% depending on the assay protocols, interpretation criteria and intrinsic biology of the tumors. HPV DNA testing may therefore be required in settings where precise determination of HPV status is necessary.

Conclusion

This study, which is the largest cohort of Canadian patients with OPC yet reported, shows that approximately 80% of cases are attributable to HPV. HPV tumors are more likely in men, younger individuals and in those who do not smoke. These findings highlight the increasing prevalence of OPC in Canada, and support gender-neutral HPV vaccination as an important public health strategy to prevent head and neck cancer.

Acknowledgments

We are grateful to the clinical research teams at the participating sites for their support in the study and acknowledge Paul Keown for support with data analysis and manuscript preparation.

Disclosure statement

Voica Racovitan is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock in Merck & Co., Inc., Rahway, NJ, USA.

Elizabeth Goodman is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock in Merck & Co., Inc., Rahway, NJ, USA.

Winson Cheung received support from Merck Canada Inc., Kirkland, QC, Canada. for this study but declares no other competing interests.

Anthony Nichols received support from Merck Canada Inc., Kirkland, QC, Canada. for this study and grant funding from Novartis Canada Inc for other clinical trials. He holds personal stock in Need Oncology but declares no other competing interests.

Lisa Caulley received support from Merck Canada Inc., Kirkland, QC, Canada. for this study but declares no other competing interests.

Sabrina Wurzba received support from Merck Canada Inc., Kirkland, QC, Canada. for this study.

Funding

This study was funded by Merck Canada Inc., Kirkland, QC, Canada.

Notes on contributors

Voica Racovitan is the Director of Global Scientific Strategies for HPV Vaccines at Merck & Co. Inc. USA, specializing in vaccines and related diseases, public health and policy. Elizabeth Goodman is the Director of Outcomes Research at Merck & Co., Inc., Rahway, NJ, USA, driving value evidence generation for early and late-stage vaccine products and clinical and health outcomes research. Winson Cheung is a Professor in the Department of Oncology at the University of Calgary and the Arnie Charbonneau Cancer Institute who is an expert in cancer epidemiology and population health. Anthony C Nichols is an Associate Professor in the Department of Otolaryngology and Director of the Translational Head and Neck Cancer Research Program as well as Chair of the Head and Neck Disease Site team at Western University and the Verspeeten Family Cancer Centre, London, Ontario. Lisa Caulley is an Assistant Professor of Otolaryngology and Head and Neck Surgery at the University of Ottawa who is an expert in the epidemiology and management of factors driving head and neck diseases. Sabrina Wurzba is an Assistant Professor in the Department of Otolaryngology at McGill University whose expertise is in carcinogenesis, cancer progression, metastasis and signaling.

Elizabeth Goodman is a pediatrician, adolescent medicine subspecialist, and epidemiologist. She is an accomplished, mission-driven physician scientist with more than 25 years clinical and observational research experience After a long career in academia, she joined Merck & Co., Inc., Rahway, NJ, USA where she is a currently a Principal Scientist in Outcomes Research, driving evidence generation for early and late stage vaccine products.

Author contributions

Voica Racovitan conceived the study, supported data acquisition, reviewed and interpreted results and revised and edited the manuscript. Elizabeth Goodman guided the analyses, reviewed and interpreted results, and significantly revised and edited the manuscript. The four remaining authors extracted the data and reviewed results of the analyses. All authors reviewed and approved the manuscript and agree to be accountable for the work.

Data sharing

Reasonable requests for data sharing sent to the corresponding author will be reviewed by the publication committee as required to comply with the provincial legislation respecting the privacy and confidentiality requirements under which the data were assembled.

Ethics approval

The study was undertaken in accordance with the World Medical Association Declaration of Helsinki and the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans (TCPS 2). The Research Ethics Board in each of the four participating centers (the Jewish General Hospital, Montreal; the Ottawa Hospital, Ottawa, Ontario; the London Health Sciences Centre, London, Ontario; and the Tom Baker Cancer Centre, Calgary, Alberta) waived the requirement for individual informed patient consent due to minimal risk, approving this retrospective chart review.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–1953. doi: 10.1002/ijc.31937.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. doi: 10.3322/caac.21492.
3. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92. doi: 10.1038/s41572-020-00224-3.
4. Damgacioglu H, Sonawane K, Zhu Y, Li R, Balasubramanian BA, Lairson DR, Giuliano AR, Deshmukh AA. Oropharyngeal cancer incidence and mortality trends in all 50 states in the US, 2001–2017. JAMA Otolaryngol Head Neck Surg. 2022;148(2):155–165. doi: 10.1001/jamaoto.2021.3567.
5. Lechner M, Liu J, Masterson L, Fenton TR. Hpv-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022;19(5):306–327. doi: 10.1038/s41571-022-00603-7.
6. Bruno L, Albero G, Serrano B, Mena M, Collado J, Gomez D. CO/IARC information centre on HPV and Cancer (HPV information centre). Human Papillomavirus and Related Diseases (in) Canada: ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre); 2023.
7. Government of Canada. Canadian cancer statistics: special topic: HPV associated cancers 2016. Canadian cancer society. 2016. https://publications.gc.ca/collections/collection_2016/statcan/CS2-37-2016-eng.pdf.
8. Habbous S, Chu KP, Qiu X, La Delfa A, Harland LT, Fadhel E, Hui A, Perez-Ordonez B, Weinreb I, Liu F-F, et al. The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a comprehensive cancer centre. Cancer Epidemiol. 2013;37(6):820–829. doi: 10.1016/j.canep.2013.09.011.
9. Habbous S, Chu KP, Lau H, Schorr M, Belayneh M, Ha MN, Murray S, O'Sullivan B, Huang SH, Snow S, et al. Human papillomavirus in oropharyngeal cancer in Canada: analysis of 5 comprehensive cancer centres using multiple imputation. CMAJ. 2017;189(32):E1030–E1040. doi: 10.1503/cmaj.161379.
10. National Cancer Institute. PDQ oropharyngeal cancer treatment (adult). Bethesda (MD): National Cancer Institute; 2023. https://www.cancer.gov/types/head-and-neck/patient/adult/oropharyngeal-treatment-pdq.
11. Høxbroe Michaelsen S, Grønhøj C, Høxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: a systematic review and meta-analysis of 1366 patients. Eur J Cancer. 2017;78:91–102. doi: 10.1016/j.ejca.2017.03.006.
12. Canadian Cancer Statistics: Special topic. HPV associated cancers 2016 produced by Canadian cancer society, statistics Canada, public health agency of Canada, provincial/territorial cancer registries. cancer.ca/statistics.
13. Brianti P, De Flammineis E, Mercuri SR. Review of hpv-related diseases and cancers. New Microbiol. 2017;40(2):80–85.
14. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24(Suppl 1):SS4–S15. doi: 10.1016/j.vaccine.2005.09.054.
15. Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomarker Prev. 2003;12(6):485–490.
16. Della Fera AN, Warburton A, Coursey TL, Khurana S, McBride AA. Persistent human papillomavirus infection. Viruses. 2021;13(2):321. doi: 10.3390/v13020321.
17. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180–e190. doi: 10.1016/S2214-109X(19)30488-7.
18. Alemany L, Felsher M, Giuliano AR, Waterboer T, Mirghani H, Mehanna H, Roberts C, Chen Y-T, Lara N, Lynam M, et al. Oral human papillomavirus (HPV) prevalence and genotyping among healthy adult populations in the United States and Europe: results from the PROGRESS (PRevalence of Oral HPV infection, a global assessment) study. EClinicalMedicine. 2025;79:103018. doi: 10.1016/j.eclinm.2024.103018.
19. McBride AA. Oncogenic human papillomaviruses. Philos Trans R Soc Lond B Biol Sci. 2017;372(1732):20160273. doi: 10.1098/rstb.2016.0273.
20. Michaud DS, Langevin SM, Eliot M, Nelson HH, Pawlita M, McClean MD, Kelsey KT. High-risk HPV types and head and neck cancer. Int J Cancer. 2014;135(7):1653–1661. doi: 10.1002/ijc.28811.
21. Hibbert J, Halec G, Baaken D, Waterboer T, Brenner N. Sensitivity and specificity of human papillomavirus (HPV) 16 early antigen serology for HPV-Driven oropharyngeal cancer: a systematic literature review and meta-analysis. Cancers (Basel). 2021;13(12):1–18.
22. Ndon S, Singh A, Ha PK, Aswani J, Chan JY, Xu MJ. Human papillomavirus-associated oropharyngeal cancer: global epidemiology and public policy implications. Cancers (Basel). 2023;15(16):4080. doi: 10.3390/cancers15164080.
23. Choi SE, Choudhary A, Huang J, Sonis S, Giuliano AR, Villa A. Increasing HPV vaccination coverage to prevent oropharyngeal cancer: a cost-effectiveness analysis. Tumour Virus Res. 2022;13:200234. doi: 10.1016/j.tvr.2021.200234.
24. Wasserman JK, Rourke R, Purgina B, Caulley L, Dimitroulakos J, Corsten M, Johnson-Obaseki S. HPV DNA in saliva from patients with SCC of the head and neck is specific for p16-positive oropharyngeal tumours. J Otolaryngol Head Neck Surg. 2017;46(1):3. doi: 10.1186/s40463-016-0179-6.
25. Lewis JS, Thorstad WL, Chernock RD, Haughey BH, Yip JH, Zhang Q, El-Mofty SK. p16 positive oropharyngeal squamous cell carcinoma: an entity with a favorable prognosis regardless of tumor HPV status. Am J Surg Pathol. 2010;34(8):1088–1096. doi: 10.1097/PAS.0b013e3181e84652.
26. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407–420.
27. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944–1956. doi: 10.1056/NEJMoa065497.
28. Goyette A, Yen GP, Racovitan V, Bhangu P, Kothari S, Franco EL. Evolution of public health human papillomavirus immunization

programs in Canada. Curr Oncol. 2021;28(1):991–1007. doi: 10.3390/curroncol28010097.
29. Nichols AC, Palma DA, Dhaliwal SS, Tan S, Theuer J, Chow W, Rajakumar C, Um S, Mundi N, Berk S, et al. The epidemic of human papillomavirus and oropharyngeal cancer in a Canadian population. Curr Oncol. 2013;20(4):212–219. doi: 10.3747/co.20.1375.
30. Chen AM. The epidemic of human papillomavirus virus-related oropharyngeal cancer: current controversies and future questions. Infect Agent Cancer. 2024;19(1):58. doi: 10.1186/s13027-024-00616-0.
31. Arboleda LPA, de Souza DL, Mendonça E, Silva DR, Curado MP. Oropharyngeal cancer incidence and trends in Brazil. Cancer Epidemiol Biomarker Prev. 2025; OF1–OF9. doi: 10.1158/1055-9965.EPI-24-0863.
32. Lorenzoni V, Chaturvedi AK, Vignat J, Laversanne M, Bray F, Vaccarella S. The current burden of oropharyngeal cancer: a global assessment based on GLOBOCAN 2020. Cancer Epidemiol Biomarker Prev. 2022;31(11):2054–2062. doi: 10.1158/1055-9965.EPI-22-0642.
33. Wittekindt C, Wagner S, Bushnak A, Prigge ES, von Knebel Doeberitz M, Würdemann N, Bernhardt K, Pons-Kühnemann J, Maulbecker-Armstrong C, Klussmann JP. Increasing incidence rates of oropharyngeal squamous cell carcinoma in Germany and significance of disease burden attributed to human Papillomavirus. Cancer Prev Res (Phila). 2019;12(6):375–382. doi: 10.1158/1940-6207.CAPR-19-0098.
34. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, 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.
35. Venuti A, Paolini F. HPV detection methods in head and neck cancer. Head Neck Pathol. 2012;6(Suppl 1):S63–74. doi: 10.1007/s12105-012-0372-5.
36. Osazuwa-Peters NN, Davies L. Population trends and long-term outlook for oropharyngeal cancer: have we found a silver lining? JAMA Otolaryngol Head Neck Surg. 2022;148(2):97–98. doi: 10.1001/jamaoto.2021.3786.
37. D'Souza G, Clemens G, Troy T, Castillo RG, Struijk L, Waterboer T, Bender N, Pierorazio PM, Best SR, Strickler H, et al. Evaluating the utility and prevalence of HPV biomarkers in oral rinses and serology for HPV-related oropharyngeal cancer. Cancer Prev Res (Phila). 2019;12(10):689–700. doi: 10.1158/1940-6207.CAPR-19-0185.
38. Canadian Partnership Against Cancer. Opportunities to increase HPV vaccination. 2023. https://www.partnershipagainstcancer.ca/topics/hpv-immunization-policies/increase-hpv-vaccination/.
39. Nielsen KJ, Jakobsen KK, Jensen JS, Grønhøj C, Von Buchwald C. The effect of prophylactic HPV vaccines on oral and oropharyngeal HPV infection—A systematic review. Viruses. 2021;13(7):1339. doi: 10.3390/v13071339.
40. Castillo A, Osorio JC, Fernández A, Méndez F, Alarcón L, Arturo G. Effect of vaccination against oral HPV-16 infection in high school students in the city of Cali, Colombia. Papillomavirus Res. 2019;7:112–117.