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Title	An analysis of the temporal, age and gender trends in human papillomavirus virus (HPV)-related non-cervical cancers in Alberta, Canada
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Reviewer	Wang Feng
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General comments	<p>This manuscript aims to describe the incidence trends of HPV-related cancers in Alberta from 1975 to 2009 using data from the Alberta Cancer Registry. It is interesting and important to report the trends in HPV-related cancers from an area of relative high HPV infection rate. Although it is a well-prepared manuscript, two issues should be addressed.</p> <ol style="list-style-type: none"> 1. The authors suggested that the increased incidences of oropharyngeal and anal cancers are contributed to the HPV infection. But there is no evidence directly from this manuscript supported this point. The trends might be contributed to the improvement of diagnosis. It's a better way to do an age-period-cohort modeling to discuss the potential reasons. 2. The case number of OPC in men under 35 years-old was few in each diagnosis years-group. The increase or decrease of one case might distort the APC dramatically. It's better to list the actual number of the age groups with few cases by calendar year or years-group as supplementary which may help the audience make their own judgment.
Author response	<p>1. Comment #1 – “We have not provided direct evidence of HPV infection in the tumours.”</p> <ul style="list-style-type: none"> • The aim of this paper was not to prove causality, but rather to evaluate the trends in incidence of HPV-associated malignancies. The association between HPV and cervical cancer has been well known for many decades, but its association with other cancers (anus, penis, vagina, vulva and oropharyngeal) has already recently been defined in the literature(1). Our epidemiologic study focused specifically on evaluating age-specific trends of all HPV associated malignancies, which to date has not previously been reported in Canada. • It is important to note that the two previous Canadian epidemiologic studies examining only HPV-associated oropharyngeal cancers did not evaluate tissue specimens(2,3). • Given the scope our of study, evaluating trends in incidence of HPV-associated malignancies over 40 years, evaluating causality would be unfeasible, as there are no practical means of obtaining tissue dating over this time frame, due to administrative restructuring, regulation changes etc. Therefore, under the circumstances, we believe it is appropriate to make an inference regarding HPV-association of these cancers, based on the available published information and the findings of our research. In the manuscript, we are clear about this limitation and have acknowledged in our discussion that, “A weakness of this study is the inability to histologically confirm definitive HPV status in tumours. Although we included tumour sites with known HPV-association, it is possible that we have either over- or under-estimated the incidence of true HPV-associated cancers”(page 5, 2nd paragraph under discussion). <p>2. Comment#2 – “The manuscript was not novel enough.”</p> <ul style="list-style-type: none"> • Our study is the first to comprehensively evaluate age-specific trends of all HPV-associated malignancies in any Canadian province. While there have been individual papers about trends in oropharyngeal cancer in British Columbia² and nationally³, no other paper has characterized the changing incidence of all HPV-associated malignancies. Similar epidemiologic studies of the incidence of other HPV-associated malignancies (anal canal, vaginal and vulvar, penile and oropharyngeal cancers) - each reported separately - from various Western countries have been published in a number of other high impact journals(4-10), but no publication has address all HPV-associated malignancies collectively. • In addition to comprehensively examining all HPV-associated malignancies, our paper differs from the two previous Canadian epidemiologic studies cited above in that we evaluated incidence over the longest time interval (1975-2009). The British Columbia study examined trends in only oropharyngeal versus oral cavity cancers between 1980 and 2006², while the second group evaluated trends only in HPV-associated oropharyngeal cancers nationally between 1992 and 2009(3). • Finally, we agree with the reviewers that HPV vaccination is currently a topic of great importance and significant debate within the public health forum. We strongly feel that our finding that the incidence of anal canal cancer and oropharyngeal cancer is rising in younger females and males is novel, interesting, and topical, and could help inform the ongoing debate, and therefore merits the broad dissemination which CMAJ can uniquely provide. <p>We thank the reviewers and editorial staff for their thorough review and comments, and we thank you in advance for your re-consideration of our manuscript.</p> <p>Kind Regards,</p> <p>Lorraine Shack</p>