Author's response to reviews

Title: Population-based incidence trends of oropharyngeal and oral cavity cancers by sex among the poorest and underprivileged populations

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Author's response to reviews:

We thank the reviewers for their comments. Please find below in a point-by-point fashion: the reviewer comment, our response and the actual text alteration and location where the change occurs.

Reviewer's report (R1): Pamela Minicozzi

1) Abstract. “It is absent”.
Response: Our apologies. There was some difficulty with the uploading of separate documents to the website. The abstract did not fuse with the rest of the text. We have added the abstract to the revision on pages 4 and 5 of the current upload.
Text alteration:

“ABSTRACT
Introduction
Oral cancer is an important health issue, with changing incidence in many countries. Oropharyngeal cancer (OPC, in tonsil and oropharyngeal areas) is increasing, while oral cavity cancer (OCC, other sites in the mouth) is decreasing. There is the need to identify high risk groups and communities for further study and intervention. The objective of this study was to determine how the incidence of OPC and OCC varied by neighbourhood socio-economic status (SES) in British Columbia (BC), including the magnitude of any inequalities and temporal trends.
Methods
ICDO-3 codes were used to identify OPC and OCC cases in the BC Cancer Registry from 1981-2010. Cases were categorized by postal codes into SES quintiles (q1-q5) using VANDIX, which is a census-based, multivariate weighted index based on neighbourhood average household income, housing tenure,
educational attainment, employment and family structure. Age-standardized incidence rates were determined for OPC and OCC by sex and SES quintiles and temporal trends were then examined.

Results

Incidence rates are increasing in both men and women for OPC, and decreasing in men and increasing in women for OCC. This change is not linear or proportionate between different SES quintiles, for there is a sharp and dramatic increase in incidence according to the deprivation status of the neighbourhood. The highest incidence rates in men for both OPC and OCC were observed in the most deprived SES quintile (q5), at 1.7 times and 2.2 times higher, respectively, than men in the least deprived quintile (q1). For OPC, the age-adjusted incidence rates significantly increased in all SES quintiles with the highest increase observed in the most deprived quintile (q5). Likewise, the highest incidence rates for both OPC and OCC in women were observed in the most deprived SES quintile (q5), at 2.1 times and 1.8 times higher, respectively, than women in the least deprived quintile (q1).

Conclusion

We report on SES disparities in oral cancer, emphasizing the need for community-based interventions that address access to medical care and the distribution of educational and health promotion resources among the most SES deprived communities in British Columbia.

2) Background: “SES: could the authors explain what types of indicators were included in it?”

Response: We have added a description of the variables that are included in the VANDIX algorithm that are used for stratifying cases for SES. This is shown on page 6.

Text alteration:

“The objective of our paper is to analyze the relationship between neighbourhood SES status (using a composite index with multiple socioeconomic features including income, housing, education, family demographics and employment obtained from both census data and local health surveys)[22, 23] … ’

3) Background: “OPC should be defined before using it.”

Response: We have added a definition of OPC in the early background on page 6.

Text alteration:

“In our previous research in British Columbia (BC), we found that the incidence is increasing among both men and women for oropharyngeal cancers (OPC, in tonsil and oropharyngeal areas), and decreasing among men for oral cavity cancer (OCC, other sites in the mouth)[18].”

4) Background: “Sentence “These observed....at these different sites” needs a reference”.


Response: Two references are added on page 6.

Text alteration:

“…These observed differences were attributed to differences in the aetiology of oral cancers at these different sites[4, 12] ”

5) Methods – Study population: “ICD0-3 codes like 8050, 8076, and so on are not histology codes but morphology codes.”
Response: We agree with this comment and have made the appropriate change on page 7.

Text alteration:

“Morphology codes for selected cases included if they were suggestive of invasive characteristics: 80003, 80103, 80203, 80213, 80323, 80333, 80503, 80513, 80523, 80703, 80713, 80723, 80733, 80743, 80753, 80763, 80833, 80943 and 81233.”

6) Methods – Study population: “Only some listed ICDO-3 codes showed the code for the behaviour (3): please, harmonise.”
Response: Codes ending with (3) indicate invasive characteristics and this is explained on page 7.

Text alteration:

“Morphology codes for selected cases included if they were suggestive of invasive characteristics: 80003, 80103, 80203, 80213, 80323, 80333, 80503, 80513, 80523, 80703, 80713, 80723, 80733, 80743, 80753, 80763, 80833, 80943 and 81233.” (Please see above comment 5.)

7) Methods – Study population: “Please, explain or define the following variables: “anatomic site”, “histology”, “tumour stage”, “age” and “sex” (Ex: sex –men, women).”
Response: These variables are defined on page 7.

Text alteration:

“Registry data were collected on cancer characteristics including anatomic site (location of the tumour in the head and neck region), histology (morphology of the tumour), date of diagnosis (when the tumour diagnosis was first made), and tumour stage (extent and severity of the cancer based on tumour size, lymph node involvement and evidence of metastasis); and patient demographics including name, age at the time of tumour diagnosis, and sex or gender.”

8) Methods – Study population: “Additionally, please change “age *at diagnosis*” and add “ethnicity –definition.”
Response: We have made the appropriate changes and added information about ethnicity on page 7. Text addition for “age at diagnosis” is shown above in point 7.

Text alteration:
“Since ethnicity and place of birth are not recorded in the BCCR, South Asian (SA) and Chinese cases were identified from the selected cases using previously generated ethnic surname lists[25, 26]. When surnames of cases were found to match the ethnic surname list, these names were then manually verified by SA and Chinese researchers.”

9) Results: "The authors analyzed data from 1981 to 2010, but they talked about the ICDO-3 only or tumour stage in general. Could the authors please clarify?"
Response: Table 1 describes demographics and characteristics of our selected cases. Detailed analysis of temporal trends in stage at diagnosis according to SES status and its relationship with cancer survival are beyond the scope of this article and is included in another paper.

10) Methods – Statistical analysis: “Please add a reference for the statistical tests used and the indicators estimated in the analyses (Student’s t-test, ANOVA, AAIR, etc.).”
Response: References are added on page 8.
Text alteration:
“…Differences in demographic, clinical and pathologic characteristics between OPC and OCC were tested for significance using Student’s t-test, Pearson’s chi-square test and one-way ANOVA[27]. OPC and OCC age-adjusted incidence ratios (AAIR) and age-specific incidence rates (ASIR) with 95% confidence intervals (CI) were calculated separately by neighbourhood deprivation quintiles[28].”

11) Methods – Statistical analysis: “Could the authors please clarify why they used the 1991 BC general population to standardize the incidence rates knowing that the cases under study were diagnosed in 1981-2010?”
Response: Although rates can be standardized to any population, we chose to standardize them to the BC general population of 1991 because this was the midpoint of the study period and was previously used in our earlier published paper. (Reference: Auluck A, Hislop G, Bajdik C, Poh C, Zhang L, Rosin M: Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer 2010, 116(11): 2635-2644.) This is stated on page 8.

12) Results – ASIR in the most deprived quintile (q5): “Page 8, last paragraph: please modify from “Figure 3A” to “Figure 4A”.”
Response: Thank you for this correction. The change has been made on page 11.
Text alteration:
“…and 1.97 (95% CI, 0.43-4.97) for 75 years and older (Figure 4A).”

13) Results – ASIR in the most deprived quintile (q5): “Please rephrase the sentence “the highest increased in OPC......55-64 years.”
Response: This sentence is rephrased on page 11.

Text alteration:
“The highest ASIRs for both OPC and OCC were seen in recent years (2006-2010). The ages of highest ASIR differed for OPC and OCC, being ages 55-64 years and 75 years and older, respectively.”

14) Results – ASIR in the most deprived quintile (q5): “Page 9, line 3: “years...and older for OCC”, the sentence is not totally true. Please rephrase.”
Response: This sentence has been changed and the text alteration is shown above in point 13.

15) Results – Temporal trends in AAIR for OPC and OCC by SES quintile: “Page 10, line 5. Please, rephrase the sentence “OCC, men...”
Response: This sentence has been clarified on page 12.

Text alteration:
“The incidence of OCC for men in q5 showed a peak in 1986-1990, then a plateau followed by a decreased incidence around 1996-2000. However, the incidence of OCC for women rates gradually increased and approached that observed in men in 2006-10.”

16) Results and Discussion: “The authors in Table 1 showed the descriptive analyzed referring to cases under study, by tumor stage and ethnicity. Nothing is done in the Results and said in the Discussion to support and justify this data. It should be interesting including and comment on trends by SES quintile and tumour stage, for example.”
Response: We intended to only provide a description of our selected cases. A detailed analysis of tumor stage and ethnicity was not in the objectives of this paper but will be the focus of another article. Please see response to comment 9 above.

17) Results and Discussion: “And what about incidence by ethnicity in relation to SES?”
Response: Again, this was not part of the objectives of this paper but will be the focus of another article.

18) Tables: “The Tables should be self explanatory. Thus, meaning of AAIR, SES, OPC, OCC, and so on have to be clarify in the footnotes or, directly, in the titles of all figures. Please include axes titles in Figures 1-4. Please harmonise colours in Figure 4: blue and red should show the same thing in all sub-figures.”
Response: Changes to the footnotes and legends have been made more informative; the colors in the sub-figures have been harmonized; and title axes have been included.

Reviewer’s report (R2): Antonio Boing
1) Background: “In the first paragraph it is not clear why the authors emphasized
the ‘health services dimension’ of the inequalities in health. The socioeconomic differences in the exposure to risk factors should be highlighted as well.”

Response: Additional references and discussion are given on pages 5 and 6.

Text alteration:

“Disparities in incidence have been observed at multiple scales, varying between global regions[3-5], within countries[6, 7], and between neighbourhoods[8]. It is known that socioeconomic inequalities persist in cancer incidence[9] but little recognition has been given to the effects of socioeconomic status (SES) on the risk of developing oral cancers[10], a cancer showing significant change in trajectory worldwide[11-14]. A study from Scotland suggested that the risk for oral cancer is higher among people living in deprived neighbourhoods (OR = 4.66), a finding mainly attributed to higher rates of smoking (OR = 15.53)[6]. Another study from Canada suggested that SES status affects incidence of oral cancer, with higher rates reported among people with lower median income, less than 8th grade education and visiting dentists less than once a year[15]. Although several studies have shown associations between SES and oral cancer risk, none have shown an independent effect of SES on risk for developing oral cancer. Conway et al[16] conducted a systematic review and meta-analysis exploring the relationship between socio-economic inequalities and oral cancer risk. His research suggested that in comparison to populations with higher SES, the risk of developing oral cancer was 1.85 times higher with lower educational attainment, 1.84 times higher with low occupational social class and 2.41 times higher with lower income. Further, he suggested that lower SES was significantly associated with increased oral cancer risk in high and lower income countries, which remained after adjusting for potential behavioural confounders. However, after controlling for age, sex, smoking, and alcohol consumption, SES was no longer a significant variable[6, 7, 17]. Therefore, it is important to ascertain the risk of oral cancers according to SES status.”

2) Background: “In the second paragraph the authors asserted that “Studies on SES disparities in oral cancer research are emerging from the European Union[12], Scotland[13], California (US)[11], and Canada[14, 15]”. Actually, this relationship has been analyzed for decades. Furthermore, there are studies on the subject in many other countries.- I suggest the authors to emphasize the socioeconomic disparities in oral cancer research. What do the articles have shown? What is not known yet?

Response: Data and literature related to socio-economic disparities in oral cancer research is added on pages 5 and 6.

Text alteration:

“Disparities in incidence have been observed at multiple scales, varying between global regions[3-5], within countries[6, 7], and between neighbourhoods[8]. It is known that socioeconomic inequalities persist in cancer incidence[9] but little recognition has been given to the effects of socioeconomic status (SES) on the risk of developing oral cancers[10], a cancer showing significant change in trajectory worldwide[11-14]. A study from Scotland suggested that the risk for
oral cancer is higher among people living in deprived neighbourhoods \((\text{OR} = 4.66)\), a finding mainly attributed to higher rates of smoking \((\text{OR} = 15.53)\)[6].

Another study from Canada suggested that SES status affects incidence of oral cancer, with higher rates reported among people with lower median income, less than 8th grade education and visiting dentists less than once a year[15]. Although several studies have shown associations between SES and oral cancer risk, none have shown an independent effect of SES on risk for developing oral cancer. Conway et al[16] conducted a systematic review and meta-analysis exploring the relationship between socio-economic inequalities and oral cancer risk. His research suggested that in comparison to populations with higher SES, the risk of developing oral cancer was 1.85 times higher with lower educational attainment, 1.84 times higher with low occupational social class and 2.41 times higher with lower income. Further, he suggested that lower SES was significantly associated with increased oral cancer risk in high and lower income countries, which remained after adjusting for potential behavioural confounders. However, after controlling for age, sex, smoking, and alcohol consumption, SES was no longer a significant variable[6, 7, 17]. Therefore, it is important to ascertain the risk of oral cancers according to SES status.

3) Methods – Study population: “More details on the BC cancer registry should be given (pros and cons).- Some background on the region of BC would be good – e.g population, size, socioeconomic status.”

Response: Information about the BC population and registry is added on pages 6 and 7.

Text alteration:
“Our study was conducted in the province of BC, Canada, which had a population of 4,113,487 persons in 2006. In BC, cancer is a reportable disease to the population-based BC cancer registry (BCCR). The BCCR, established in 1969, maintains a high quality database, consistently recording more than 85% of all cancer cases in the province and has well-established linkages with BC Vital Statistics database to capture death data. The quality of data is found to be acceptable for inclusion in the North American Association of Central Cancer Registries (NAACCR) and International Agency for Research on Cancer (IARC).”

4) Methods – Statistical analysis: “AAIR is age-adjusted incidence rate, isn’t it? The text must be corrected.”

Response: We calculated both age-adjusted incidence rates (AAIR) and age-specific incidence rates (ASIR), as described on page 8.

Text alteration:
“OPC and OCC age-adjusted incidence ratios (AAIR) and age-specific incidence rates (ASIR) with 95% confidence intervals (CI) were calculated separately by neighbourhood deprivation quintiles[23].”

5) Methods – Statistical analysis: “Why in order to calculate the temporal trend the AAIRs were grouped into 5-year intervals? Why didn’t the authors analyze year by year? Actually, the authors mentioned “annual percent change”.”
Response: The sample size was not large enough to calculate rates annually, especially among OPC in females. Therefore, temporal trend analysis used 5 year aggregates.

6) Methods – Study population: “How many individuals did not have a permanent residence address in the dataset? And what about other information?”

Response: The BC Cancer Registry maintains a high quality database, which is described on page 6. However, we did not select cases diagnosed prior to 1981 because the data on permanent residence address was often missing information over this time period. However, after 1980 only 3.9% of cases had missing residence information. Missing information for tumour stage is already mentioned in Table 1. Tumour stage information is mainly missing for cases not referred to the BC Cancer Agency for treatment. Completeness of accuracy of BC Cancer Registry database is mentioned in point 3.

7) Methods – Study population: “Primary tumours of the external lip, salivary glands and nasopharynx have different etiology when compared to other OCC and OPC cancers. What is the implication of analysing all these tumours together?”

Response: We had excluded these cancers from our analysis, but had not clearly identified this step in the original version of the paper. This is reflected in the ICDO-3 codes used for our eligibility criteria. External lip cancers are mainly caused by sunlight, whereas Epstein Barr Virus plays a role in the development of nasopharyngeal cancers and salivary glands tumors. OCC are caused by alcohol and tobacco consumption, while OPC are caused by HPV infection. If we group all these tumors together we would not be able to see incidence trends for head and neck cancers at different subsites which would truly reflect changes in risk behaviours, such as smoking cessation or an increasing prevalence of HPV infection. Text changes are shown on page 7.

Text alteration:

“Site codes were then used for etiological clustering of cases into OPC and OCC excluding tumors at external lips (COO-C001), salivary glands (C079, C080), nasopharynx (C119), hypopharynx (C139), as described in our earlier papers[12, 19], since these cancers are associated with other etiological factors.”.

8) Methods – Neighbourhood socioeconomic status: “It should be clear that the 2006 Census Dissemination Area data was used to reflect the neighbourhood SES over the total study period.”

Response: We clearly state this on page 8 and mention it as a limitation in the Discussion on page 17.

Text alteration:

(on page 8): “The Vancouver Area Neighbourhood Deprivation Index (VANDIX)[22] score was calculated for each 2006 Census Dissemination Area (DA) (N=6,900)”.

(on page 17): “Finally, there may be some inherent error in our use of the
VANDIX index for it contained variables from the 2006 census which may change over time and not accurately reflect the neighbourhoods over the total study period.”

9) Results: “The results described in the paragraph 2 could be included in the Table 1.”
Response: We intended in this paragraph to give the reader a brief description of the study sample as an introduction to the paper. Although not necessary, it does provide a quick synopsis of key information of the study population.

10) Discussion: “The link between increase in incidence of OPC and increase prevalence of HPV is not sufficiently explored and justified (paragraph 2).”
Response: As with many other cancer registries, the BC Cancer Registry does not record HPV status; this is mentioned as a limitation on page 16. We therefore cannot comment further on the prevalence of HPV in these tumours.
Text alteration:
“Our study has limitations similar to other registry-based studies. BCCR does not record parameters to determine individual SES, nor does it record a patient’s HPV status or risk behaviours such as smoking or alcohol consumption.”

11) Discussion: “The mediators of the association between SES and H&N cancer should be highlighted in the discussion.”
Response: As with many other cancer registries, the BC Cancer Registry does not record education, employment, social status or income status of its registered cases. This limits our ability to elaborately discuss these potential associations in the discussion of the results. Although VANDIX incorporates all the SES characteristics which are associated with tumor outcomes which is a major strength of our study; individual components of SES measures are not proven to be reliable predictors of outcomes and therefore not discussed in detail. However, we provide brief background of relevant literature on pages 5 and 6.

12) Discussion: “The authors should include the potential role of the social services in the trends observed.”
Response: We have added the potential role of less access to social services in the discussion about social determinants of health on page 15.
Text alteration:
“They may also have less access to social services,”

13) Background and Discussion: “The phrase “new developing technologies such as optical screening devices for detection of OCC need to include the poor and underprivileged communities to obtain maximum benefit” is not clear. Why not emphasize the importance of policies that aim to reduce smoking, drinking, access to health professionals, etc. - My suggestion is to improve the literature review. There are many important articles on the subject that were not included in the “Background” and “Discussion”.”
Response: We included additional articles in the Background on pages 5 and 6,
and Discussion on page 16.

Text alteration:

(on pages 5 and 6): “Disparities in incidence have been observed at multiple scales, varying between global regions[3-5], within countries[6, 7], and between neighbourhoods[8]. It is known that socioeconomic inequalities persist in cancer incidence[9] but little recognition has been given to the effects of socioeconomic status (SES) on the risk of developing oral cancers[10], a cancer showing significant change in trajectory worldwide[11-14]. A study from Scotland suggested that the risk for oral cancer is higher among people living in deprived neighbourhoods (OR = 4.66), a finding mainly attributed to higher rates of smoking (OR = 15.53)[6]. Another study from Canada suggested that SES status affects incidence of oral cancer, with higher rates reported among people with lower median income, less than 8th grade education and visiting dentists less than once a year[15]. Although several studies have shown associations between SES and oral cancer risk, none have shown an independent effect of SES on risk for developing oral cancer. Conway et al[16] conducted a systematic review and meta-analysis exploring the relationship between socio-economic inequalities and oral cancer risk. His research suggested that in comparison to populations with higher SES, the risk of developing oral cancer was 1.85 times higher with lower educational attainment, 1.84 times higher with low occupational social class and 2.41 times higher with lower income. Further, he suggested that lower SES was significantly associated with increased oral cancer risk in high and lower income countries, which remained after adjusting for potential behavioural confounders. However, after controlling for age, sex, smoking, and alcohol consumption, SES was no longer a significant variable[6, 7, 17]. Therefore, it is important to ascertain the risk of oral cancers according to SES status.”

(on page 16); “Although there is a need to develop targeted prevention approaches for the deprived neighbourhoods it’s important to also address the broader social determinants of health and address the underlying causes of inequitable distribution of wealth and resources which influences the lifestyle and risk behaviours increasing their risk for developing oral cancers[37]. Poor clients needs to be empowered and encouraged to participate in health promotion and prevention services for reducing smoking and alcohol consumption, encouraged to adopt a healthy lifestyle and efforts should be made to improve their access to health care facilities[2, 38]. We need an integrated approach and political action for framing the social and health polices to tackle the root causes of disadvantage.”

14) Discussion: “What public policies could reduce inequalities in the incidence of oral cancer?”

Response: We have included further discussion about social determinants of heath and action of health policies on page 16.

Text alteration:

“Although there is a need to develop targeted prevention approaches for the
deprived neighbourhoods it’s important to also address the broader social determinants of health and address the underlying causes of inequitable distribution of wealth and resources which influences the lifestyle and risk behaviours increasing their risk for developing oral cancers[37]. Poor clients needs to be empowered and encouraged to participate in health promotion and prevention services for reducing smoking and alcohol consumption, encouraged to adopt a healthy lifestyle and efforts should be made to improve their access to health care facilities[2, 38]. We need an integrated approach and political action for framing the social and health polices to tackle the root causes of disadvantage.”