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ORIGINAL RESEARCH

Cigarette Smoking and Alcohol Ingestion as Risk Factors for Laryngeal Squamous Cell Carcinoma at Kenyatta National Hospital, Kenya

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Abstract: Laryngeal squamous cell carcinoma (SCC) is strongly linked to cigarette smoking. It is estimated to account for more than 70% of laryngeal SCCs and up to 89% in combination with alcohol. We wished to determine the prevalence of cigarette smoking and alcohol ingestion among patients with laryngeal squamous cell carcinoma and estimate risk attributed to cigarette smoking and alcohol ingestion. Fifty experimental group patients and fifty controls were recruited of matching age, sex and region of residence. History of smoking and alcohol intake was taken and analyzed to estimate the relative strengths of these exposures. Cessation of smoking was associated with reduced risk of SCC. Smokers had increased risk compared to controls. Those who smoked only had a higher glottic cancer risk. Those who smoked and drank alcohol had a higher supraglottic cancer risk. Being a current smoker and long duration of smoking were independent risk factors of laryngeal SCC.

Keywords: cigarette smoking, risk factors, laryngeal squamous cell carcinoma (SCC)

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Introduction

In human history, tobacco inhalation dates as far back as 5000 BC when it was used for various religious, medicinal and later recreational purposes, though no specific mention is made about it in the bible.[1] The most common mode of tobacco inhalation is cigarette smoking.[1] In the International Agency for Research on Cancer (IARC) monograph, it was concluded that there was sufficient evidence that the habit could cause not only lung cancer, but also cancers of the upper aerodigestive tract including the larynx, pharynx and upper esophagus.[1]

In Kenya, cancer as a disease ranks third as a cause of death after infectious and cardiovascular diseases.[2] Currently Kenya has no reliable cancer registry and data availability is scanty and mainly hospital based. It was reported that in 2005, approximately 18,000 deaths were due to cancer, with most victims under the age of 70 years.[2] Mutuma and colleagues[2] found that head and neck cancer, of which laryngeal cancer was most common, is the leading cancer in males at 14.8% in Kenya, and is third among females after cancer of the breast and cervix. Furthermore, there seems to be a steady rise in the incidence of head and neck cancer, as evidenced by trends documented by Mutuma and colleagues.[2] Onyango and colleagues[3,4] reported a 39% prevalence of laryngeal cancer among patients with head and neck cancer (n = 793) followed by cancers of the tongue, mouth and the nasopharynx, in that order. This differs with earlier reports from the Kenyatta National Hospital inpatient admission registry that showed laryngeal cancer as the third most common after laryngeal and oral cancers. However, Nyandusi in his dissertation study [University of Nairobi 2007] in the same hospital showed that cancer of the larynx was now the most common head and neck tumor followed by nasopharyngeal, hypopharyngeal and oral ones in that order. Specific and detailed accounts on the amount, type and duration of smoking in relation to cancer of the larynx were not carried out. These studies did not have control groups and no statistical testing was done.

During tobacco inhalation, the larger particles are mainly deposited to laryngeal mucosa during inspiration. The fine and ultrafine particles have been shown to be deposited during secondary flows generated by turbulence created by the reduced cross sectional area and convoluted topographic anatomy of the human larynx.[5] Further deposition occurs during exhalation phase of smoking, especially in regard to the fine and micro fine particles.[7] Martonen and colleagues[6] showed that the higher deposition of cigarette smoke to this site predisposed it to a higher incidence of cancer compared to other regions of the airway. This is supported by a study by Yang[9] that showed a 3,000-fold chance of upper airway cancer compared to lower airway cancer. The presence of laminar flow of tobacco smoke in all the regions of the airway apart from the narrow larynx is thought to explain this increased risk.[7]

Chronic exposure of upper airway epithelium to tobacco smoke has been shown to induce premalignant morphological changes.[8] These changes are accompanied by increasing chromosomal damage, which leads to formation of a population of metaplastic epithelial cells. It has also has been found that pulmonary alveolar macrophages are activated by cigarette smoke to produce superoxides and hydrogen peroxide, which also cause oxidative damage to DNA and RNA and add to the risk of carcinogenesis.[9]

The risks associated with cigarette smoking are also modified by alcohol consumption in a multiplicative manner. Alcohol ingestion increases cancer risk by increasing topical absorption of tobacco carcinogens and induction of microsomal enzymes, leading to increased generation of tobacco carcinogens that bind to DNA.[10] Because of this interaction, cigarette smoking should be examined within the context of alcohol consumption.[11]

In view of the fact that cancer of the larynx is now the most common head and neck cancer in Kenya, we sought to assess cigarette smoking, which is known to be the most important risk factor for laryngeal squamous cell carcinoma (SCC). The paucity of local data indicates a knowledge gap; risk factor assessment has not been analytically studied with respect to head and neck cancer. This paper will form a basis for future planning strategies aimed at reducing the burden of this cancer through reduction of cigarette smoking.

Methodology

This is a hospital based case-control study conducted from March 2011 to May 2011 at Kenyatta National Hospital (KNH). Patients of all ages presenting in the Ear Nose Throat Head and Neck (ENT H&N) surgery department and radiation-oncology department

of KNH with histologically proven SCC of the larynx were recruited sequentially for the study. A total of 39 experimental group patients were recruited from the ENT H&N department whereas 11 were recruited from radiation-oncology department. Eight patients were excluded from the study; two had verrucous carcinoma whereas four had spindle cell carcinoma. Two other patients declined to participate.

Controls were recruited from patients in the orthopedics department and matched for age (within 5 years), sex and region with the experimental group to control for confounding factors. A total of 50 controls were recruited. 36 were recruited from the in-patient units of the orthopedic wards, whereas 14 were recruited from the orthopedic clinic. Among the controls, three patients were found to have hoarseness of voice and one had a swelled neck. They were therefore referred to the ENT H&N clinic for further evaluation. 62% of controls were diagnosed with traumatic orthopedic conditions (fractures and or dislocations), 25% had non-traumatic conditions (mainly low back pain and disc disorders), while the remaining 13% had osteoarthritis and acute infections (for instance, septic arthritis and cellulitis). Informed consent was obtained from the participants and a study number was assigned. Demographic data were then entered into a questionnaire.

A medical history with a primary focus on laryngeal malignancy was obtained to include onset of symptoms, severity, duration and involvement of other regions among the controls. An indirect laryngoscopy was then performed on all patients in the control group. Those found to have any laryngeal lesion suspected to be malignant were excluded from the study and referred for further evaluation.

History of smoking was then obtained to include whether participants were current smokers, how long they stopped smoking if they were former smokers, age of onset of cigarette smoking, duration, type (filtered or non-filtered cigarettes), and number of sticks in pack years (number of years one has smoked 20 cigarettes each day).

History of alcohol intake was obtained to include whether they drank alcohol or not, age of onset of alcohol intake, duration, number of days they drank per week, type of alcohol taken and number of alcoholic drinks taken per week. The respondents were then classified as no drinkers, light drinkers, moderate drinkers, heavy drinkers and very heavy drinkers as per the National Institute on Alcohol Abuse and Alcoholism (NIAAA)[12] guidelines. Ethical approval was obtained from Kenyatta National Hospital/ University of Nairobi- Ethics Research Committee, approval number P8/01/2011. Written informed consent was obtained from all study participants.

Data management and analysis

All the information was recorded in a data collection form and thereafter entered into computer software and analyzed using SPSS 17.0 statistical software.

Results

Age distribution and sex ratio

Among the experimental group and control group, the male to female ratio was 24:1. Age range was 42 to 84 years with a mean of 61 (61 ± 11.7 years) for experimental group patients and 63 years (63.7 ± 10.58 years) for controls ($P = 0.297$) with a peak age at 55 to 69 years (59.6%).

Smoking history

33 (66%) of the experimental group patients had a positive history of current cigarette smoking compared to controls (6%). Being a current smoker increased laryngeal cancer risk with an odds ratio (OR) of 30.4 ($P \leq 0.0001$; 95% CI: 8.2–112.2).

The duration since stopping smoking among controls was found to be significantly longer (mean 24.57 ± 12.3 years) than the duration among experimental group patients (mean 12.13 ± 16.1 years); $P \leq 0.029$. Those who had stopped smoking for <10 years had a reduced risk for laryngeal SCC with an OR of 19.5 (95% CI: 2.0–190.9) compared to controls. This is a significant reduction when compared to current smokers.

The experimental group patients started cigarette smoking at an earlier age (mean 20.18 ± 8.6 years) compared to controls (mean 25 ± 5.7 years); $P \leq 0.004$. Those who began smoking before the age of 20 years had the highest risks for laryngeal SCC with an OR of 31, whereas later onset of smoking was associated with less risk compared to controls (Table 1).

There was a significant difference in the mean total number of pack years among the experimental group patients (31.4 ± 23 pack years) compared to

Table 1. Risks associated with earlier age of smoking debut.

Age of debut cigarette smoking	B	*P* value	OR	95% CI	
				Lower	Upper
Never smoked		0.000			
≤20 years	3.457	<0.001	31.733	8.754	115.040
21–40 years	2.045	0.001	7.727	2.409	24.787
≥40 years	22.937	1.000	9.154E+09	0.000	–

Notes: B = beta value; *P* value = probability value; OR = odds ratio; 95% CI = 95% confidence interval.

the controls (5.4 ± 6.5 pack years) with an OR of 21.3; $P \leq 0.0001$ (95% CI: 2.6–176.1) compared to controls. This shows a strong association between cumulative cigarette smoking and laryngeal SCC.

Mean duration of smoking was longer among experimental group patients (38 ± 15 years) compared to controls (14.8 ± 9.4 years); $P \leq 0.0001$, with an OR of 12.7 (95% CI: 3.4–47.5). It should be noted that 92% of controls who are former smokers ceased smoking at various times before being recruited for the study.

Among the experimental group patients who smoked, 69.8% smoked filtered cigarettes whereas 30.20% smoked non-filtered cigarettes ($P \leq 0.2$). This did not have a statistically significant effect on laryngeal SCC.

Alcohol consumption

Among the experimental group patients recruited, 38 (76%) gave a positive history of alcohol intake compared to the controls, among whom 29 out of 50 drank alcohol corresponding to 58%; $P < 0.05$, with an OR of 2.3 (95% CI: 1.0–5.4), showing elevated alcohol related risks for laryngeal SCC. When stratified into the various categories of alcohol drinking as outlined by NIAAA,[12] only those who were very heavy drinkers had increased risk; $P \leq 0.002$, with an OR of 6.0 (95% CI: 11.957–18.398).

Cigarette smoking as the only exposure

Among patients who smoked and did not drink alcohol, 4 (20%) had glottic cancer ($P = 0.001$) with an OR of 19.75 (2.069–188.552), which was statistically significant. Other laryngeal subsites did not have any patients who smoked and did not drink alcohol. It should be highlighted that these respondents who smoked only, were few.

Cigarette smoking and alcohol intake as joint exposures

Compared to controls, combined consumption of cigarette smoke and alcohol had a significant effect on the risk of supraglottic, glottic and transglottic SCC. The highest significant risk was observed for supraglottic SCC with an OR of 10.5 ($P \leq 0.0001$; 95% CI: 2.6–41.7) followed by transglottic SCC with an OR of 4.8 ($P \leq 0.002$, 95% CI: 1.7–13.5) and last glottic SCC with an OR of 2.8 ($P \leq 0.004$, 95% CI: 1.025–7.7).

Having smoked in one's lifetime has a significant positive relationship with developing laryngeal SCC. The highest risk was noted for supraglottis SCC with an OR of 6.7778 ($P \leq 0.003$, 95% CI: 1.7–27.021) followed by glottis with an OR of 6.151 ($P < 0.0001$, 95% CI: 2.1–18.023) and lastly transglottic SCC with an OR of 3.5 ($P < 0.012$, 95% CI: 1.269–9.652). A good number of the experimental group patients reported to have stopped smoking after diagnosis and hence had higher risks than those listed earlier for joint exposure of cigarette smoking and alcohol intake in some subsites, so these findings should be interpreted as such.

Multivariate analysis

When a multivariate logistic regression was run, only two variables were independently associated with increased risk for laryngeal SCC. These were being a current smoker with an OR of 14.576 ($P \leq 0.002$, 95% CI: 2.624–80.979) and duration of smoking with an OR of 7.312 ($P \leq 0.01$, 95% CI: 1.619–33.024). Being a current smoker and having smoked for a prolongued duration are the most important independent factors contributing to development of laryngeal SCC.

Lastly, based on the prevalence of smoking among experimental group patients and controls, the population-attributable risk associated with cigarette smoking was found to be 62%. This is the proportion by which laryngeal SCC would be reduced if cigarette smoking were to be eliminated.

Discussion

SCC of the larynx is the most common head and neck cancer among men in Kenya and the third most common among women in Kenya as seen at ENT H&N and radiation-oncology departments of Kenyatta National Hospital.[2] It is, however, known that laryngeal SCC is a predominantly male disease, possibly because of the fact that men tend consume more alcohol and smoke more tobacco than females, as is found in other parts of the world.[1]

The male-to-female ratio in this series was 24:1, confirming the strong association of risk with the male sex, and is similar to findings by Oburra and colleagues[13] in an earlier publication in this region. This is comparable to what has been found around the world. Indeed, some studies in a systematic review carried out by Farhad and colleagues[14] showed 100% male prevalence while the rest showed male predominance. Male to female ratios ranged from 9:1 to 25:1, especially those studies done in North America, some parts of Southern Europe and Asia.[14] The reason for this distribution was cited to be a higher level of abuse of cigarettes and alcohol among males compared to females, similar to conclusions from the KDHS survey in 2009.[15] This hypothesis is further supported by a case control study carried out by Sylvano and colleagues[16] among female patients diagnosed with laryngeal SCC (n = 68), which showed cigarette smoking as the most important risk factor of laryngeal SCC followed by alcohol consumption. He also found that reproductive and hormonal factors were not consistently associated with increased risk for laryngeal tumors. The high male-to-female ratio found in the current study is therefore consistent with what has been found in the rest of the world.

Out of the 50 experimental group patients in this study, 33 of them (66%) were current smokers compared to controls where only 3 (6%) smoked. Patients who are current smokers had a significant risk for laryngeal SCC in general compared to controls (OR = 30.4) regardless of whether they drank alcohol. This result is comparable to those found by Francheschi and colleagues[17] in Northern Italy, where ORs ranged from 2 to 15.6 for the shortest and greatest durations respectively. A meta-analysis carried out by Hashibe in central Europe[18,19] showed similar findings with an OR of 12.83 for cigarette smokers only and an OR of 36.7 for those who also consumed alcohol. This may be explained by the fact that the KDHS[15] survey's maximum age range was 45–49 years, whereas the average age of controls in this study is 61 years. Furthermore, the controls were hospital-based and therefore their characteristics may not compare well with a population-based group, as this group has been educated about the harmful effects of cigarette smoking and alcohol intake during clinic attendance. Most patients in this study smoked filtered cigarettes, which is consistent with findings across the globe, although we did not obtain the mode of curing the tobacco. The effect of filtering on SCC risk was, however, not statistically significant.

Various studies conducted previously[17,19–24] have demonstrated a reduced risk for laryngeal SCC after smoking cessation, although the degree of reduced risk differs greatly depending on the age and time since cessation. Bosetti and colleagues[23,24] showed that those who quit cigarette smoking before the age of 35 years or who stopped smoking for more than 20 years did not have a significantly higher risk than individuals who had never smoked. Results in this study show that there is a progressive drop in risk after smoking cessation, which is apparent even under 10 years of quitting (OR = 19.5) and is similar to findings in previous studies.

Maier and colleagues[25] in the Heidelberg case control study found that those who started smoking at a younger age and smoked for longer had a higher risk association with development of laryngeal SCC (OR = 9.7). This positive risk association is in keeping with our findings where the OR was 31.7 for those who began smoking before the age of 20 years. Those who began smoking between the ages of 21–40 years had an OR of 7.7 (95% CI: 2.409–24.787). This risk is higher than that published by Francheschi and colleagues,[17] who also found increased risk in other subsites in the head and neck where cigarette smoking was a risk factor. Wiencke and colleagues[26] have

published molecular epidemiologic evidence showing that early age of onset of smoking produces biologic changes that enhance susceptibility to the effects of cigarette smoke carcinogens in the airway. They showed that among SCC experimental group patients, there was a strong association of increased 3p21 loss of heterozygosity (LOH) with increasing polynuclear aromatic hydrocarbon-DNA adducts levels ($P = 0.03$), as well as an increased prevalence loss of heterozygosity with earlier age of smoking initiation ($P = 0.02$). This study similarly shows that early age of onset is a significant risk factor for development of SCC larynx. This is in keeping with studies conducted previously.[10,27–29] On the other hand, there was a lower positive risk among those who started smoking after the age of 40, although this was not of statistical significance due to the few respondents at this age bracket.

There was an increased risk for laryngeal SCC with cumulative smoking measured in pack years. Dosemeci and colleagues[30] found an OR of 6.0 (n = 197) for those who had >21 pack years whereas Hashibe[18] found a lower OR of 12.8 for the highest rank of mean pack years. These studies did not provide ORs for pack years of more than 30, but rather grouped them as >20 years. This may explain the relatively higher estimates in the current study (OR = 21.3) considering the well-known dose-response risk for laryngeal SCC as shown in many studies. Over-reporting among experimental group patients may be a factor.

Various studies[17,19–31] have shown that duration of smoking was one of the most important risk factors for laryngeal SCC. The highest stratification of duration of smoking of 40 years showed greater risk for laryngeal SCC of 15.6 as seen in Francheschi's study[18] whereas lower durations (<20 years) showed lower ORs of 2.13 as seen in Lee's study.[31] The present study showed similar findings, especially for those who smoked for >20 years (OR = 12.7). The majority (92%) of controls who smoked in the present study had quit smoking cigarettes at various time intervals during the study, and this may have contributed to these increased risk ratios.

Alcohol consumption has been positively associated with laryngeal SCC mostly as a co-factor rather than as an independent factor. In this study there is an overall increased risk for laryngeal SCC with an OR of 2.3 ($P \leq 0.005$, 95% CI: 1.0–5.4). The mean average drinks per week in this study were 58, which correlates quite well with the Italian study.[17] Other studies performed in Europe showed similar ORs.[17–20,29,30] On the other hand, societal biases and stigma differ between countries and may alter how the study participants respond. In the current study, those who were very heavy drinkers were found to have a higher risk for laryngeal SCC compared to controls, with an OR of 6.0 ($P \leq 0.002$, 95% CI: 1.957–18.398).

Subsite distribution of laryngeal cancer has been shown to be risk factor dependent.[22,30,32] Various studies have shown an increased risk for glottic cancer among those patients who smoked only, whereas those who smoked and drank alcohol developed supraglottic cancer more than glottic cancer.[22,30–32] Other studies have, however, disputed these findings. For instance, Hashibe and colleagues[19] found similar risks between supraglottic and glottic cancer. The present study is in agreement with these earlier studies, showing a strong risk for glottic cancer among patients who smoked cigarettes but did not drink compared to controls.

Furthermore, the results in the present study suggest that being a former smoker confers a positive risk for laryngeal SCC across all laryngeal subsites, the highest being for supraglottic cancer (OR = 6.7), which is comparable to glottic SCC (OR = 6.1) when compared to controls. Lewis and colleagues[33] and other authors[5–7] demonstrated that the glottis is anatomically the narrowest part of the upper airway, and is therefore more susceptible to deposition of inhaled carcinogens found in cigarette smoke. This anatomic region also exhibits the transition zone from squamous epithelium to pseudo-stratified columnar epithelium. It is also at a greater risk of metaplasia that may progress to dysplasia and eventually to invasive carcinoma with exposure to inhaled and ingested carcinogen, as shown by Renne and colleagues.[34]

Various authors have studied the combined effect of cigarette smoking and alcohol intake and many have shown that there is either an additive or multiplicative effect when compared to controls, and when tested on multiplicative or additive models.[20,30,32] This study shows a significant risk (OR = 10.476) for supraglottic cancer among those who inhale tobacco and consume alcohol. The supraglottis is unique from the other subsites of the larynx since it is consistently exposed to both inhaled and ingested agents. As is known from published studies, alcohol is a topical

mucosal solvent for cigarette smoke carcinogens, and therefore enhances their absorption.[10,20] There was an overall increased risk for all subsites when the two were consumed concurrently. In this study, it is apparent that the duration of smoking and whether one is a current smoker show more consistent associations with laryngeal SCC development than other measures of cigarette smoking. Those who stopped smoking cigarettes had a significantly reduced risk for laryngeal SCC, although former smokers still had a higher risk compared to controls. There was an increased risk among those who smoked and drank alcohol across all laryngeal subsites. The population-attributable risk attributed to cigarette smoking was found to be 62%, reaffirming the fact that cigarette smoking is a major risk factor for this cancer and may be reduced via a reduction of tobacco inhalation in the population.

Lastly, this was a hospital based study and therefore it may not reflect the true picture of the general population, considering Berksonian selection bias where hospital based respondents tend to participate more readily in research projects compared to controls.

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Author Contributions
Conceived and designed the experiments: PM, HOO, AP. Analysed the data: PM. Wrote the first draft of the manuscript: PM. Contributed to the writing of the manuscript: PM, HOO, AP. Agree with manuscript results and conclusions: PM, HOO, AP. Jointly developed the structure and arguments for the paper: PM, HOO, AP. Made critical revisions and approved final version: HOO. All authors reviewed and approved of the final manuscript.

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References
1. World Health Organization International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. Tobacco Smoke and Involuntary Smoking. Available at: http://monographs.iarc.fr/ENG/Monographs/vol83/volume83.pdf. Last updated Jul 2002. Accessed Sep 2, 2012
2. Mutuma GZ, Rugutt-Korir A. Nairobi Cancer Registry Kenya Medical Research Institute. Nairobi, Kenya. Cancer Incidence Report NAIROBI 2000–2002. Available at: http://www.healthresearchweb.org/files/CancerIncidenceReportKEMRI.pdf. Last updated 2006. Accessed Sep 2, 2012.
3. Onyango JF, Macharia IM. Delays in diagnosis, referral and management of head and neck cancer presenting at Kenyatta National Hospital, Nairobi. *East Afr Med J*. 2006;83(4):85–91.
4. Onyango JF, Awange DO, Njiru A, Macharia IM. Pattern of occurrence of head and neck cancer presenting at Kenyatta Hospital, Nairobi. *East Afr Med J*. 2006;83(5):288–91.
5. Jinxiang Xi, Longest P. Characterization of sub micrometer aerosol deposition in extrathoracic airways during nasal exhalation. *Aerosol Sci Tech*. 2009; 43(8):808–27.
6. Martonen TB. *Surrogate Experimental Models for Studying Particle Deposition in the Human Respiratory Tract*. Washington, DC: US Environmental Protection Agency; 1985.
7. Yang CP, Gallagher RP, Weiss NS, Band PR, Thomas DB, Russell DA. Difference in incidence rates of cancers of the respiratory tract by anatomic subsite and histologic type: An etiologic implication. *J Natl Cancer Inst.* 1989;81(23):1828–31.
8. Nina G, Michaels L, Luzar B, et al. Current review on squamous intraepithelial lesions of the larynx. *Histopathology*. 2009;54(6):639–56.
9. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ Health Perspect*. 1985;64:111–26.
10. Zeka A, Gore R, Kriebel D. Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis. *Cancer Causes Control*. 2003;14(9):897–906.
11. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer*. 2007;7(8):599–612.
12. National Institutes of Health. National Institute on Alcohol Abuse and Alcoholism. Available at: http://www.niaaa.nih.gov/guide. Accessed Sep 2, 2012.
13. Oburra HO, Scholz T, Werner JA, et al. Presentation and initial assessment of laryngeal cancer at Kenyatta National Hospital. *MEDICOM-The African Journal of Hospital and Scientific Medicine*. 2010;25:29–32.
14. Islami F, Tramacere I, Rota M, et al. Alcohol drinking and laryngeal cancer: overall and dose-risk relation—a systematic review and meta-analysis. *Oral Oncol*. 2010;46(11):802–10.

15. Kenya National Bureau of Statistics (KNBS) and ICF Macro. *Kenya Demographic and Health Survey* 2008–2009. Calverton, Maryland: KNBS and ICF Macro; 2010.
16. Gallus S, Bosetti C, Franceschi S, Levi F, Negri E, La Vecchia C. Laryngeal cancer in women: tobacco, alcohol, nutritional and hormonal factors. *Cancer Epidemiol Biomarkers Prev*. 2003;12(6):514–7.
17. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx and esophagus in northern Italy. *Cancer Res*. 1990;50(20):6502–7.
18. Hashibe M, Paul Brennan, Shuchun Chuang, Stefania Boccia, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):541–50.
19. Hashibe M, Boffetta P, Zaridze D, et al. Contribution of tobacco and alcohol to the high rates of squamous cell carcinoma of the supraglottis and glottis in Central Europe. *Am J Epidemiol*. 2007;165(7):814–20.
20. Talamini R, Bosetti C, La Vecchia C, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control*. 2002;13(10):957–64.
21. Altieri A, Bosetti C, Talamini R, et al. Cessation of smoking and drinking and the risk of laryngeal cancer. *Br J Cancer*. 2002;87(11):1227–9.
22. De Stefani E, Boffetta P, Deneo-Pellegrini H, et al. Supraglottic and glottic carcinomas: epidemiologically distinct entities? *Int J Cancer*. 2004;112(6): 1065–71.
23. Bosetti C, Garavello W, Gallus S, La Vecchia C. Effects of smoking cessation on the risk of laryngeal cancer: an overview of published studies. *Oral Oncol*. 2006;42(9):866–72.
24. Bosetti C, Gallus S, Peto R, et al. Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. *Am J Epidemiol*. 2008;167(4):468–73.
25. Maier H, Tisch M. Epidemiology of laryngeal cancer: results of the Heidelberg case-control study. *Acta Otolaryngol Suppl*. 1997;527:160–4.
26. Wiencke JK, Thurston SW, Kelsey KT, et al. Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. *J Natl Cancer Inst*. 1999; 91(7):614–9.
27. Austin DF, Reynolds P. Laryngeal cancer. In: Schottenfeld D, Fraumeni JF, editors. *Cancer Epidemiology and Prevention.* 2nd ed. New York: Oxford University Press; 1996.
28. Chin D, Boyle GM, Theile DR, Parsons PG, Coman WB. Molecular introduction to head and neck cancer (HNSCC) carcinogenesis. *Br J Plast Surg*. 2004;57(7):595–602.
29. Secretan B, Straif K, Baan R, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*. 2009;10(11):1033–4.
30. Dosemeci M, Gokmen I, Unsal M, Hayes RB, Blair A. Tobacco, alcohol use, and risks of laryngeal and lung cancer by subsite and histologic type in Turkey. *Cancer Causes Control*. 1997;8(5):729–37.
31. Lee YC, Marron M, Benhamou S, et al. Active and involuntary tobacco smoking and upper aerodigestive tract cancer risks in a multicenter case-control study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(12): 3353–61.
32. Menvielle G, Luce D, Goldberg P, Bugel I, Leclerc A. Smoking, alcohol drinking and cancer risk for various sites of the larynx and hypopharynx. A case-control study in France. *Eur J Cancer Prev*. 2004;13(3):165–72.
33. Lewis DJ. Factors affecting the distribution of tobacco smoke-induced lesions in the rodent larynx. *Toxicol Lett*. 1981;9(2):189–94.
34. Renne RA, Gideon KM. Types and patterns of response in the larynx following inhalation. *Toxicol Pathol*. 2006;34(3):281–5.