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Review Article

Laryngeal Cancer: Epidemiology, Etiology, and Prevention: A Narrative Review

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Abstract

Laryngeal cancer comprises 30%-40% of head and neck malignancies, and it is the most common malignancy in otolaryngology. The main risk factors for laryngeal cancer are tobacco use, excessive alcohol consumption, gastroesophageal reflex, Plummer-Vinson syndrome, exposure to heat, chemicals, and some viral infections. This literature review summarizes all known data over the past decade with an assessment of the main etiological factors related to cancer incidence, general measurement issues in the cancer epidemiology and the current state of science in relation to laryngeal cancer. The geographical distribution of laryngeal cancer also reveals some important aspects. Europe remains the most prevalent continent for this type of malignancy, whilst the epidemiologic burden in Africa remains low. Overall, there are clear differences in morbidity and mortality from laryngeal cancer between urban and rural areas, with gender inequalities. In some countries, the incidence rates are high in rural areas, and in some, such as in China, the urban population is more affected. High rates of laryngeal cancer are closely associated with both low average income and a high percentage of the population with lower-than-average education countries with higher Socio-demographic Index (SDI) have made greater improvements in the treatment of LC than countries with lower SDI. Epidemiological data on risk factors can provide valuable information for developing cancer prevention strategies.

Keywords: Laryngeal cancer; Epidemiology; Etiology; Prevention

Introduction

Head and neck cancer is the seventh most common type of cancer worldwide and comprise of a diverse group of tumors affecting the upper aerodigestive tract. Although many different histologies exist, the most common is squamous cell carcinoma (1). Head and neck cancers can also begin in the salivary glands, sinuses, or muscles or nerves in the head and neck, but these types of cancer are much less common than squamous cell carcinomas (2). Laryngeal cancer is the most

common neoplasm in this group. Laryngeal cancer is a disease in which cancer cells form in the tissues of the larynx. The clinical picture of laryngeal cancer varies greatly and depends on the location and size of the primary tumor. Symptoms may include a lump or a sore that does not heal, sore throat, difficulty swallowing, and hoarseness of voice (3).

Epidemiology of Laryngeal Cancer

Global epidemiology

Laryngeal cancer (LC) comprises 30%-40% of head and neck malignancies, and it is the most common malignancy in otolaryngology. Worldwide, LC is registered annually in 184,615 people, which corresponds to 1.1% of all cancer cases, and 99,840 deaths, which accounts for 1% of all cancer-related deaths. High rates of incidence in the world are registered in Cuba (7.8 per 100,000) and Montenegro (7.0 per 100,000) (Fig. 1). And the lowest rates were recorded in Eswatini (0.18 per 100,000) and Cameroon (0.31 per 100,000) (4).

Residents of countries with medium, high and very high Human Development Index (HDI) suffer from this pathology in almost the same amounts. Residents of countries with low HDI suffer the least. The number of cases was highest in regions with high Socio-demographic Index (SDI) levels and decreased with increasing SDI levels (5). Overall, LC incidence rates were moderately strongly correlated with lower SES scores. High rates of LC are closely associated with both low average income and a high percentage of the population with lower-than-average education (6).

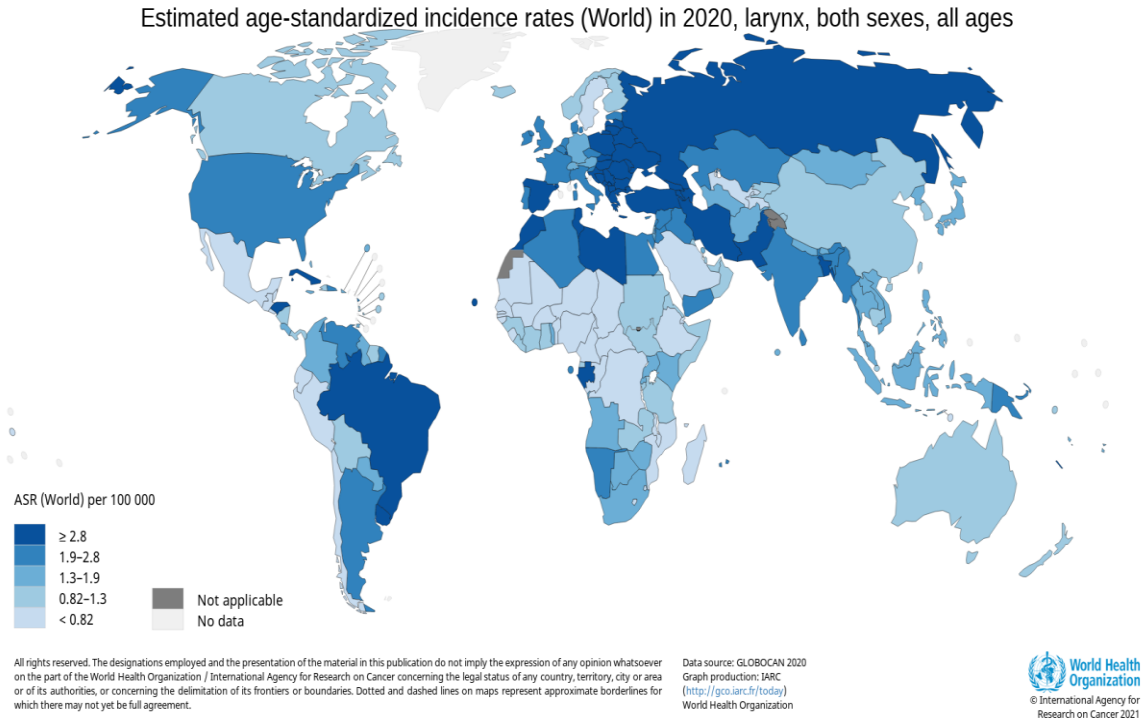

Fig. 1: Age-standardized incidence rates of laryngeal cancer in the world, 2020 (https://gco.iarc.fr/today/online-analysis-map)

Age standardized incidence (ASR) and mortality rates (ASMR) of LC were 2.0 and 1.0 per 100,000 (1). Globally, while ASMR LC decreased by 1.49% per year, the number of deaths from LC over 30 years increased by 41.0% in 2019 (7). Most of LC deaths occurred in males (85,351 deaths); which was 6-fold higher than that in females (14,489 deaths) (8).

High mortality rates in the world (Fig. 2) are registered in Cuba (3.9 per 100,000) and Montenegro (3.5 per 100,000). And the lowest rates were recorded in Iceland (0.08 per 100,000) and Martinique (0.11 per 100,000) (4).

The number of deaths is highest in Asia (58.9%). Even if the number of cases increased with an increase in HDI, the number of deaths on the contrary decreases. This is most likely due to the fact that in developing countries the level of medical care is lower, there are not enough staff, medicines, funding, screening and early detection services, as well as models of care for oncological diseases (9). ASMR indicator decreased in all SDI regions. The most significant reductions in ASMR were found in high-SDI regions. Countries with higher SDI have made greater improvements in the treatment of LC than countries with lower SDI (5). The number of deaths increased in all regions, with the exception of the region with a high level of SDI. In the region with low SDI, the most pronounced increase in the number of deaths from LC was observed, followed by the region with low and medium SDI (7,10).

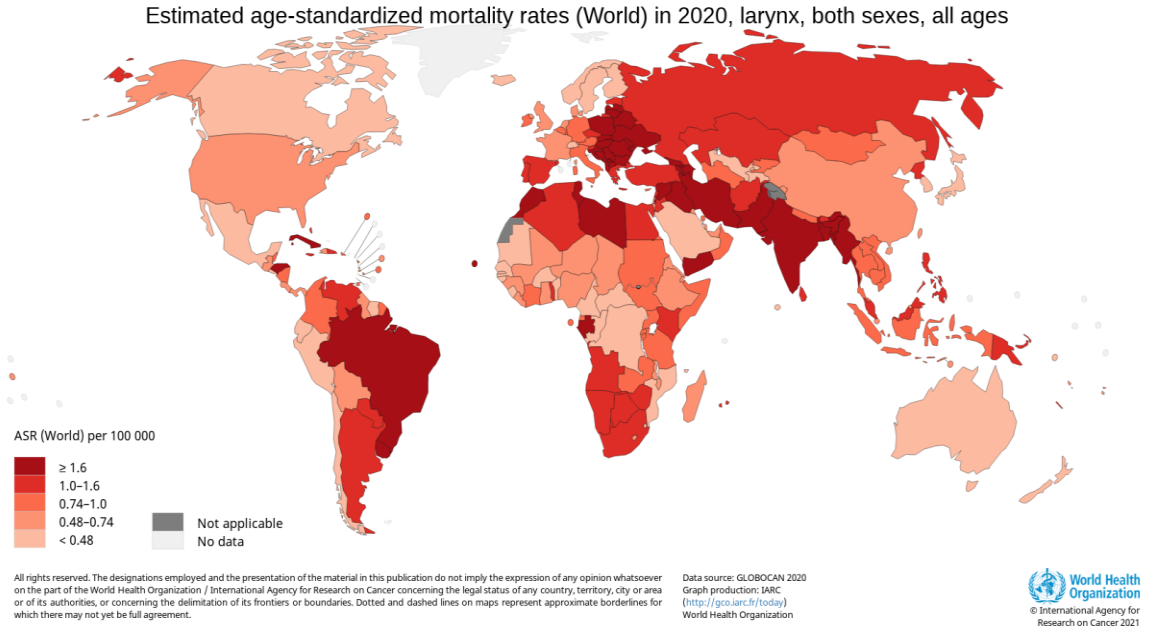

Fig. 2: Age-standardized mortality rates of laryngeal cancer in the world, 2020 (https://gco.iarc.fr/today/online-analysis-map)

LC is generally subdivided into supraglottic, glottic and subglottic cancer with squamous cell carcinoma (SCC) as the far most common histology type (11). Most malignant neoplasms of the larynx (which is more than 98%) are well-differentiated SCC, while chondrosarcomas, leiomyosarcomas and melanomas account for only 2%-5% of all types of laryngeal cancers (12).

According to the GBD 2017, 86.5% of larynx cancer patients are in primary therapy or controlled phase, 7.3% are in metastatic stage, 1.0% are in terminal stage, whist 5.1% are surviving with laryngectomy (13). Survival rates in the United States are not improving due to the increased proportion of patients with terminal stages of LC. There was no improvement in observed survival (5 year observed survival ranged from 54.26% to 56.52%) or relative survival (5-year relative survival ranged from 61.72% to 63.97%) rates (14).

As with any disease with LC, timely and specialized full-fledged medical care plays an important

role. Analyzing the impact of insurance status on overall survival and disease-specific survival, at insured patients with LC had longer overall survival and disease-specific survival compared to patients receiving Medicaid and uninsured patients (15). The type of insurance has powerful predictive characteristics, while the relative income has little impact (16).

Gender and age epidemiology

Worldwide, 160,265 new cases were reported in men and 24,350 in women, which corresponds to an ASR of 3.6 and 0.49 per 100,000, respectively. Therefore, the incidence in men is more than 7 times higher. This suggests that LC burden is mainly concentrated in men (17,18). The highest incidence rates in the male population were recorded in Cuba (14.2 per 100,000) and Montenegro (12.9 per 100,000) (4). However, the lowest rates were in Eswatini (0.41 per 100,000) and Cameroon (0.47 per 100,000) (Fig. 3). High incidence rates in the female population were recorded in Cuba (1.9 per 100,000) and Hungary (1.8 per 100,000). However, the lowest rates were in Benin (0.07 per 100,000) and Guadeloupe France (0.09 per 100,000) (Fig. 4) (4).

Diagnosis of LC in young people is considered rare. LC in non-drinking, non-smoking young patients (<40 yr old) was rarely registered as a separate topic, mainly because data must be collected prospectively, and they can only be compared in head and neck institutions with a very large population. After 35 years, both sexes have a constant increase in all epidemiological indicators. "The incidence of laryngeal malignancies peaks after 65 years in both sexes, and then remains stable and amounts to about 25-30 new cases per 100,000 in men and about 4 cases per 100,000 in women" (19). The prevalence follows a similar trend, peaking around the age of 60-80 yr in both sexes (120-140 cases per 100,000 in men and 17-20 cases per 100,000 in women), but then gradually decreases. The mortality trend exactly reflects the morbidity trend, but peaks at the age of 80 in both sexes, and then remains fairly stable (23 per 100,000 in men and 3 per 100,000). LC death rate tended to increase gradually with age. Disability associated with LC peaks at the age of 60-75 yr in both sexes (approximately 350 per 100,000 in men and 56 per 100,000 in women), but then decreases sharply (19). LC incidence rate showed unimodal distribution among different age groups, with peak at 60-80 yr (8).

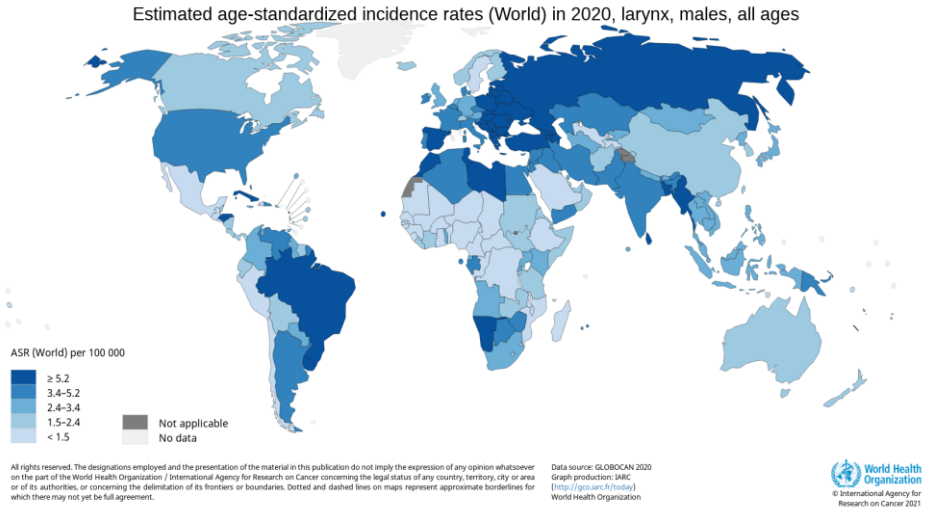

Fig. 3: Age-standardized indicators of LC incidence in the male population of the world, 2020 (https://gco.iarc.fr/today/online-analysis-map)

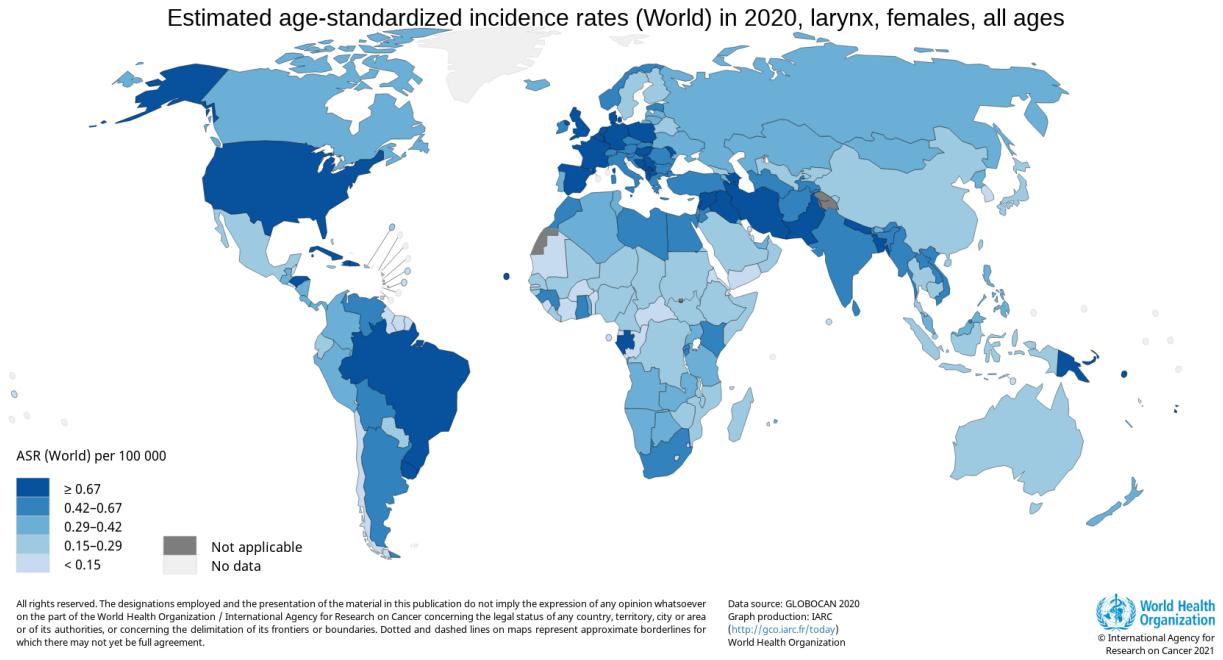

Fig. 4: Age-standardized indicators of LC incidence in the female population of the world, 2020 (https://gco.iarc.fr/today/online-analysis-map)

A nationwide study conducted in Denmark from 1980 to 2014 found: a significant decrease in LC incidence in men stratified by gender, but there was no significant change in the incidence among women (20). A decrease in male incidence was found in Ukraine (21). Median age at diagnosis was 60 yr. The highest incidence was observed for the age group 70–80 yr for both men and women. LC has been decreasing during the last 38 years. Similar trends have been observed in other European countries, e.g., Italy, Spain and the Netherlands. These findings are presumably related to changes in smoking patterns as studies have shown a strong dose–response and time-response correlation between smoking and LC (22,23).

Geographic epidemiology

The geographical distribution of LC also reveals some important aspects. Europe remains the most prevalent continent for this type of malignancy, whilst the epidemiologic burden in Africa remains low (19). In general, other European studies have shown a decreasing incidence of LC in men from mid-1990s, although the incidence in Europe varies; e.g., the incidence was found to be above 12 per 100,000 inhabitants in Spain but less than 5 per 100,000 in the UK (23).

In addition, there are obvious differences in the incidence and mortality from LC between urban and rural areas with distinct gender inequality. In some countries, like China (24), the urban population suffers more, and in some the incidence rates are high in rural areas (25).

Future projections

Global morbidity and mortality rates from this pathology are growing every year, and presumably by 2040 the number of cases and deaths registered per year will reach up to 284 thousand and 160 thousand, respectively (26).

Etiology

According to the American Cancer Society, the main risk factors for LC are: tobacco use, excessive alcohol consumption, gastro-esophageal reflex, Plummer-Vinson syndrome, anatomical abnormalities, exposure to heat, chemicals, asbestos, nickel or ionizing radiation,

as well as some viral infections (27). Increasing the duration and frequency of tobacco smoking, betel chewing habits and alcohol consumption increases the risk of HNC with clear dose-dependent trends in the Nepalese population. Individuals who had all three habits: smoking tobacco, chewing betel and drinking alcohol, had a 12.83 times higher risk of developing HNC compared to individuals without these habits (28).

Tobacco

Tobacco is obviously the most important risk factor for LC. In most US states about a third of cancer deaths in men and a quarter in women are attributed to cigarette smoking (29). The risk is associated with the duration of exposure to this habit, as well as with the total dose of *tobacco* consumption. To date, cigarette smoking correlates with an approximately sevenfold increase in the risk of LC. The risk remains elevated for 15 years after quitting smoking, but subsequently decreases. In Indonesia, in addition to active smoking, passive smoking also leads to death. According to the number of cancer deaths due to passive smoking among men, LC was among the three highest (30). After investigating the combined effect of the intensity and duration of cigarette smoking on the risk of LC, results were obtained showing that there was no threshold effect on the risk of LC of a shorter duration or lower intensity of *tobacco* smoking. The presence of a dose-response relationship between cigarette smoking and the risk of LC is confirmed (31). The dose-response relationship with the risk of LC is still far from linear, with a sharper increase with intermediate consumption and possible plateaus indicating a "saturation effect" in smokers with a duration of more than 20 years and more than 30 cigarettes per day (32). The widespread decrease in ASMR from LC worldwide was due to a decrease in LC associated with smoking. Most likely, this is due to the fact that huge efforts have been made over the past decades to combat smoking (33).

Most of the patients with LC smoked, moreover, for a very long time (about 30 years or more), while smoking cigarettes without alcohol intake has a higher association with well-differentiated carcinoma, whereas simultaneous cigarette smoking and alcohol intake are more predisposed to less differentiated LC (34). 41.4% of patients who used cigarettes died from causes associated with LC, compared with 13.8% of patients who did not abuse cigarettes (35).

As for cigarette smoking and the risk of LC, they were slightly higher among blacks compared to whites, while estimates of the relationship between alcohol consumption and cancer risk were similar or slightly higher. The reason for these differences in risk by race is unknown, but perhaps it may be due to differences in the metabolism of alcohol and tobacco, differences in the methods of use and cessation of use depending on race. The fact that black smokers are at increased risk is an important public health issue (36).

Alcohol

The American Society of Clinical Oncology has stated that 5% of cancer cases worldwide may be alcohol-related (37). Alcohol is an important risk factor in LC pathogenesis (38). The World Cancer Research Foundation has concluded that there is strong evidence that alcohol consumption at any level increases the risk of developing LC (39). In Europe, more than 30% of all LC-related deaths were alcohol-related. This corresponds to the high level of alcohol consumption in this region (40,41). Indeed, the relationship between alcohol consumption and the development of LC is proportional to the dose and duration of exposure (42,43). The number of cases associated with alcohol consumption was significantly higher in men than in women (44). Every year, global alcohol consumption increases, in this regard, alcohol may become the leading risk factor for developing LC (45).

Human papillomavirus (HPV) infection

Part of invasive LC may be caused by *HPV*. In most cases, *HPV*-positive tumors manifest as moderately differentiated SCC. *HPV*-positive

LCs are more likely to be associated with higher histological scores compared to *HPV*-negative cases (46). *HPV* may be a more important cause of LC in women (47). In China, the number of new cases and deaths from HNC, including LC, was higher in men (48). A similar situation was observed in almost all regions of the world (49,50). The prevalence of *HPV* is relatively high in Chinese patients with LC compared to those in Europe and North America (51). The etiological proportion of *HPV* in LC is significantly lower than previously reported and is also less heterogeneous (52). Among the many pathogenic factors of LC, high-risk *HPV* infection may be one of the most important, since the results show that high-risk *HPV* infection is closely associated with LC, even after taking into account the confounding influence of demographic factors, tobacco and alcohol use (53). The results of rt-PCR revealed that *HPV*-positivity was noted in 57.8% of cases (54). When studying the prevalence of *HPV* in cancerous tumors, including LC in residents of western Algeria, the prevalence of *HPV* in patients with LC is 0% (55). Other scientists came to the same result when studying the etiological fraction of *HPV* among LC in Algerian patients (56). The low prevalence of *HPV* infection among patients with LC suggests that *HPV* is not the main cause of LC (57). Genetic diversity, environmental conditions, lifestyle, and *HPV* detection method may explain the difference in *HPV* infection rates with LC in different regions (58). "Meanwhile, tobacco's carcinogenic effect can have a synergistic effect with *HPV* infection, and the replication of viral cells can enhance mutagenesis and metaplasia caused by smoking "(59). Further studies of *HPV* and its role in LC are needed.

Chewing betel (ChB)

ChB affects the epigenetic modulation of gene expression, which leads to carcinogenesis (60). Betel quad users chew in their free time and during working hours to obtain pharmacological effects: euphoria, increased alertness, focused attention, appetite suppression and improved digestion (61). Unlike other countries, *ChB* with a pound sterling poses a serious threat to public health in Taiwan, in addition to smoking and drinking alcohol. Patients who usually *ChB* nut have a higher incidence of epiglottis cancer (62).

Asbestos

Since the 1950s, there has been a causal relationship between exposure to *asbestos* and various malignant tumors (63). A significantly increased likelihood of developing LC in patients exposed to *asbestos* has been reported (64). Exposure to *asbestos*, as well as tobacco and alcohol consumption are often combined. The combined effect of *asbestos* exposure and tobacco, alcohol consumption was significantly higher than the sum of each effect. However, tobacco use is a key factor explaining the increased risk of LC among male drinkers and smokers exposed to *asbestos*. Exposure to *asbestos* combined with exposure to tobacco and alcohol has led to a significant number of cases of LC (65). Since smoking and alcohol are often used in combination with each other, there is increasing concern about the synergistic relationship of exposure to *asbestos*, tobacco and alcohol. This combined risk is important, even if, ultimately, exposure to *asbestos* alone is not the cause of LC. During the study of the risks of LC in workers exposed to lung carcinogens, results were found confirming hypotheses about the carcinogenic effects of four lung carcinogens (*asbestos*, respirable crystalline silica, chromium-IV and chromium-VI with nickel) on LC (66).

H. pylori infection and LC

There is also a correlation between *H. pylori* infection and LC. In the Zhou et al. study, the risk of developing LC in people infected with *H. pylori* was 2.87 times higher than in the control group. Among patients infected with *H. pylori*, there is a higher incidence of LC than among the general population (67). The high detection rate of *HP* DNA in the cancer tissue confirms that *HP* is a part of the oropharyngeal area microbiota since only 7.2% of cancer patients were negative for both *Helicobacter pylori* and HPV (54).

Population with peptic ulcer disease had the highest risk of LC (HR:2.27). An increase in the incidence of malignancy was observed for more than 6 years after suffering from an ulcer disease (68).

Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR)

GERD is a common gastrointestinal disorder. There is evidence of a link between *GERD* and HNC, in particular LC. Currently, the study of HNC screening protocols in patients with *GERD* may benefit from attention to the larynx compared to other anatomical sites (69). In most of the studies reviewed, patients suffering from *GERD* were 2.37 times more likely to be diagnosed with LC (70). This means that chronic or recurrent inflammatory tissue damage can lead to the development of malignant neoplasms. When examining the saliva of patients with early LC, a high level of typical *LPR* components was found, suggesting the possibility that *LPR*, especially biliary reflux, plays a role in the development of LC (71).

Metabolic syndrome (MS)

In a population study conducted in Korea, MS is an independent risk factor for LC, and LC incidence with MS is 1.13 times higher than in patients without *MS* (72). The chronic course of *MS* is associated with the highest risk of developing LC (RR:1.420). High fasting blood glucose (HR:1.252), waist circumference (HR:1.242), triglyceride (HR:1.166), high blood pressure (RR:1.161) and low high-density lipoprotein cholesterol (RR:1.146) were associated with an increased risk of LC (73).

Prevention

One of the main tasks of reducing the burden of HNC is due to earlier detection. Secondary prevention of HNC focuses on two goals: identification of high-risk individuals and screening methods (61). Kravets et al. analyzed data from the National Health and Nutrition Examination Survey to understand differences in screening for HNC (74). Patients who smoke cigarettes, that is, a group at high risk of developing LC, were never informed about the benefits of quitting smoking or the need for screening for HNC. A reduction in screening may lead to a delay in the diagnosis and treatment of HNC, as a major factor in the increase in mortality among minorities and the uninsured population (75). The link between delays in screening or diagnosis of HNC and increased mortality among minorities with LC is necessary to understand the relationship between race, ethnicity, age, socio-economic status (SES) and insurance coverage (76). Suicide rates are higher in patients with LC compared to other malignant neoplasms of the head and neck, especially in unemployed people living in poverty or having a lower level of education (77). Patients with insufficient and uninsured insurance often suffer from advanced LC (78).

"In the next 30 years, with a reduction in alcohol consumption, a large number of cancers could be avoided. Despite this, the public is little aware of the causal relationship between alcohol and cancer, and alcohol consumption is increasing in several regions of the world" (41). In this connection, the main preventive measure to reduce the incidence of LC is to reduce alcohol consumption or completely abandon it. Moderate drinkers are a higher priority for the prevention of cancer cases than heavy drinkers, mainly because the proportion of heavy drinkers is relatively small (79).

Since gender is an independent prognostic indicator for patients with LC, and male patients have the worst short- and long-term survival (80), male gender should be a priority target in the prevention of this disease.

Conclusion

Epidemiological data from different regions can be used to prioritize risk factors associated with LC for effective prevention programs. Systems for the surveillance and reporting of new cases of LC need to be improved. LC burden increases with the absence of targeted intervention because

of poverty, associated with higher cancer risk, aging, and the prevalence of risk factors associated with urbanization. The rise in morbidity and mortality can be prevented by promoting healthy lifestyles against alcohol abuse.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

References

1. Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF (2021). Head and neck cancer. *Lancet*, 398(10318):2289-2299.
2. Son E, Panwar A, Mosher CH, Lydiatt D (2018). Cancers of the Major Salivary Gland. *J Oncol Pract,* 14(2):99-108.
3. National Cancer Institute (2023). Head and Neck Cancers. Available from: *https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet*
4. Ferlay J, Ervik M, Lam F, et al (2022). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer [cited 2022 Aug 25].
5. Wang JY, Zhang QW, Wen K, et al (2021). Temporal trends in incidence and mortality rates of laryngeal cancer at the global, regional and national levels, 1990-2017. *BMJ Open*, 11(10):e050387.
6. Tang JA, Lango MN (2019). Diverging incidence trends for larynx and tonsil cancer in low socioeconomic regions of the US. *Oral Oncol*, 91:65-68.
7. Zhang QW, Wang JY, Qiao XF, et al (2021). Variations in disease burden of laryngeal cancer attributable to alcohol use and smoking in 204 countries or territories, 1990-2019. *BMC Cancer,* 21(1):1082.
8. Deng Y, Wang M, Zhou L, et al (2020). Global burden of larynx cancer, 1990-2017: estimates from the global burden of disease 2017 study. *Aging (Albany NY),* 12(3):2545-2583.
9. Balogun O, Rodin D, Ngwa W, et al (2017). Challenges and Prospects for Providing Radiation Oncology Services in Africa. *Semin Radiat Oncol,* 27(2):184–88.
10. GBD 2019 Viewpoint Collaborators (2020). Five insights from the Global Burden of Disease Study 2019. *Lancet,* 396(10258):1135–59.
11. Steuer CE, El-Deiry M, Parks JR, et al (2017). An update on larynx cancer. *CA Cancer J Clin*, 67(1):31–50.
12. Ciolofan MS, Vlăescu AN, Mogoantă CA, et al (2017). Clinical, histological and immunohistochemical evaluation of larynx cancer. *Curr Health Sci J,* 43(4):367–75.
13. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* 392(10159):1789-1858.
14. Li MM, Zhao S, Eskander A, et al (2021). ASO Visual Abstract: Stage Migration and Survival Trends in Laryngeal Cancer. *Ann Surg Oncol*, 28(12):7300-7309.
15. Abt NB, Miller LE, Parikh A, et al (2022). Insurance Status Effect on Laryngeal Cancer Survival: A Population Based Study. *Ann Otol Rhinol Laryngol*, 131(7):775-781.
16. Lebo NL, Khalil D, Balram A, et al (2019). Influence of Socioeconomic Status on Stage at Presentation of Laryngeal Cancer in the United States. *Otolaryngol Head Neck Surg*, 161(5):800-806.
17. Perdomo S, Martin Roa G, Brennan P, et al (2016). Head and neck cancer burden and preventive measures in Central and South

America. *Cancer Epidemiol*, 44 Suppl 1:S43-S52.
18. Bray F, Ferlay J, Soerjomataram I, et al (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 68(6):394–424.
19. Nocini R, Molteni G, Mattiuzzi C, et al (2020). Updates on larynx cancer epidemiology. *Chin J Cancer Res*, 32(1):18-25.
20. Nahavandipour A, Jakobsen KK, Grønhøj C, et al (2019). Incidence and survival of laryngeal cancer in Denmark: a nation-wide study from 1980 to 2014. *Acta Oncol,* 58(7):977-982.
21. Ryzhov A, Bray F, Ferlay J, et al (2020). Recent cancer incidence trends in Ukraine and short-term predictions to 2022. *Cancer Epidemiol*, 65:101663.
22. Lyhne NM, Johansen J, Kristensen CA, et al (2016). Incidence of and survival after glottic squamous cell carcinoma in Denmark from 1971 to 2011—a report from the Danish Head and Neck Cancer Group. *Eur J Cancer*, 59:46–56.
23. Zuo JJ, Tao ZZ, Chen C, et al (2017). Characteristics of cigarette smoking without alcohol consumption and laryngeal cancer: overall and time-risk relation. A meta-analysis of observational studies. *Eur Arch Otorhinolaryngol*, 274(3):1617-1631.
24. Wei KR, Zheng RS, Liang ZH, et al (2018). [Incidence and mortality of laryngeal cancer in China, 2014]. *Zhonghua Zhong Liu Za Zhi*, 40(10):736-743.
25. Zuniga SA, Lango MN (2018). Effect of rural and urban geography on larynx cancer incidence and survival. *Laryngoscope*, 128(8):1874–80.
26. Ferlay J, Laversanne M, Ervik M, et al (2022). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: *International Agency for Research on Cancer* [cited 2022 Aug 26].
27. American Cancer Society. Cancer Facts and Figures 2019. Atlanta: American Cancer Society, 2019. Available from: *https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf*
28. Chang CP, Siwakoti B, Sapkota A, et al (2020). Tobacco smoking, chewing habits, alcohol drinking and the risk of head and neck cancer in Nepal. *Int J Cancer*, 147(3):866-875.
29. Lortet-Tieulent J, Goding Sauer A, Siegel RL, et al (2016). State-Level Cancer Mortality Attributable to Cigarette Smoking in the United States. *JAMA Intern Med*, 176(12):1792-1798.
30. Permitasari NPAL, Satibi S, Kristina SA (2018). National Burden of Cancers Attributable to Secondhand Smoking in Indonesia. *Asian Pac J Cancer Prev*, 19(7):1951-1955.
31. Chang CP, Chang SC, Chuang SC, et al (2019). Age at start of using tobacco on the risk of head and neck cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (INHANCE). *Cancer Epidemiol*, 63:101615.
32. Di Credico G, Edefonti V, Polesel J, et al (2019). Joint effects of intensity and duration of cigarette smoking on the risk of head and neck cancer: A bivariate spline model approach. *Oral Oncol,* 94:47-57.
33. Suliankatchi RA, Sinha DN, Rath R, et al (2019). Smokeless tobacco use is "replacing" the smoking epidemic in the South-East Asia region. *Nicotine Tob Res*, 21(1):95–100.
34. Menach OP, Patel A, Oburra HO (2014). Demography and histologic pattern of laryngeal squamous cell carcinoma in Kenya. *Int J Otolaryngol*, 2014:507189.
35. Allegra E, Bianco MR, Ralli M, et al (2021). Role of Clinical-Demographic Data in Survival Rates of Advanced Laryngeal Cancer. *Medicina (Kaunas),* 57(3):267.
36. Voltzke KJ, Lee YA, Zhang ZF, et al (2018). Racial differences in the relationship between tobacco, alcohol, and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium. *Cancer Causes Control,* 29(7):619-630.
37. (NIPH) NI of PH (2007). Folkesundhedsrapporten Danmark 2007 [Public Health Report, Denmark 2007]; 2007.
38. LoConte NK, Brewster AM, Kaur JS, et al (2018). Alcohol and Cancer: A Statement of the American Society of Clinical Oncology. *J Clin Oncol,* 36(1):83-93.
39. Klein WMP, Jacobsen PB, Helzlsouer KJ (2020). Alcohol and Cancer Risk: Clinical and Research Implications. *JAMA*, 323(1):23–24.

40. World Cancer Research Fund, American Institute for Cancer Research (2018). Diet, nutrition, physical activity, and cancer: a global perspective. Continuous update project expert report. London: World Cancer Research Fund.
41. Manthey J, Shield KD, Rylett M, et al (2019). Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *Lancet,* 393(10190):2493–2502.
42. Berdzuli N, Ferreira-Borges C, Gual A, et al (2020). Alcohol control policy in Europe: overview and exemplary countries. *Int J Environ Res Public Health*, 17(21):8162.
43. Bagnardi V, Rota M, Botteri E, et al (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *Br J Cancer*, 112(3):580–593.
44. Grevers X, Ruan Y, Poirier AE, et al (2019). Estimates of the current and future burden of cancer attributable to alcohol consumption in Canada. *Prev Med*, 122:40-48.
45. Bradley PJ (2016). Laryngeal cancer in nondrinker nonsmoker young patients: a distinct pathological entity? *Curr Opin Otolaryngol Head Neck Surg*, 24(2):140-147.
46. Al-Qudah MA, Al-Shaikh AF, Haddad HK, et al (2020). Prevalence and Detection of Sexually Transmitted Cases of Laryngeal Carcinoma. *Head Neck Pathol*, 14(4):909-914.
47. Hernandez BY, Goodman MT, Lynch CF, et al (2014). Human papillomavirus prevalence in invasive laryngeal cancer in the United States. *PLoS One*, 9(12):e115931.
48. Lu Y, Li P, Luo G, et al (2020). Cancer attributable to human papillomavirus infection in China: Burden and trends. *Cancer*, 126(16):3719-3732.
49. Buttmann-Schweiger N, Delere Y, Klug SJ, et al (2017). Cancer incidence in Germany attributable to human papillomavirus in 2013. *BMC Cancer*, 17(1):682.
50. Senkomago V, Henley SJ, Thomas CC, et al (2019). Human papillomavirus–attributable cancers–United States, 2012-2016. *MMWR Morb Mortal Wkly Rep*, 68(33):724-728.
51. Syrjänen S, Syrjänen K (2019). HPV in Head and Neck Carcinomas: Different HPV Profiles in Oropharyngeal Carcinomas - Why? *Acta Cytol,* 63(2):124-142.
52. Castellsagué X, Alemany L, Quer M, et al (2016). HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. *J Natl Cancer Inst,* 108(6):djv403.
53. Tsimplaki E, Argyri E, Sakellaridis A, et al (2017). Oropharyngeal and laryngeal but not oral cancers are strongly associated with high-risk human papillomavirus in 172 Greek patients. *J Med Virol*, 89(1):170-176.
54. Astl J, Holy R, Maute E, et al (2021). Genome of Helicobacter pylori and Serotype of HPV Detected in Oropharyngeal and Laryngeal Cancer and Chronic Inflammation Patients. *Int J Environ Res Public Health*, 18(18):9545.
55. Nahet A, Boublenza L, Hassaine H, et al (2016). [HPV DNA genotyping: A study of anogenital, head and neck and skin cancers in a population from west Algerian. HPV detection in different cancers from an Algerian population]. *Bull Cancer*, 103(5):455-460.
56. Kariche N, Hortal MT, Benyahia S, et al (2018). Comparative assessment of HPV, alcohol and tobacco etiological fractions in Algerian patients with laryngeal squamous cell carcinoma. *Infect Agent Cancer*, 13:8.
57. Chen WC, Chuang HC, Lin YT, et al (2017). Clinical impact of human papillomavirus in laryngeal squamous cell carcinoma: a retrospective study. *Peer J*, 5:e3395.
58. Yang D, Shi Y, Tang Y, et al (2019). Effect of HPV Infection on the Occurrence and Development of Laryngeal Cancer: A Review. *J Cancer*, 10(19):4455-4462.
59. He J, Meng H, Yao G, et al (2017). New research progress of HPV and Larynx cancer. *Progress in Modern Biomedicine*, 17:5989–92
60. Wang TH, Hsia SM, Shih YH, et al (2017). Association of Smoking, Alcohol Use, and Betel Quid Chewing with Epigenetic Aberrations in Cancers. *Int J Mol Sci*, 18(6):1210.
61. Hashim D, Genden E, Posner M, et al (2019). Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden. *Ann Oncol*, 30(5):744-756.
62. Wu Y-H, Yen C-J, Hsiao J-R , et al (2016). A comprehensive analysis on the association between tobacco-free betel quid and risk of head and neck cancer in Taiwanese men. *PLoS One*, 11(10): e0164937.

63. Ferster APO, Schubart J, Kim Y, et al (2017). Association Between Laryngeal Cancer and Asbestos Exposure: A Systematic Review. *JAMA Otolaryngol Head Neck Surg*, 143(4):409-416.
64. Peng WJ, Mi J, Jiang YH (2016). Asbestos exposure and laryngeal cancer mortality. *Laryngoscope*, 126 (5):1169-1174.
65. Menvielle G, Fayossé A, Radoï L, et al (2016). The joint effect of asbestos exposure, tobacco smoking and alcohol drinking on laryngeal cancer risk: evidence from the French population-based case-control study, ICARE. *Occup Environ Med*, 73(1):28-33.
66. Hall AL, Kromhout H, Schüz J, et al (2020). Laryngeal Cancer Risks in Workers Exposed to Lung Carcinogens: Exposure-Effect Analyses Using a Quantitative Job Exposure Matrix. *Epidemiology*, 31(1):145-154.
67. Zhou J, Zhang D, Yang Y, et al (2016). Association between helicobacter pylori infection and carcinoma of the larynx or pharynx. *Head Neck*, 38 Suppl 1:E2291-E2296.
68. Lu YT, Hsin CH, Lu YC, et al (2021). Risk of head and neck cancer in patients with peptic ulcers and the effect of Helicobacter pylori treatment. *Sci Rep*, 11(1):6229.
69. Eells AC, Mackintosh C, Marks L, et al (2020). Gastroesophageal reflux disease and head and neck cancers: A systematic review and meta-analysis. *Am J Otolaryngol*, 41(6):102653.
70. Parsel SM, Wu EL, Riley CA, et al (2019). Gastroesophageal and Laryngopharyngeal Reflux Associated with Laryngeal Malignancy: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*, 17(7):1253-1264.e5.
71. Sereg-Bahar M, Jerin A, Hocevar-Boltezar I (2015). Higher levels of total pepsin and bile acids in the saliva as a possible risk factor for early laryngeal cancer. *Radiol Oncol,* 49(1):59-64.
72. Kim SY, Han KD, Joo YH (2019). Metabolic Syndrome and Incidence of Laryngeal Cancer: A Nationwide Cohort Study. *Sci Rep*, 9(1):667. Published 2019 Jan 24.
73. Kim HB, Kim GJ, Han KD, et al (2021). Changes in metabolic syndrome status and risk of laryngeal cancer: A nationwide cohort study. *PLoS One*, 16(6):e0252872.
74. Kravietz A, Angara P, Le M, et al (2018). Disparities in screening for head and neck cancer: evidence from the NHANES, 2011-2014. *Otolaryngol Head Neck Surg*, 159(4):683–91.
75. Graboyes EM, Hughes-Halbert C (2019). Delivering Timely Head and Neck Cancer Care to an Underserved Urban Population-Better Late Than Never, but Never Late Is Better. *JAMA Otolaryngol Head Neck Surg*, 145(11):1010-1011.
76. McMaughan DJ, Oloruntoba O, Smith ML (2020). Socioeconomic status and access to healthcare: interrelated drivers for healthy aging. *Front Public Health,* 8:231.
77. Abdel-Rahman O (2019). Socioeconomic predictors of suicide risk among cancer patients in the United States: a population-based study. *Cancer Epidemiol*, 63:101601.
78. Fullmer T, Wilde DC, Shi JW, et al (2020). Demographic and Tumor Characteristic Impact on Laryngeal Cancer Outcomes in a Minority Underserved Patient Population. *Otolaryngol Head Neck Surg*, 162(6):888-896.
79. Andersson TM, Engholm G, Pukkala E, et al (2018). Avoidable cancers in the Nordic countries-The impact of alcohol consumption. *Eur J Cancer,* 103:299-307.
80. Wang N, Lv H, Huang M (2020). Impact of gender on survival in patients with laryngeal squamous cell carcinoma: a propensity score matching analysis. *Int J Clin Exp Pathol*, 13(3):573-581