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Global variations and socioeconomic inequalities in lifetime risk of lip, oral cavity, and pharyngeal cancer: a population-based systematic analysis of GLOBOCAN 2022

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Background: In 2021, the World Health Organization (WHO) identified poor oral health as a major health expenditure burden. While lip, oral cavity, and pharyngeal cancers (LOCP) are an important group of diseases threatening oral health, there have been limited studies assessing global variations in lifetime risks (LR) according to socioeconomic inequalities.

Materials and methods: We obtained national incidence and mortality estimates of LOCP in 185 countries from the GLOBOCAN database of the International Agency for Research on Cancer (IARC), corresponding all-cause mortality, population data, and the Human Development Index (HDI, with higher values indicating superior socioeconomic level) through the United Nations, alongside oral health-related data through WHO and INDEXBOX. LR were calculated using the adjusted multiple primary method.

Results: In 2022, the global LR of developing and dying from LOCP were 0.92% (95% CI: 0.92%–0.92%) and 0.48% (95% CI: 0.48%–0.48%), respectively, with the highest burden associated with cancers of the lip and oral cavity. The LR of being diagnosed with LOCP or dying from the disease were 2.24 (95% CI: 2.22–2.25) and 2.30 (95% CI: 2.27–2.33) times higher among males relative to females. The highest LR for lip and oral cavity, salivary gland, oropharynx, and hypopharynx cancers were largely concentrated in Australia/New Zealand, Europe, and North America; whereas nasopharynx cancer was more frequent in parts of Asia and Africa. The LR of developing and dying from LOCP were positively associated with HDI, dental healthcare expenditure, areca nut consumption, the availability of refined sugar, and early screening for oral diseases, and negatively associated with the prevalence of severe periodontal disease. Although the LR of LOCP decreased with age, the rate of decline was relatively slow until the age of 50, and even at age 70, there remained non-negligible risks.

Conclusion: Global variations in the LR of developing and dying from LOCP by subsite, sex and age reveal significant disparities by world region, socioeconomic levels and oral healthcare factors.

Keywords: oral cavity and pharyngeal cancers, burden, epidemiology, global, lifetime risk, lip

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Introduction

In 2022, lip, oral cavity, and pharyngeal cancers (LOCP) were responsible for close to 4% of all cancer diagnoses and deaths worldwide[1]. LOCP comprises malignancies of the lip, oral cavity, salivary glands, oropharynx, nasopharynx, and hypopharynx, that are characterized by diagnoses in topographical areas that have intricate anatomical structures and high nerve density. The clinical management of LOCP is particularly challenging given the propensity of these cancers to go undetected at early asymptomatic stage, being often diagnosed at a late stage. The consequences of delays result in debilitating effects on essential functions including chewing and speech, facial disfigurement, a decline in overall quality of life, and fatal outcomes[2–4].

The lifetime risk of developing or dying from cancer is a measure that longitudinally assesses the cumulative probability that a person will be diagnosed with or die from cancer over the remainder of his or her lifetime (from birth to death). Compared with incidence rates, mortality rates, or 0–74 cumulative risks, lifetime risk is more intuitive and accounts for competing risks of

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death from other causes[5-7]. In 2021, the World Health Organization (WHO) identified poor oral health as a leading health expenditure burden, comparable to diabetes and cardiovascular disease[8]. Spatial analysis coupled with socioeconomic disparity evaluation flagged areas of significant disease risk variation and guided appropriate resource management. Despite LOCP being one of the most important diseases to threaten oral health, there have been a paucity of studies investigating global variations in these diseases according to socioeconomic inequities in lifetime risk.

The aim of this study is therefore to examine such differences so as to contribute to the implementation of the 2021 WHO Oral Health Resolution, so as to optimizer the allocation of health resources within existing resources and systems, and to inform the development of targeted interventions and disease prevention policies for comprehensive LOCP control.

HIGHLIGHTS

- Lip, oral cavity, and pharyngeal cancer (LOCP) is a relatively infrequent cancer class with <1% lifetime diagnosis risk and 0.5% death risk, and males have twofold risks compared to females.
- The highest lifetime risks for lip and oral cavity, salivary gland, oropharynx, and hypopharynx cancers were predominantly concentrated in Australia/New Zealand, Europe, and North America. In contrast, nasopharynx cancer exhibited a higher frequency in certain regions of Asia and Africa.
- The lifetime risk of developing and dying from LOCP was positively correlated with the human development index, dental healthcare expenditure, areca nut consumption, availability of refined sugar, and early oral disease screening, and inversely correlated with the prevalence of severe periodontal disease.
- Although the lifetime risk LOCP decreases with age, the rate of decline is relatively slow until the age of 50. Notably, even at the age of 70, the risk remains non-negligible.

Methods

Data sources

Drawing from the GLOBOCAN 2022 estimates of cancer incidence and mortality in 185 countries worldwide, developed and disseminated by the International Agency for Research on Cancer (IARC), we obtained sex- and age-specific (ranging from 0–4 to 85+ years by 5 years) incidence and mortality cases for LOCP and its subtypes[1,9]. These cancers were classified under the tenth edition of the International Classification of Diseases (ICD-10). The relevant cancer dictionary and ICD-10 codes were provided in Supplemental Digital Content, Table S1, available at: http://links.lww.com/JS9/E89. Population and all-cause mortality figures were sourced from the United Nations World Population Prospects 2019[10]. We stratified these data according to the 20 aggregated areas defined by the United Nations Population Division[1] and into quartiles based on the for-tier Human Development Index (HDI), which is a composite indicator that assesses human development through three dimensions: health, education, and income indicators[11]. The HDI components (life expectancy at birth, gross national income per capita, mean years of schooling, and expected years of schooling), health system factors (including human resources for health [HRH], universal health coverage [UHC], and healthcare access and quality index [HAQ]), and lifestyle factors (tobacco use among persons aged 15 years and older, total alcohol consumption per capita among persons aged 15 years and older, and mortality due to low physical activity) were obtained from the WHO[11,12] and the Global Burden of Disease[13].

Oral health related data, including per 100,000 population areca nut consumption, per capita dental healthcare expenditure, per capita availability of refined sugar, prevalence of severe periodontal disease among people aged 15 and above, and availability early screening for oral diseases were obtained through INDEXBOX[14] and WHO[15].

Statistical methods

In estimating lifetime risks, we employed the Adjusted Multiple Primary (AMP) method[16,17], which accounts for deaths due to other causes and adjusts for multiple primary cancers included in the incidence rates. We utilized age-specific incidence, mortality, and all-cause mortality rates for LOCP, stratified by 5-year age groups, to calculate the sex-specific lifetime risks of developing or dying from LOCP across different age brackets, which represents the probability of developing or dying from LOCP from the starting age group onwards[7,18]. The detail of the method is shown in Supplemental Digital Content Item S1 (available at: http://links.lww.com/JS9/E89). The mortality-to-incidence ratio (MIR) was calculated as the ratio of lifetime mortality risk to lifetime incidence risk.

We calculated the lifetime risk of developing or dying from LOCP and its subtypes at global, regional, country, and HDI quartile levels, and stratified these risks by sex. We assessed the relative risks by sex, and evaluated the association of lifetime risk of LOCP with HDI and oral health factors, using Spearman correlation coefficients. Additionally, we calculated the remaining risks for LOCP development and death at various age groups. For comparison, we contrasted the lifetime risk with the cumulative risk for the age group of 0–74 years, a standard measure of cancer burden that serves as a proxy of lifetime risk without adjustments for competing non-cancer risks, multiple primary conditions, and life expectancy[16,17,19]. A Poisson distribution of LOCP incidence and mortality was assumed, and corresponding 95% confidence intervals (CIs) were calculated on this basis.

To assess the stability of the results, we conducted a sensitivity analysis based on the GLOBOCAN estimation methodologies and data quality tiers (https://gco.iarc.who.int/today/en/data-sources-methods), excluding 39 countries with incidence/mortality estimation method codes 4 (estimates derived from partitioning frequency data of neighboring countries) or 9 (estimates based on rates of neighboring countries or registries within the same area).

To explore the association of HDI with the lifetime risks of developing and dying from LOCP and MIR, post hoc analyses were conducted to analyze the mediating roles of HDI components, health system factors, and lifestyle factors among all countries, countries with higher and lower HDI. To highlight

the specificity of LOCP, we compared LOCP with other major cancers, including lung cancer and other digestive system cancers (esophagus, stomach, colorectum, liver, gallbladder, pancreas). The analyses examined three key metrics for each cancer: lifetime risk of development, lifetime risk of death, and MIR, assessing geographical variations in these parameters and their associations with HDI.

All analyses were conducted using SAS version 9.4 and world maps were created with the QGIS version 3.36. All reported *P* values were based on a two-sided test of significance, with $P < 0.05$ considered statistically significant. The work has been reported in line with the STROCSS criteria[20].

Results

Global lifetime risks of LOCP

In 2022, it was estimated that the global lifetime risk of developing and dying from LOCP were 0.92% (95% CI: 0.92%–0.92%) and 0.48% (95% CI: 0.48%–0.48%), respectively. Among these, lip, oral cavity cancer had the highest risks of development and death, of 0.48% (95% CI: 0.48%–0.49%) and 0.24% (95% CI: 0.24%–0.24%). Salivary gland cancers had the lowest lifetime risks, of 0.07% (95% CI: 0.07%–0.07%) and 0.03% (95% CI: 0.03%–0.03%), respectively.

The lifetime risk of developing and dying from LOCP among males was 1.26% (95% CI: 1.25%–1.26%) and 0.66% (95% CI: 0.66%–0.66%) respectively, while in females the risks corresponded to 0.56% (95% CI: 0.56%–0.56%) and 0.29% (95% CI: 0.28%–0.29%). The respective male lifetime risks for development of, or death from LOCP were 2.24 (95% CI: 2.22–2.25) and 2.30 (95% CI: 2.27–2.33) times higher than those for females. The most significant sex difference was seen for hypopharyngeal cancer, with males exhibiting respective lifetime risks of development and death that were 4.87 (95% CI: 4.74–5.00) and 5.08 (95% CI: 4.87–5.29) times greater than those of females.

Global variations in lifetime risks of LOCP

Significant differences in the lifetime risk of developing and dying from LOCP were observed across countries and geographic regions (Fig. 1A-B). In terms of the latter, Australia/New Zealand had the highest lifetime risks for LOCP development of 1.63% (95% CI: 1.58%–1.68%), followed by Melanesia, Western Europe and South-Central Asia. Conversely, Western Africa had the lowest risks of 0.24% (95% CI: 0.23%–0.26%), with risks in Middle Africa, Central America, and Eastern Africa also ranking low (Fig. 2A and Supplemental Digital Content, Table S2, available at: http://links.lww.com/JS9/E89). For the

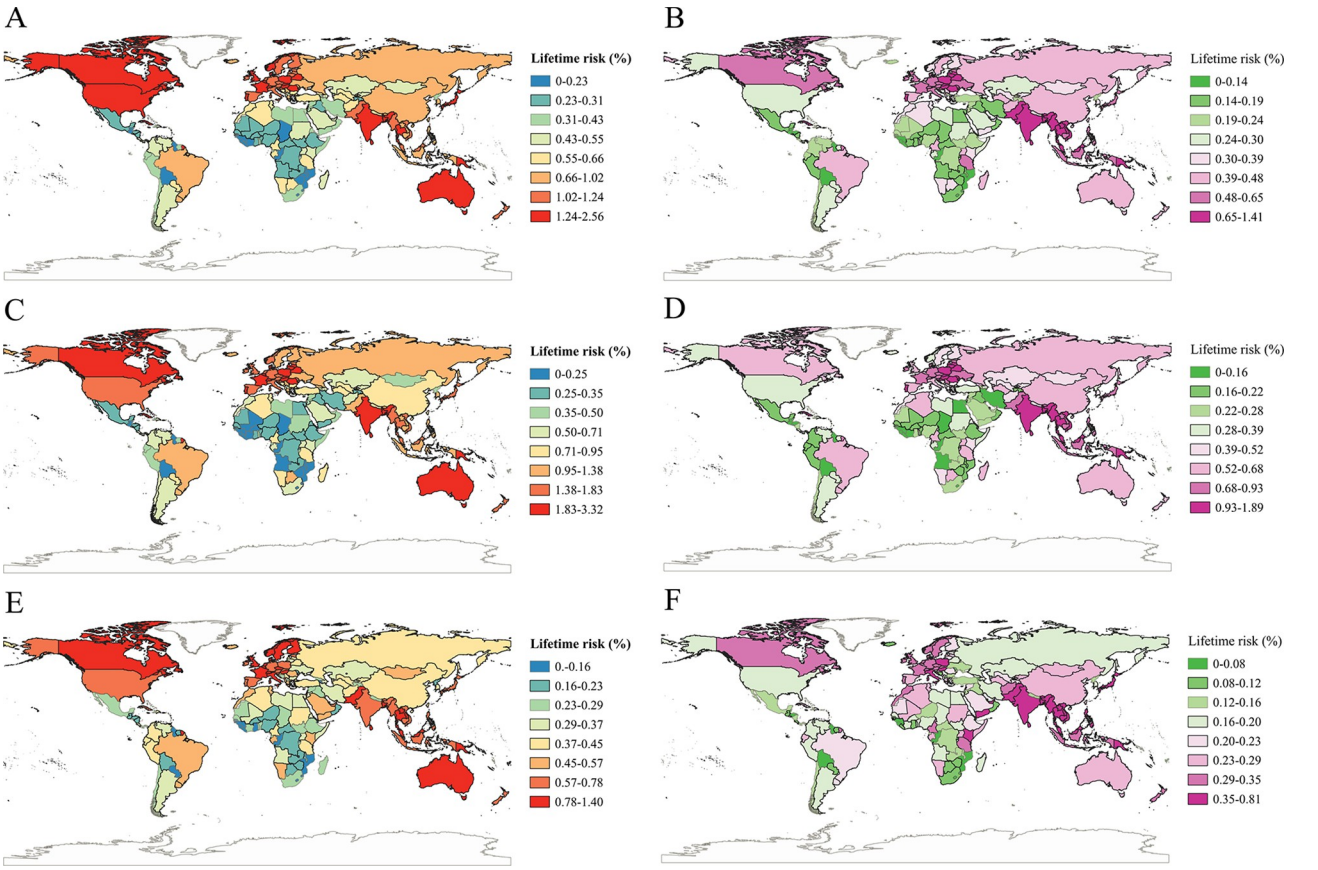

Figure 1. Lifetime risks of developing or dying from LOCP for the whole population, males and females. (A) Lifetime risks of developing LOCP in the whole population; (B) lifetime risks of dying from LOCP in the whole population; (C) lifetime risks of developing LOCP in males; (D) lifetime risks of dying from LOCP in males; (E) lifetime risks of dying from LOCP in males; (F) lifetime risks of dying from LOCP in females. Abbreviation: LOCP, lip, oral cavity, and pharynx cancers.

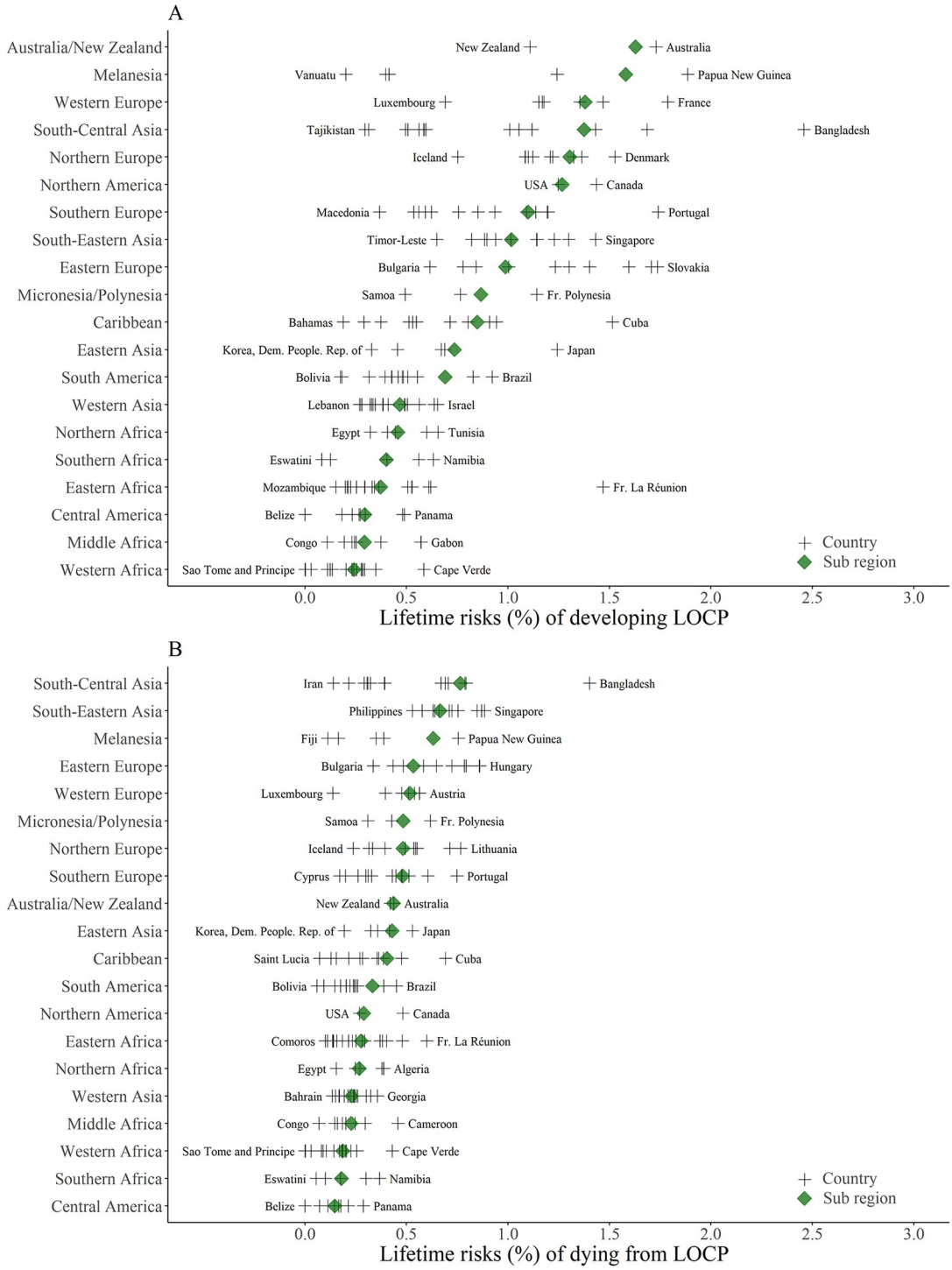

Figure 2. Lifetime risks of developing or dying from LOCP for the whole population, by country and region. (A) Lifetime risks of developing LOCP; (B) lifetime risks of dying from LOCP. Abbreviation: LOCP, lip, oral cavity, and pharynx cancers.

lifetime risks of dying from LOCP, South-Central Asia ranked first at 0.77% (95% CI: 0.76%–0.78%), followed by South-Eastern Asia, Melanesia, and Eastern Europe. Notably, Australia/New Zealand, leading in terms of risk of developing LOCP, ranked much lower (9 of 20 regions) in terms of risk of death. Central America had the lowest lifetime risk of LOCP at 0.15% (95% CI: 0.14%–0.16%), with Africa regions also showing low risk (Fig. 2B and Supplemental Digital Content, Table S2, available at: http://links.lww.com/JS9/E89). The MIR of LOCP across regions, ranging from 0.23 (95% CI: 0.22–0.23) in North America to 0.78 (95% CI: 0.67–0.89) in Middle Africa, were presented in Supplemental Digital Content, Table S3 (available

at: http://links.lww.com/JS9/E89). At the country level, Bangladesh exhibited the highest lifetime risks for both development and death of LOCP, reaching 2.46% (95% CI: 2.41%–2.50%) and 1.40% (95% CI: 1.37%–1.44%), respectively. The country-specific lifetime risks for developing and dying from LOCP in 2022 are detailed in Supplemental Digital Content, Tables S4 and S5 (available at: http://links.lww.com/JS9/E89). The national and regional distributions of lifetime risks of LOCP was similar by sex (Fig. 1C-F, Supplemental Digital Content, Figure S1 and Tables S6–9, available at: http://links.lww.com/JS9/E89), but the risk was almost always higher among males relative to females (Supplemental Digital Content, Tables S10–12, available at: http://links.lww.com/JS9/E89).

The global burden of subtypes of LOCP varied considerably, with lip and oral cavity cancer being the most common, having the highest lifetime risks of development and death in 163 and 149 countries, respectively. Nasopharyngeal cancer ranked second, leading in 15 and 22 countries (Supplemental Digital Content, Figure S2 and Tables S13–14, available at: http://links.lww.com/JS9/E89). The highest lifetime risks for lip and oral cavity, salivary gland, oropharynx, and hypopharynx cancers were largely concentrated in Australia/New Zealand, Europe, and North America; whereas nasopharyngeal cancer was more common in parts of Asia, Africa and Micronesia/Polynesia (Supplemental Digital Content, Figures S3 and S4, available at: http://links.lww.com/JS9/E89).

Inequities in socioeconomic and oral health factors in lifetime risk of LOCP

As shown in Table 1 and Fig. 3, the lifetime risk of LOCP increased with HDI globally, by sex, and for each of the subsites other than nasopharynx (Supplemental Digital Content, Figure S5, available at: http://links.lww.com/JS9/E89). Notably, medium HDI countries (including India) were observed to have the highest lifetime risks of developing or dying from LOCP at 1.27% (95% CI: 1.26–1.28) and 0.71% (95% CI: 0.71%–0.72%). Despite an increasing trend in the lifetime risk of LOCP with increasing HDI, the MIR exhibited a decreasing trend (Supplemental Digital Content, Figures S6–7, available at: http://links.lww.com/JS9/E89). The MIR was 0.52 (0.52–0.52) globally, 0.39 (0.39–0.40) for countries with very high

Table 1

Lifetime risks (%) of developing and dying from LOCP by sex and level of human development index, 2022

	LOCP	Lip, oral cavity	Salivary glands	Oropharynx	Nasopharynx	Hypopharynx
Development in both sexes						
World	0.92(0.92–0.92)	0.48(0.48–0.49)	0.07(0.07–0.07)	0.13(0.13–0.13)	0.13(0.13–0.13)	0.11(0.11–0.11)
Very high HDI country	1.13(1.12–1.13)	0.59(0.59–0.60)	0.10(0.10–0.10)	0.24(0.24–0.25)	0.07(0.07–0.07)	0.12(0.12–0.12)
High HDI country	0.69(0.69–0.70)	0.27(0.26–0.27)	0.06(0.06–0.06)	0.07(0.07–0.07)	0.24(0.24–0.24)	0.06(0.06–0.06)
Medium HDI country	1.27(1.26–1.28)	0.79(0.78–0.80)	0.05(0.05–0.06)	0.15(0.15–0.15)	0.07(0.07–0.08)	0.20(0.20–0.21)
Low HDI country	0.48(0.47–0.49)	0.29(0.29–0.30)	0.05(0.05–0.05)	0.03(0.03–0.04)	0.07(0.06–0.07)	0.04(0.04–0.04)
Dying in both sexes						
World	0.48(0.48–0.48)	0.24(0.24–0.24)	0.03(0.03–0.03)	0.07(0.07–0.07)	0.09(0.09–0.09)	0.05(0.05–0.05)
Very high HDI country	0.44(0.44–0.45)	0.20(0.20–0.20)	0.04(0.04–0.04)	0.10(0.10–0.10)	0.04(0.04–0.04)	0.06(0.06–0.07)
High HDI country	0.41(0.41–0.41)	0.15(0.15–0.15)	0.03(0.03–0.03)	0.05(0.04–0.05)	0.16(0.15–0.16)	0.03(0.03–0.03)
Medium HDI country	0.71(0.71–0.72)	0.45(0.44–0.45)	0.03(0.03–0.04)	0.09(0.09–0.09)	0.05(0.05–0.05)	0.09(0.08–0.09)
Low HDI country	0.33(0.32–0.34)	0.20(0.19–0.21)	0.04(0.04–0.04)	0.02(0.02–0.02)	0.05(0.05–0.06)	0.02(0.02–0.03)
Development in male						
World	1.26(1.25–1.26)	0.62(0.62–0.63)	0.08(0.07–0.08)	0.20(0.20–0.21)	0.18(0.18–0.18)	0.17(0.17–0.17)
Very high HDI country	1.55(1.54–1.56)	0.75(0.74–0.76)	0.12(0.12–0.12)	0.38(0.38–0.39)	0.10(0.10–0.10)	0.21(0.20–0.21)
High HDI country	0.93(0.92–0.93)	0.32(0.32–0.33)	0.07(0.07–0.07)	0.11(0.11–0.11)	0.33(0.33–0.33)	0.10(0.09–0.10)
Medium HDI country	1.77(1.75–1.78)	1.07(1.06–1.09)	0.05(0.05–0.05)	0.24(0.24–0.25)	0.09(0.09–0.10)	0.31(0.31–0.32)
Low HDI country	0.59(0.58–0.61)	0.36(0.35–0.37)	0.05(0.05–0.06)	0.05(0.04–0.05)	0.08(0.08–0.09)	0.05(0.05–0.06)
Dying in male						
World	0.66(0.66–0.66)	0.31(0.30–0.31)	0.04(0.04–0.04)	0.10(0.10–0.11)	0.12(0.12–0.13)	0.09(0.08–0.09)
Very high HDI country	0.62(0.61–0.63)	0.24(0.24–0.25)	0.05(0.05–0.05)	0.15(0.15–0.16)	0.06(0.06–0.06)	0.11(0.11–0.11)
High HDI country	0.56(0.55–0.56)	0.18(0.18–0.18)	0.03(0.03–0.03)	0.07(0.07–0.07)	0.22(0.22–0.23)	0.06(0.05–0.06)
Medium HDI country	0.99(0.98–1.00)	0.60(0.60–0.61)	0.03(0.03–0.03)	0.15(0.14–0.15)	0.07(0.07–0.07)	0.13(0.13–0.14)
Low HDI country	0.41(0.39–0.42)	0.24(0.23–0.25)	0.04(0.03–0.05)	0.03(0.02–0.03)	0.06(0.06–0.07)	0.03(0.03–0.04)
Development in female						
World	0.56(0.56–0.56)	0.33(0.33–0.34)	0.06(0.06–0.06)	0.05(0.05–0.05)	0.08(0.08–0.08)	0.04(0.03–0.04)
Very high HDI country	0.69(0.69–0.70)	0.44(0.43–0.44)	0.08(0.08–0.09)	0.10(0.10–0.10)	0.04(0.04–0.04)	0.03(0.03–0.03)
High HDI country	0.44(0.43–0.44)	0.20(0.20–0.20)	0.05(0.05–0.06)	0.03(0.03–0.03)	0.14(0.13–0.14)	0.01(0.01–0.01)
Medium HDI country	0.71(0.70–0.72)	0.48(0.47–0.48)	0.06(0.05–0.06)	0.05(0.05–0.05)	0.05(0.05–0.05)	0.08(0.08–0.08)
Low HDI country	0.36(0.35–0.38)	0.23(0.22–0.24)	0.05(0.04–0.05)	0.02(0.01–0.02)	0.05(0.05–0.06)	0.02(0.02–0.03)
Dying in female						
World	0.29(0.28–0.29)	0.16(0.16–0.17)	0.03(0.03–0.03)	0.03(0.03–0.03)	0.05(0.05–0.05)	0.02(0.02–0.02)
Very high HDI country	0.26(0.26–0.27)	0.15(0.15–0.16)	0.03(0.03–0.03)	0.04(0.04–0.04)	0.02(0.02–0.02)	0.02(0.02–0.02)
High HDI country	0.24(0.24–0.25)	0.11(0.11–0.11)	0.02(0.02–0.02)	0.02(0.02–0.02)	0.08(0.08–0.09)	0.01(0.01–0.01)
Medium HDI country	0.41(0.40–0.41)	0.27(0.27–0.28)	0.04(0.03–0.04)	0.03(0.03–0.03)	0.04(0.03–0.04)	0.03(0.03–0.04)
Low HDI country	0.26(0.24–0.27)	0.16(0.15–0.16)	0.04(0.03–0.04)	0.01(0.01–0.01)	0.04(0.04–0.04)	0.01(0.01–0.01)

Abbreviation: LOCP, lip, oral cavity, and pharynx cancers.

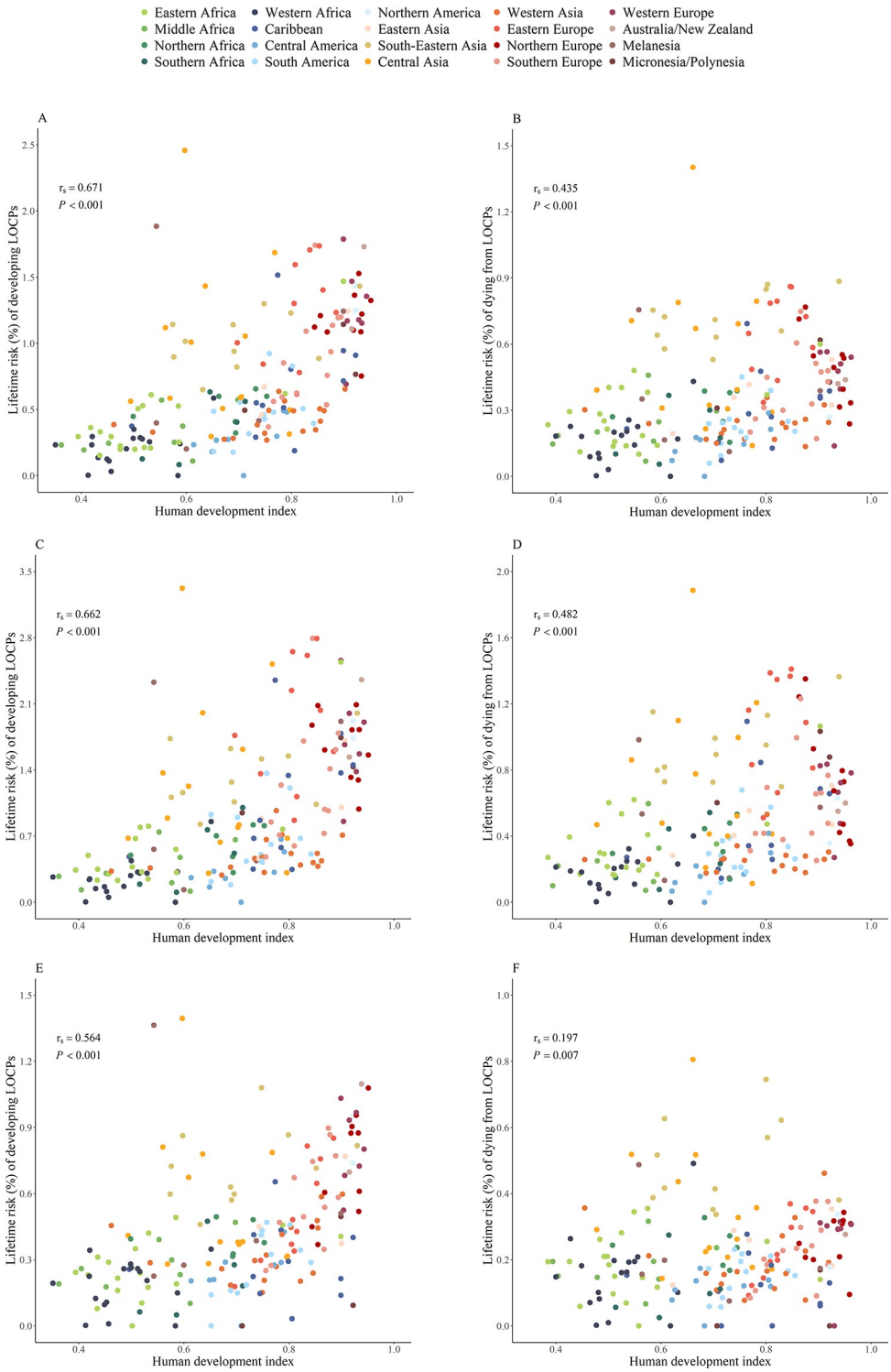

Figure 3. Association of lifetime risks of LOCP with human development index for the whole population, males and females; 183 countries were used for this analysis. (A) Lifetime risks of developing LOCP in the whole population; (B) lifetime risks of dying from LOCP in the whole population; (C) lifetime risks of developing LOCP in males; (D) lifetime risks of dying from LOCP in males; (E) lifetime risks of developing LOCP in females; (F) lifetime risks of dying from LOCP in females. Abbreviation: LOCP, lip, oral cavity, and pharynx cancers.

HDI, and 0.69 (0.66–0.72) for countries with low HDI (Supplemental Digital Content Table S15, available at: http://links.lww.com/JS9/E89).

The lifetime risks for LOCP and the constituent subtypes were higher in countries with early screening for oral diseases available (Supplemental Digital Content, Figures S8 and S9, http://links.lww.com/JS9/E89), and positively associated with per capita dental healthcare expenditure (Supplemental Digital Content, Figures S10 and S11, http://links.lww.com/JS9/E89), areca nut consumption (Supplemental Digital Content, Figures S12 and S13, available at: http://links.lww.com/JS9/E89), and per capita availability of refined sugar (Supplemental Digital Content, Figures S14 and S15, available at: http://links.lww.com/JS9/E89), while negatively associated with the prevalence of severe periodontal disease (among people aged 15 and above; Supplemental Digital Content, Figures S16 and S17, available at: http://links.lww.com/JS9/E89).

Remaining lifetime risks of LOCP by age

The lifetime risk of LOCP and its subtypes generally decreased with age, and the decline was slower before the age of 50 years (Fig. 4 and Supplemental Digital Content, Figure S18, available at: http://links.lww.com/JS9/E89). At age 50, the remaining risks of developing LOCP was 0.77% (95% CI: 0.77%–0.78%), representing 0.84 (95% CI: 0.83–0.84) of the lifetime development risks. Despite a sharp decline in lifetime risks between ages 50 to 70, the remaining risks at 70 years were 0.34% (95% CI: 0.33%–0.34%), which still constituted 0.37 (95% CI: 0.36–0.37) of the lifetime risks; a similar pattern was observed for the lifetime risks of death (Supplemental Digital Content, Tables S16–17, available at: http://links.lww.com/JS9/E89). The distribution of remaining risks by age in countries by region is detailed in Supplemental Digital Content, Tables S18-S24, available at: http://links.lww.com/JS9/E89. Although the pattern of changing remaining risks with age was consistent across sexes, females experienced a slower rate of decline in remaining risk compared to males after the age of 50 (Fig. 4; Supplemental Digital Content, Figure S18 and Table S25, available at: http://links.lww.com/JS9/E89).

Sensitivity analysis

The sensitivity analyses demonstrated robust consistency in the primary findings. Socioeconomic disparities persisted as evidenced by a sustained positive association between lifetime LOCP risk and HDI (Supplemental Digital Content, Figure S19, available at: http://links.lww.com/JS9/E89), while the MIR of LOCP exhibited an inverse relationship with HDI (Supplemental Digital Content, Figure S20, available at: http://links.lww.com/JS9/E89). Oral health analysis revealed significant positive associations between lifetime LOCP risk and four determinants: dental expenditure (Supplemental Digital Content, Figure S21, available at: http://links.lww.com/JS9/E89), areca

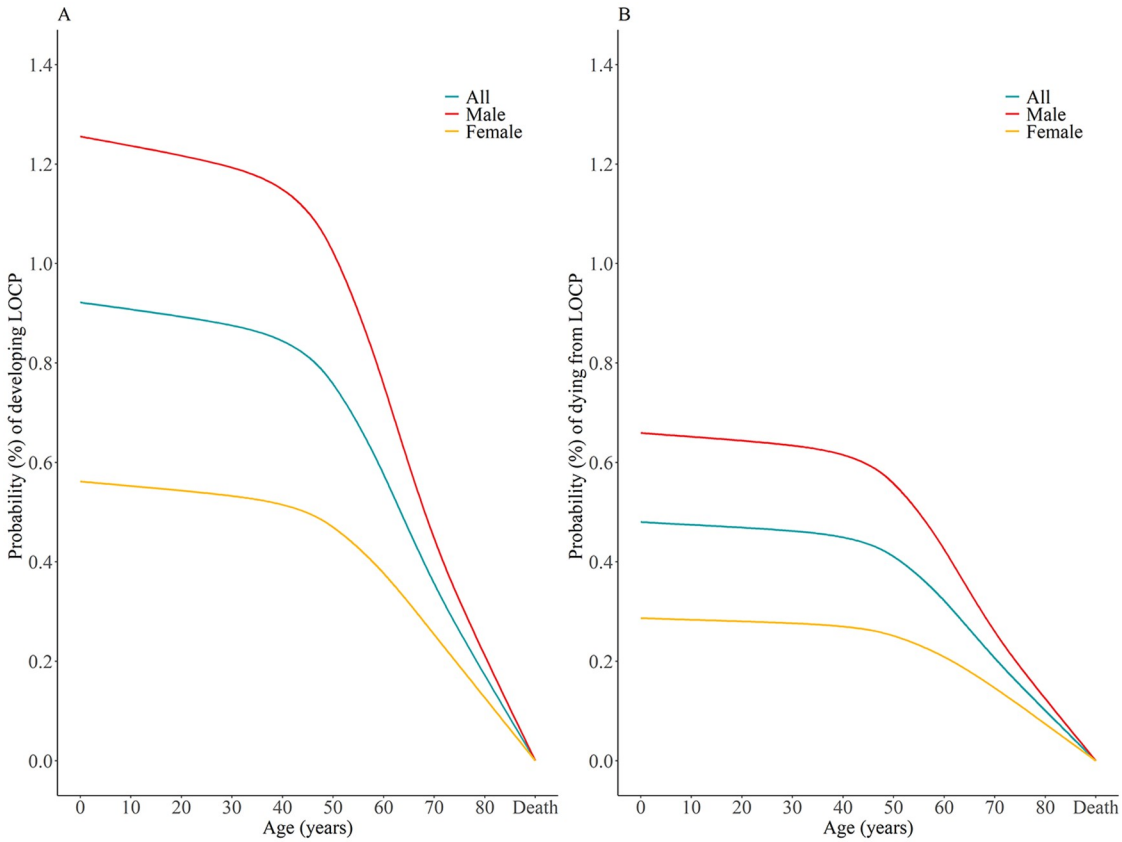

Figure 4. Remaining lifetime risks of developing or dying from LOCP across ages. (A) Lifetime risks of developing LOCP; (B) lifetime risks of dying from LOCP. Abbreviation: LOCP, lip, oral cavity, and pharynx cancers.

nut consumption (Supplemental Digital Content, Figure S22, available at: http://links.lww.com/JS9/E89), refined sugar availability (Supplemental Digital Content, Figure S23, available at: http://links.lww.com/JS9/E89), and early screening rates (Supplemental Digital Content, Figure S24, available at: http://links.lww.com/JS9/E89), contrasting with an inverse relationship for severe periodontal disease prevalence (Supplemental Digital Content, Figure S25, available at: http://links.lww.com/JS9/E89).

The association between lifetime risks and cumulative risks for age of 0–74 years is detailed in Item S2 (Supplemental Digital Content, Table S29 and Figure S26–27, available at: http://links.lww.com/JS9/E89.

Post-hoc analysis

Post hoc analyses revealed that health system factors play a significant mediating role in the association between HDI and the burden of LOCP in countries with higher HDI levels, whereas life expectancy serves as the primary mediator in countries with lower HDI levels (Supplemental Digital Content, Table S26 and Table S27, available at: http://links.lww.com/JS9/E89). Compared with lung cancer and other digestive system cancers, the regional disparities in the MIR of LOCP (the highest MIR was 3.47 [95% CI: 2.99–3.95] times the lowest) and its association with the HDI (Spearman's correlation coefficient: –0.75, $P < 0.001$) were particularly pronounced (Supplemental Digital Content, Table S28, available at: http://links.lww.com/JS9/E89).

Discussion

LOCP is a relatively infrequent class of cancers, characterized by a lifetime risk of diagnosis of <1% and of death of 0.5%. It is characterized by marked sex disparities, with males having two-fold higher risks than females. Compared with the most common respiratory organs cancer and other digestive system cancers, LOCP exhibits substantial regional disparities and a strong association with socioeconomic status, particularly evident in its MIR. Geographically, while Australia/Zealand and Melanesia exhibited the highest lifetime development risks of LOCP, South-Central and South-Eastern Asia were the world regions with the highest lifetime death risks. The lifetime risks of LOCP varied significantly across HDI and were influenced by oral health factors (e.g., per capita dental healthcare expenditure, areca nut consumption, and the prevalence of severe periodontal disease). Although the lifetime risk of LOCP decreased with age, the rate of decline was relatively slow until the age of 50 years, and even at the age of 70 years, there were remaining risks.

The regions with the most pronounced lifetime risk of developing LOCP were Oceania, Western Europe, South-Central Asia, and North America, and the regions with the highest lifetime risk of death concentrated in South-Central Asia, South-Eastern Asia, Melanesia, Eastern Europe, and Western Europe. These findings are broadly aligned with prior studies that have explored the global distribution of LOCP burden incidence or mortality[5,21,22]. Socioeconomic inequalities are postulated to contribute to the global variations in the lifetime risk of LOCP. Countries with higher HDI typically have a greater number of healthcare workers, more comprehensive health coverage, and higher accessibility and quality of medical services[23,24], which enable more effective screening and diagnosis of LOCP, thereby reducing the likelihood of missed diagnoses. Additionally, higher HDI countries often possess more advanced treatment technologies, which can significantly improve the survival rates of LOCP patients. As the study reveals, health system factors play a pivotal mediating role in the association between HDI and the burden of LOCP in those countries. Concurrently, these countries often tend to exhibit higher rates of unhealthy lifestyle behaviors (such as smoking and heavy alcohol consumption), and greater exposure to carcinogenic chemicals or radiation, all of which may contribute to the occurrence of LOCP[7,25]. In contrast, our study identifies life expectancy as the predominant mediating factor in the association between HDI and the lifetime risk of LOCP in countries with lower HDI. LOCP typically occurs after 60 years old and the lower life expectancy in these countries may lead to mortality from other diseases prior to the development of LOCP[7,25,26]. Additionally, countries with lower HDI have limited healthcare coverage and often lack resources for oral health examinations[27,28], resulting in either undiagnosed cases or diagnoses only at advanced stages of the disease, leading to a poorer prognosis for LOCP patients. Furthermore, the absence of high-quality population-based cancer registries in lower HDI countries may underestimate the burden of LOCP[25].

Global variations in the lifetime risks of LOCP are also influenced by oral health factors. The availability of early screening is crucial for the early diagnosis and treatment of the diseases, which naturally leads to a higher detection rate of cases and mortality, so it is not surprising to observe a higher lifetime risk of LOCP in countries with oral health screening. Although integrating oral health care into universal health care may facilitate early diagnosis and timely treatment of LOCP, it is unaffordable in many countries[5].

Our analysis revealed a positive correlation between lifetime risk of LOCPs and per capita dental healthcare expenditure, while an inverse association was observed with the prevalence of severe periodontal disease. This phenomenon should be interpreted with caution, and the possible explanations including at least two aspects. First, countries with a high prevalence of severe periodontal disease generally exhibit lower socioeconomic development levels and poorer healthcare service capacity and diagnostic capabilities[29,30]. Overt symptoms of advanced periodontitis demand less diagnostic complexity[31,32], compared to LOCP detection, potentially leading to underreported cases and artificially reduced LOCP burden. Second, severe periodontal disease already shows a sizable prevalence around age 35[33,34], well before the age of LOCP onset. In countries with high prevalence of severe periodontal disease, lower life expectancies may lead to patient mortality before LOCP onset[29,30], thereby reducing the observed LOCP burden. In contrast, countries with higher per capita oral healthcare expenditure demonstrate higher socioeconomic levels, better diagnostic capabilities, and longer life expectancy, thereby exhibiting a positive correlation with LOCP burden.

In South and East Asia, and the Pacific islands, such as India, China, and Melanesia, areca nut consumption is prevalent[35]. Our study indicated a positive correlation between the lifetime risks of LOCP and areca nut consumption, which partially explains the higher burden of LOCP in these regions. Availability of refined sugar may reflect national socioeconomic levels, and high refined sugar intake is associated with an increased prevalence of metabolic syndrome[36], which is considered a risk factor for LOCP[37].

We demonstrated a positive association between the availability of refined sugar and the lifetime risks of LOCP, suggesting its potential role in the global variations. In addition, factors such as lifestyle (smoking, drinking)[21,38], viral infections (human papillomavirus, Epstein-Barr virus [EBV], simplex sporadic virus)[39], and the natural environment (solar radiation, air pollution)[21,40] may influence the regional distribution of the lifetime risks of LOCP.

Unlike other types of LOCP, nasopharyngeal cancer exhibited a different geographic distribution, with higher lifetime risks in South and Eastern Asia; Northern, Eastern, and Central Africa; and Micronesia/Polynesia, as found previously[41]. The distribution of the lifetime risk of nasopharynx cancer may be attributed to regional environmental, lifestyle, and genetic factors[42-44]. Residents of these regions frequently consume preserved foods, such as salted fish, preserved meat, and salted vegetables, which contain high levels of N-nitrosamine, an established risk factor for nasopharyngeal cancer[42,45]. The high prevalence of EBV also contributes to the burden of the disease in East and South-East Asia[44]. In addition, nasopharynx cancer demonstrates a strong familial aggregation[46], with individuals having a family history at a 4-10 fold increased risk[42]. The variability in lifetime risk distributions across LOCP types implies the necessity for tailored interventions, reflecting the distinct risk profiles and etiologies of individual cancer types, rather than a generalized strategy.

In this study, we found that males had significantly higher lifetime risks of developing and dying from LOCP and its subtypes than females, which is consistent with previous findings[5,21,22]. Besides the potential protective effect of estrogens[47,48], males are more likely to engage in unhealthy lifestyle choices, such as higher smoking and alcohol consumption[49]. Occupational exposures to carcinogens, including ultraviolet light, electromagnetic radiation, and chemical pollutants, are also more common among males[49]. Furthermore, this study revealed that the association between the lifetime risk of LOCP and HDI was stronger in males than in females, suggesting that females may derive less benefit from socioeconomic development in terms of the burden of LOCP compared to males. These findings may provide supportive evidence for the consideration of sex differences in the allocation of healthcare resources, the development of public health policies, and the design of clinical trials for LOCP.

The lifetime risks of LOCP were relatively stable until the age of 50 years and decreased rapidly between the ages of 50 and 70, which may be related to the higher morbidity and mortality rates of LOCP in this age group[22,26]. These findings imply that the age window after 50 years is critical to LOCP screening. Despite the absence of guidelines for LOCP screening[26], existing studies indicate that visual inspection during dental practice and screening for EBV in nasopharyngeal cancer endemic areas are cost-effective for the prevention of LOCP[50,51]. Additionally, our data revealed residual risks of 30–40% for LOCP even at the age of 70, underscoring the necessity for continued vigilance and preventative efforts against LOCP throughout the entire human lifespan.

Previous studies on the burden of LOCP, which focused on incidence and mortality rates and presented results in the form of "per 1 000 000"[5,6], were less comprehensible to the general public and less conducive to individual risk assessment. In contrast, the lifetime risk perspective provides a more intuitive representation of disease burden by presenting it as a percentage, which is more easily understood by the public and more advantageous for government departments to develop targeted strategies for addressing disease burden. In addition, the global trends of increasing life expectancy and population aging have significant implications for disease burden assessment[52-55]. Previous studies focusing on 0–74 cumulative risk[1,56], especially in populations with longer life expectancy, may underestimate the true disease burden. The lifetime risk estimated using the AMP method mitigates the overestimation of primary cancer incidence risk and accounts for competing risks due to other causes of death and life expectancy, thereby providing a more nuanced perspective for disease burden assessment[57].

In addition to its methodological strengths, this study reveals substantial regional disparities and socioeconomic inequities in the burden of LOCP compared with lung cancer and other digestive system cancers, while elucidating the impact of modifiable risk factors, including dental healthcare expenditure, access to dental screening, areca nut consumption, the availability of refined sugar, and he prevalence of severe periodontal disease. These results pinpoint research priorities for LOCP that are oriented towards regional and socioeconomic differences and emphasize the urgent need to refine policies in health, education, and economics. To be specific, it highlight the necessity for equity-oriented oral health policies that optimize the allocation of healthcare resources, enhance interregional cooperation among areas with different HDI levels, and focus on regions with high behavioral risk exposure and inadequate services. Policy makers should integrate LOCP prevention into universal health coverage through targeted interventions, such as expanding community-based dental screening infrastructure, regulating betel nut and sugar-related products, and launching public awareness campaigns. Moreover, addressing the observed geographical heterogeneity will require strategies tailored to local contexts, ensuring that oral health system strengthening is adapted to local ecological environments and living customs. These evidence-based recommendations provide a roadmap for achieving the oral health goals of WHO by 2030, particularly in reducing the double burden of oral diseases in transitioning economies.

This study offers valuable insights for surgical practitioners through four key contributions. First, it provides a macro-level analysis of disease burden, facilitating strategic planning of healthcare resource allocation according to national development status and socioeconomic conditions. Second, the study quantifies risk of LOCP, enabling targeted health education campaigns to optimize preventive intervention strategies. Third, it also identifies research gaps from the perspective of lifetime risk, highlighting under-investigated subpopulations requiring prioritized investigation. Fourth, the study leverages multinational epidemiological evidence to support the development of unified strategies for prevention, treatment, and evidence-based care, thereby promoting global collaboration in LOCP management.

However, this study also had some limitations. Firstly, our estimates relied on local cancer registry data and national vital statistics, with a relative scarcity of high-quality incidence data in some transitioning countries, particularly in the regions of South America and Africa, while official mortality statistics currently

only cover about one-third of the world's population[58]. Despite the stability of the main findings in a set of sensitivity analyses, data of relatively lower quality may lead to underestimation of the LOCP burden and overestimation of regional disparities and socioeconomic inequities. Additionally, such data quality issues may attenuate the associations between LOCP burden and modifiable risk factors. Future studies should focus on improving data collection in regions with data scarcity and explore more effective methods for incorporating data from multiple sources to enhance representativeness. Secondly, this study is a cross-sectional observational study and cannot establish causality between LOCP burden and factors such as socioeconomic status and oral healthcare due to potential confounding influences. Further longitudinal or experimental studies are needed to determine causal associations. Thirdly, this study focused on cross-sectional analyses of the most recent GLOBOCAN data, which did not reflect the temporal evolution of the lifetime risk of LOCP. In future studies, we will use multi-temporal data to explore trends in the lifetime risk of LOCP. Lastly, as the GLOBOCAN 2022 estimates are derived largely from datasets collected prior to 2020, they fail to reflect the impact of the coronavirus disease 2019 (COVID-19) pandemic, the impact of the coronavirus disease 2019 (COVID-19) pandemic did not directly influence the data quality of this study. However, the actual situation may have changed due to the COVID-19 pandemic. For instance, disruptions in oral healthcare services, increased sedentary lifestyles due to prolonged home isolation, and a significant rise in all-cause mortality and a decline in life expectancy due to COVID-19 could have led to a reduction in LOCP diagnoses[59,60]. This may result in a short-term reduction in the observed burden of LOCP; however, the incidence is likely to increase dramatically in the coming years, with a higher proportion of patients presenting with advanced-stage cancers, placing a significant strain on the healthcare system[59]. Future studies might quantify the impact of COVID-19 on cancer burden through multinational cohorts comparing pre-/post-pandemic data on tumor stage migration, diagnosis and treatment delays, and behavioral risk shifts (e.g., increased areca nut consumption or sedentary lifestyles).

In conclusion, this study provides a novel investigation of the global burden of LOCP through the perspective of lifetime risk. We quantified the significant public health impact of LOCP, delineating substantial sex and geographic disparities in disease burden, while also investigating the role of socioeconomic and oral health inequalities on LOCP. These findings help to strengthen our understanding of LOCP risks, and inform the scale-up of the WHO Global Oral Health Strategy, highlighting areas where further research is needed, and laying the groundwork for achieving health equity and an impact reduction of LOCP on global health and economy.

Ethical approval

The ethical committee waived the need for ethical approval or informed consent for this study.

Consent

The ethical committee waived the need for ethical approval or informed consent for this study.

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Author's contributions

Conceptualization, data curation: R.Z., R.C., and F.B.; formal analysis: Y.L., Y.Y.; funding acquisition: S.W.; methodology: Y. L., Y.Y., S.W., R.Z., and F.B.; writing – original draft: Y.L., Y.Y., F.B., and J.T.; writing – review & editing: R.Z., R.C., and S.W.

Conflict of interest disclosure

The authors have no relevant financial or non-financial interests to disclose

Guarantor

Shengfeng Wang.

Research Registration Unique Identifying Number (UIN)

This study has been registered at https://www.chictr.org.cn/showproj.html?proj=30768, with the registration number ChiCTR1800018217

Provenance and peer review

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Data availability statement

The data used in this study can be obtained from the official GLOBOCAN website (https://gco.iarc.fr/).

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