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Burden, trends, projections, and spatial patterns of lip and oral cavity cancer in Iran: a time-series analysis from 1990 to 2040

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Abstract

Background Lip and oral cavity cancer (LOCC) is a significant public health concern worldwide. This study investigated the long-term trends in the LOCC burden in Iran from 1990 to 2021.

Methods We analyzed LOCC burden in Iran from 1990 to 2021 using the Global Burden of Disease (GBD) 2021 dataset, focusing on age-standardized disability-adjusted life years (ASDR), mortality rates (ASMR), and incidence rates (ASIR) stratified by sex and province. Joinpoint regression analysis was used to identify temporal trends, and the annual percent change (APC) and average APC (AAPC) were calculated. Future projections up to 2040 were generated using a hybrid forecasting model (ARIMA, ETS, and neural networks). Spatial analysis detected hotspot and coldspot regions in 1990 and 2021.

Results We observed a significant increase in the LOCC burden across all three indicators (disability-adjusted life years [DALY], ASMR, and ASIR) from 1990 to 2021. Joinpoint analysis revealed significant temporal trends, with an overall upward trajectory in the AAPC for both sexes combined and separately. Specifically, the overall AAPC for the ASDR was 0.34% (95% confidence interval [CI]: 0.26,0.39) for both sexes, 0.40% (95% CI: 0.32,0.45) for females, and 0.35% (95% CI: 0.27,0.42) for males. For the ASMR, the overall AAPC was 0.41% (95% CI: 0.34,0.46), 0.54% (95% CI: 0.48,0.58) for females, and 0.36% (95% CI: 0.29,0.42) for males. Similarly, the overall AAPC for ASIR was 1.33% (95% CI: 1.24,1.40), 1.51% (95% CI: 1.43,1.59) for females, and 1.26% (95% CI: 1.17,1.33) for males. Geographic variations were evident, with most provinces exhibiting increasing ASDR and ASMR, while ASIR displayed a consistent upward trend across all provinces. Notably, females showed a slightly more pronounced increase in ASDR, ASMR, and ASIR compared to males. Projections indicate a declining trend in DALYs, a fluctuating but stable mortality rate, and a continuous rise in incidence by 2040. Spatial analysis indicated no significant spatial autocorrelation at the national level in both 1990 and 2021.

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Conclusion Our findings highlight a rising burden of LOCC in Iran, with future projections indicating a growing incidence rate. Targeted public health interventions addressing regional disparities and risk factors are crucial. Sex-specific and region-specific policies, along with early detection strategies, are essential to mitigate the disease burden.

Keywords Lip cancer, Oral cancer, Incidence, Mortality, Disability-adjusted life years (DALYs), Iran, Global Burden of Disease (GBD)

Introduction

Lip and oral cavity cancer (LOCC) represents a significant global health burden, ranking 16th in incidence (age-standardized rate [ASR] 4.0 per 100,000) and 15th in mortality (ASR 1.9 per 100,000) in 2022. This burden disproportionately affects males, with a twofold greater incidence than females. Asia accounts for the highest proportion of global LOCC cases (66.3%) and deaths (75.1%) [1]. In contrast to the global findings, Iran exhibits a lower LOCC burden. Studies have reported age-standardized incidence rates (ASIRs) of 1.96 and 1.36 per 100,000 person-years for males and females, respectively, ranking LOCC 20th in both incidence and mortality within the Iranian population (1037 new cases and 447 deaths in 2022) [2]. However, data on age-standardized disability-adjusted life years (ASDR, Age-Standardized DALY Rate) for LOCC in Iran remain limited.

Epidemiological studies have revealed geographic disparities in LOCC trends. In China, the disease burden exhibited a significant upward trend from 1990 to 2019, with a more pronounced increase in males than in females [3]. Conversely, European studies reported a substantial decrease in LOCC incidence over the same period [4]. Similar trends of decreasing incidence and mortality have been documented in Brazil [5]. Notably, the ASDR and age-standardized mortality rate (ASMR) for LOCC displayed a downward trend from 1990 to 2019 on a global scale, while the ASIR exhibited an increase [6]. Established risk factors, such as tobacco smoking and chewing, have been consistently linked to LOCC incidence [7].

Lip and oral cavity cancer cases are projected to reach 856,000 by 2035 due to demographic and lifestyle changes [8]. This highlights the need for targeted prevention, including tobacco and alcohol reduction, and public awareness campaigns [9]. Despite this global perspective, long-term epidemiological trends and future projections for LOCC in Iran remain understudied, making it difficult for policymakers to develop targeted interventions.

This study aims to address the knowledge gap regarding long-term trends in the LOCC burden in Iran. We leveraged data from the Global Burden of Disease (GBD) study (2021 iteration), the most comprehensive observational epidemiological study to date [10, 11]. Our analyses focused on trends in ASIR, ASMR, and DALYs for LOCC in Iran and its provinces from 1990 to 2021, identifying geographic disparities and assessing temporal shifts in disease burden. To provide a forward-looking perspective, we also projected future trends up to 2040, estimating the expected burden of LOCC at both the national and provincial levels. Additionally, we conducted a spatial analysis to detect hotspot and coldspot regions in 1990 and 2021, highlighting provinces with persistently high or low disease burdens. The findings of this investigation will be valuable for Iranian policymakers in allocating resources for preventive measures, early detection initiatives, and targeted regional interventions, while also establishing best practices for LOCC prevention and diagnosis.

Materials and methods

Study design and setting

This study employed a secondary data analysis approach, using data from the GBD Study 2021 [10, 12]. The GBD study is a comprehensive, multi-institutional effort that estimates the burden of various diseases and injuries across more than 200 countries and territories. It provides data on incidence, prevalence, mortality, Years of Life Lost (YLLs), Years Lived with Disability (YLDs), and DALYs stratified by sex and age group. While most burden indicators are available from 1990 onward, mortality estimates (including YLLs) are accessible from 1980, as documented in the GBD Results Tool [10]. This rich dataset allows for the investigation of long-term trends in LOCC burden within Iran and its provinces [13].

Participants

The GBD study analyzes data at the population level. Individual participants are not directly recruited; instead, data are gathered from diverse sources, including national health surveys, vital registration systems, and disease surveillance reports. A complex statistical framework is employed to create a representative sample that encompasses the entire population of a specific country or region. This approach ensures comprehensive data collection by preventing participant exclusion based on specific characteristics. The analysis considers factors that might influence health outcomes by incorporating adjustments [13].

Variables

Our primary outcome variables were:

1. Age-Standardized Disability-Adjusted Life Years Rate (ASDR) – representing the burden of LOCC in terms of premature mortality and years lived with disability.
2. Age-Standardized Mortality Rate (ASMR) – measuring LOCC-related deaths per 100,000 population, standardized for age distribution.
3. Age-Standardized Incidence Rate (ASIR) – capturing the newly diagnosed LOCC cases per 100,000 population, adjusted for age differences

Data sources

Data were extracted from the GBD 2021 using the Global Health Data Exchange (GHDx) GBD Results Tool (http://ghdx.healthdata.org/gbd-results-tool).

Statistical analysis

Descriptive statistics were employed to report global means and 95% uncertainty intervals (UIs) for DALY rates, ASMR, and ASIR, stratified by sex.

Jointpoint regression

To identify temporal trends in these burden indices, we utilized joinpoint regression analysis. The joinpoint model for a series of observations (t_1, y_1), (t_2, y_2), …, (t_n, y_n) is expressed as:

$$yi = \beta_0 + \beta_1 ti + \gamma_1(ti - \tau_1) + ... + \gamma_k(ti - \tau_k) + \varepsilon_i, i = 1, ..., n$$

where ti denotes time points (years), yi represents the burden indices (DALY, ASMR, ASIR rates), τ_k (k = 1, 2, …, K) represents the location of potential change points (K is the number of change points), β_0, β_1, γ_1, …, γ_k are regression coefficients, and ε_i represents the model error term. The notation $(ti - \tau_k)+$ signifies $ti - \tau_k$ if positive and 0 otherwise. Joinpoint regression facilitates the calculation of Annual Percent Change (APC) in rates between estimated change points using a log-transformed model:

$$APC = 100 \times (exp(\beta_1 + \gamma_1 + \gamma_2 + ... + \gamma_j) - 1)$$

The Average Annual Percent Change (AAPC) for each fitted model is estimated as a weighted mean of APCs, with segment lengths serving as weights [14]. Finally, 95% confidence intervals (Cis) for APCs and AAPCs were computed to assess statistical significance. Joinpoint software version 5.2.0 was used for this analysis. To determine the optimal number of change points in Joinpoint regression, we applied the Weighted Bayesian Information Criterion (Weighted BIC), which is the preferred model selection method in Joinpoint software. Weighted BIC dynamically adjusts the penalty term based on data characteristics, selecting between traditional BIC and BIC3 based on effect sizes [15]. To visualize spatial trends, AAPC values of ASDR, ASMR, and ASIR were calculated for each province. Accordingly, a province was colored green if AAPC > 0 (indicating an increasing trend), whereas a province was colored red if AAPC ≤ 0 (indicating a stable or decreasing trend).

Projection approach

Historical data from 1990 to 2021 were utilized for model training, and projections were generated for the period up to 2040. The projection methodology employed a hybrid modeling approach combining Autoregressive Integrated Moving Average (ARIMA) [16], Exponential Smoothing State Space Models (ETS) [17], and Neural Networks [18]. This approach was selected to enhance the predictive accuracy by leveraging the strengths of each component model. ARIMA was applied to capture linear trends and autoregressive dependencies, ETS accounted for exponential trends and seasonality, while Neural Networks modeled nonlinear patterns that could not be captured by traditional statistical models. The dataset was structured as a time series, and data transformation techniques, including Box-Cox transformation, were considered to stabilize variance where required. Each time series was analyzed separately for each province and sex category (Female, Male, and Both), with model selection guided by the minimization of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), in addition to residual diagnostics. The hybrid model was implemented using the forecastHybrid package in R, which integrates ARIMA, ETS, and Neural Networks into a weighted ensemble model based on in-sample performance. The projection procedure involved fitting the hybrid model for each sex category within each province and generating point estimates along with 95% confidence intervals for future years. Model uncertainty was quantified through the computation of confidence intervals derived from residual error estimates.

Spatial analysis

The spatial analysis was conducted to assess the clustering patterns of LOOC burden across Iranian provinces in 1990 and 2021. Global spatial autocorrelation was evaluated using Moran's I to determine whether the distribution of disease burden exhibited significant spatial dependence at the national level. To identify local spatial clusters, Local Moran's I (LISA) statistics were computed, allowing the detection of hotspots (high-high clusters) and coldspots (low-low clusters). Spatial weights were constructed using k-nearest neighbors (k = 5) to ensure each province had a sufficient number of spatial connections, avoiding isolated regions. The spatial data, including province boundaries and centroids, were processed using the sf package in R, while spatial dependence was analyzed using the spdep package [19, 20].

Results

Increasing burden of lip and oral cavity cancers in Iran

Table 1 summarizes the changes in ASDR, ASMR, and ASIR of the LOCC per 100,000 person-years in Iran between 1990 and 2021. From 1990 to 2021, there was a modest increase in the ASDR and ASMR of LOCC. ASDR increased from 9.63 (95% UI: 8.33, 11.06) to 10.79 (95% UI: 9.64, 12.06) per 100,000 person-years, and ASMR climbed from 0.40 (95% UI: 0.35, 0.46) to 0.46 (95% UI: 0.41, 0.52) per 100,000 person-years. Notably, the ASIR of LOCC showed a more substantial increase, with cases rising from 0.61 (95% UI: 0.52, 0.70) to 0.94 (95% UI: 0.82, 1.06) per 100,000 person-years over the same period. When stratified by sex, the data revealed interesting patterns. Both males and females experienced increases in all three criteria; however, the increase appeared to be slightly more pronounced in females. AAPC by provinces were reported in Additional File 1.

Jonipoint analysis of temporal trends in ASDR for lip and oral cavity cancer

The log-transformed joinpoint analysis revealed significant trends in AAPC of ASDR, ASMR, and ASIR for LOCC in Iran from 1990 to 2021 (Table 2 and Fig. 1).

The ASDR for both sexes combined exhibited a statistically significant increasing trend from 1990 to 2002 (APC = 0.74%, p = 0.007). This was followed by a significant decline from 2002 to 2005 (APC = -1.36%, p = 0.047). The subsequent period (2005–2011) showed a slight significant increase (APC = 0.72%, p = 0.050). A notable surge was observed from 2011 to 2015 (APC = 4.71%, p = 0.002). The trend then reversed, with a nonsignificant decrease from 2015 to 2019 (APC = -1.94%, p = 0.067). The most recent period (2019–2021) displayed a significant decline (APC = -4.51%, p < 0.001). Overall, the AAPC for both sexes throughout the study period was 0.34% (p < 0.001). The ASDRs for females showed a steady increase from 1990 to 2001 (APC = 0.58%, p = 0.008), followed by a significant decline from 2001 to 2004 (APC = -1.65%, -0.53; p = 0.036). The trend remained relatively stable from 2004 to 2010, with a slight nonsignificant increase (APC = 0.46%, p = 0.053). A pronounced increase was observed from 2010 to 2015 (APC = 5.24%, p = 0.002). This was followed by a nonsignificant decrease from 2015 to 2019 (APC = -2.00%, 3.05; p = 0.071). The significant decline continued from 2019 to 2021 (APC = -4.54%, p < 0.001). The overall AAPC for females was 0.40% (p < 0.001). The ASDRs for males increased from 1990 to 2002 (APC = 1.00%, p = 0.023). This was followed by a nonsignificant decrease from 2002 to 2005 (APC = -0.80%, p = 0.254) and a stable trend from 2005 to 2011 (APC = 0.51%, p = 0.128). A substantial increase was observed from 2011 to 2015 (APC = 3.82%, p = 0.002). The trend from 2015 to 2019 showed a nonsignificant decrease (APC = -1.82%, p = 0.064), followed by a significant decline from 2019 to 2021 (APC = -4.58%, p < 0.001). The overall AAPC for males throughout the study period was 0.35% (p < 0.001).

Jonipoint analysis of temporal trends in ASMR for lip and oral cavity cancer

The ASMRs for both sexes combined exhibited a statistically significant initial increase from 1990 to 2001 (APC = 0.76%, p = 0.002), as presented in Table 2. This was followed by a significant decline from 2001 to 2006 (APC = -0.67%, p = 0.031). The subsequent period (2006–2011) displayed a renewed increase (APC = 0.81%, p = 0.037). A notable surge was observed from 2011 to 2015 (APC = 4.99%, p < 0.001). The trend then reversed, with a significant decline from 2015 to 2019 (APC = -1.82%, p = 0.038) and a further significant decrease from 2019 to 2021 (APC = -4.21%, p < 0.001). Overall, the AAPC for both sexes throughout the study period was 0.41% (p < 0.001). The ASMR trends for females generally mirrored the overall pattern observed for both sexes combined. There was a significant initial increase from 1990 to 2001 (APC = 0.58%, p = 0.004), followed by a decline from 2001 to 2004 (APC = -1.45%, p = 0.022). The rate then increased again from 2004 to 2010 (APC = 0.61%, p = 0.024). A pronounced rise was observed from 2010 to 2015 (APC = 5.41%, p = 0.001). This was followed by a decrease from 2015 to 2019

Table 1 ASDR, ASMR, and ASIR (per 100,000 person-years and 95% uncertainty interval) for lip and oral cavity in Iran, 1990 and 2021

Variable	Levels	1990			2021		
		ASDR	ASMR	ASIR	ASDR	ASMR	ASIR
Overall	--	9.63 (8.33, 11.06)	0.40 (0.35, 0.46)	0.61 (0.52, 0.70)	10.79 (9.64, 12.06)	0.46 (0.41, 0.52)	0.94 (0.82, 1.06)
Sex	**Female**	8.39 (6.89, 9.94)	0.36 (0.30, 0.43)	0.58 (0.47, 0.70)	9.64 (8.40, 10.92)	0.44 (0.38, 0.49)	0.93 (0.80, 1.06)
	Male	10.69 (8.89, 12.96)	0.44 (0.36, 0.53)	0.63 (0.51, 0.76)	11.95 (10.28, 13.40)	0.49 (0.42, 0.55)	0.94 (0.81, 1.08)

Abbreviations: DALY Disability-adjusted life years, *ASDR* age-standardized DALY rate, *ASMR* age-standardized mortality rate, *ASIR* age-standardized incidence rate

Table 2 The log-transformed joinpoint trends of lip and oral cavity cancer ASRs by sex in Iran

Measure	Sex	Segment	Years	APC		AAPC	
				Value (95% CI)	p value	Value (95% CI)	*p* value
ASDR	Both	1	1990–2002	0.74*(0.61, 0.91)	0.007	0.34*(0.26,0.39)	< 0.001
	Both	2	2002–2005	-1.36*(-1.82, -0.17)	0.047		
	Both	3	2005–2011	0.72*(0.02, 1.6)	0.05		
	Both	4	2011–2015	4.71*(3.4, 5.66)	0.002		
	Both	5	2015–2019	-1.94(-2.3, 0.71)	0.067		
	Both	6	2019–2021	-4.51*(-5.78, -3.13)	< 0.001		
	Female	1	1990–2001	0.58*(0.44, 0.76)	0.008	0.40*(0.32,0.45)	< 0.001
	Female	2	2001–2004	-1.65*(-2.1, -0.53)	0.036		
	Female	3	2004–2010	0.46(-0.06, 1.26)	0.053		
	Female	4	2010–2015	5.24*(4.6, 5.77)	0.002		
	Female	5	2015–2019	-2(-2.33, 3.05)	0.071		
	Female	6	2019–2021	-4.54*(-5.77, -3.06)	< 0.001		
	Male	1	1990–2002	1.00*(0.4, 1.46)	0.023	0.35*(0.27,0.42)	< 0.001
	Male	2	2002–2005	-0.8(-1.3, 1.6)	0.254		
	Male	3	2005–2011	0.51(-0.3, 1.85)	0.128		
	Male	4	2011–2015	3.82*(2.59, 4.79)	0.002		
	Male	5	2015–2019	-1.82(-2.23, 0.54)	0.064		
	Male	6	2019–2021	-4.58*(-5.94, -3.17)	< 0.001		
ASMR	Both	1	1990–2001	0.76*(0.63, 0.91)	0.002	0.41*(0.34,0.46)	< 0.001
	Both	2	2001–2006	-0.67*(-1.46, -0.22)	0.031		
	Both	3	2006–2011	0.81*(0.12, 1.61)	0.037		
	Both	4	2011–2015	4.99*(4.4, 5.66)	< 0.001		
	Both	5	2015–2019	-1.82*(-2.13, -1.01)	0.038		
	Both	6	2019–2021	-4.21*(-5.27, -3.12)	< 0.001		
	Female	1	1990–2001	0.58*(0.47, 0.72)	0.004	0.54*(0.48,0.58)	< 0.001
	Female	2	2001–2004	-1.45*(-1.84, -0.55)	0.022		
	Female	3	2004–2010	0.61*(0.35, 1.06)	0.024		
	Female	4	2010–2015	5.41*(5.05, 5.69)	0.001		
	Female	5	2015–2019	-1.79*(-2.09, -1.17)	0.028		
	Female	6	2019–2021	-4.02*(-4.95, -2.98)	< 0.001		
	Male	1	1990–2002	0.97*(0.63, 1.17)	0.01	0.36*(0.29,0.42)	< 0.001
	Male	2	2002–2005	-0.95(-1.4, 1.3)	0.14		
	Male	3	2005–2011	0.37(-0.26, 1.27)	0.122		
	Male	4	2011–2015	4.17*(3.49, 5.11)	0.001		

Table 2 (continued)

Measure	Sex	Segment	Years	APC		AAPC	
				Value (95% CI)	p value	Value (95% CI)	*p* value
ASIR	Both	1	1990–2002	1.56*(1.38, 1.77)	0.001	1.33*(1.24,1.4)	< 0.001
	Both	2	2002–2007	-0.43(-1.67, 0.36)	0.181		
	Both	3	2007–2011	2.42*(0.44, 3.79)	0.032		
	Both	4	2011–2015	5.91*(4.95, 7.04)	< 0.001		
	Both	5	2015–2019	-0.06(-0.59, 1.36)	0.929		
	Both	6	2019–2021	-3.78*(-5.33, -2.19)	< 0.001		
	Female	1	1990–1993	2.45*(1.64, 3.99)	< 0.001	1.51*(1.43,1.59)	< 0.001
	Female	2	1993–2002	1.23*(0.69, 1.42)	0.018		
	Female	3	2002–2007	-0.33(-1.33, 0.19)	0.144		
	Female	4	2007–2010	2.25*(0.43, 4.52)	0.01		
	Female	5	2010–2015	6.34*(5.91, 7.08)	< 0.001		
	Female	6	2015–2019	0.02(-0.42, 0.71)	0.851		
	Female	7	2019–2021	-3.75*(-5.04, -2.32)	< 0.001		
	Male	1	1990–2003	1.71*(1.56, 1.88)	< 0.001	1.26*(1.17,1.33)	< 0.001
	Male	2	2003–2006	-1.12(-1.69, 0.28)	0.092		
	Male	3	2006–2011	1.72*(0.64, 2.82)	0.025		
	Male	4	2011–2015	5.11*(4.1, 6.2)	< 0.001		
	Male	5	2015–2019	-0.1(-0.65, 1.32)	0.839		
	Male	6	2019–2021	-3.91*(-5.39, -2.26)	< 0.001		

Abbreviations: *AAPC* average annual percent change, *APC* annual percent change, *CI* confidence interval, *ASDR* age-standardized DALY rate, *DALY* disability-adjusted life years, *ASMR* age-standardized mortality rate, *ASIR* age-standardized incidence rate; *significantly different from zero, *p* value < 0.05

(APC = -1.79%, p = 0.028) and a significant decline from 2019 to 2021 (APC = -4.02%, p < 0.001). The overall AAPC for females was 0.54% (p < 0.001). The ASMR trends for males displayed a pattern somewhat different from those of the combined sexes and females. The rate showed an initial increase from 1990 to 2002 (APC = 0.97%, p = 0.01). The subsequent periods (2002–2005 and 2005–2011) exhibited nonsignificant changes, with a slight decrease from 2002 to 2005 (APC = -0.95%, p = 0.14) and a stable trend from 2005 to 2011 (APC = 0.37%, p = 0.122). A substantial increase was observed from 2011 to 2015 (APC = 4.17%, p = 0.001). The AAPC for males throughout the study period was 0.36% (p < 0.001).

Jonipoint analysis of temporal trends in ASIR for lip and oral cavity cancer

As shown in Table 2, the ASIRs for both sexes combined exhibited a statistically significant initial increase from 1990 to 2002 (APC = 1.56%, p = 0.001). This was followed by a nonsignificant decrease from 2002 to 2007 (APC = -0.43%, p = 0.181). The rate then increased again from 2007 to 2011 (APC = 2.42%, p = 0.032). A notable surge was observed from 2011 to 2015 (APC = 5.91%, p < 0.001). The trend then plateaued, with a nonsignificant change from 2015 to 2019 (APC = -0.06%, p = 0.929). Finally, a significant decline was observed from 2019 to 2021 (APC = -3.78%, p < 0.001). The overall AAPC for both sexes throughout the study period was 1.33% (p < 0.001). The ASIR trends for females displayed a pattern distinct from that of the combined sexes. There was a significant initial increase from 1990 to 1993 (APC = 2.45%, p < 0.001), followed by a steady rise from 1993 to 2002 (APC = 1.23%, p = 0.018). A nonsignificant decrease was observed from 2002 to 2007 (APC = -0.33%, p = 0.144). The rate then increased from 2007 to 2010 (APC = 2.25%, p = 0.01) and surged significantly from 2010 to 2015 (APC = 6.34%, p < 0.001). Similar to the combined sexes, the trend appeared to plateau from 2015 to 2019 (APC = 0.02%, p = 0.851), followed by a significant decline from 2019 to 2021 (APC = -3.75%, p < 0.001). The overall AAPC for females was 1.51% (p < 0.001). The ASIR trends for males generally mirrored the overall pattern observed for both

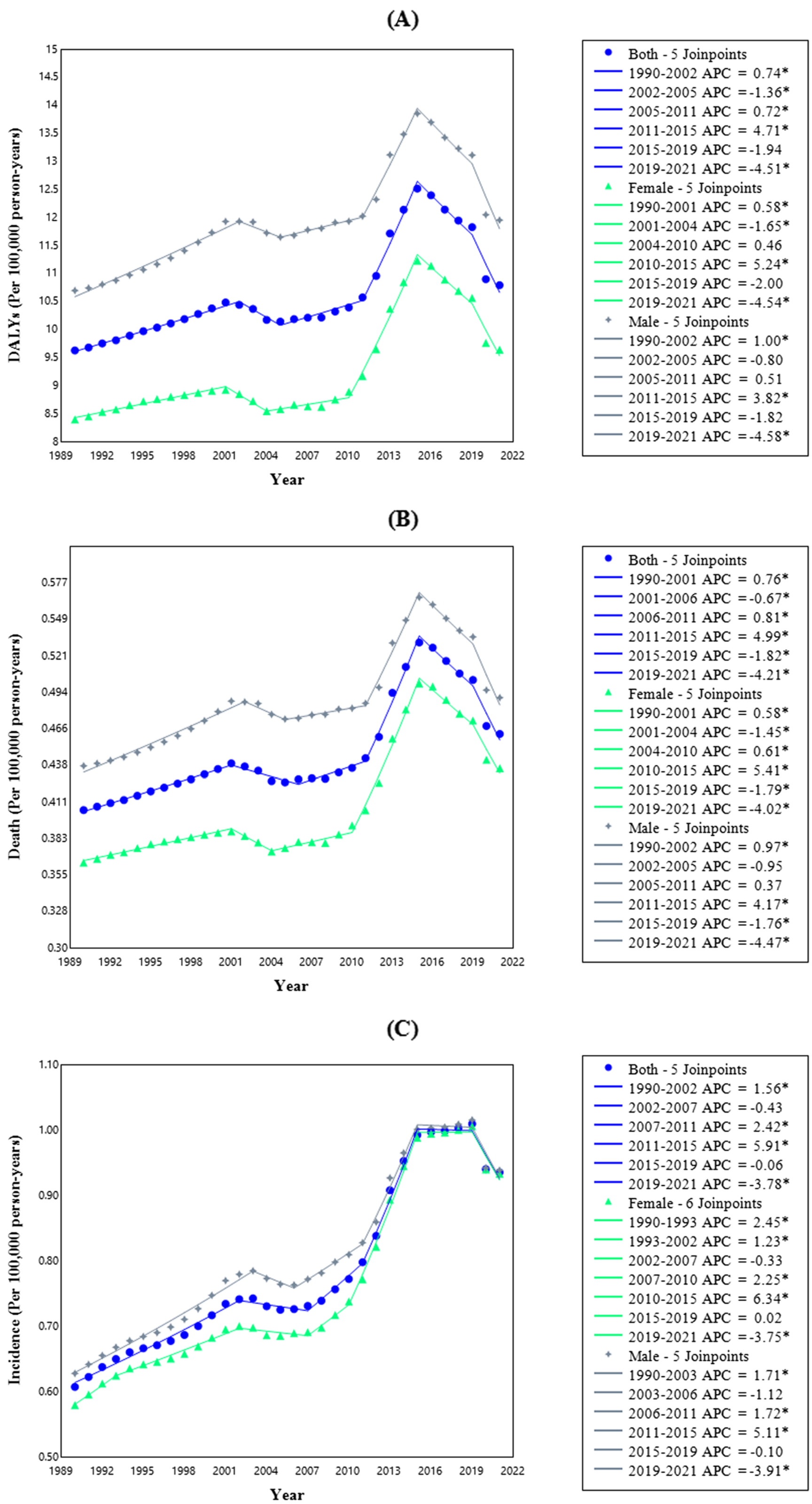

Fig. 1 APC trends in the ASDR, ASMR, and ASIR (per 100,000 person-years) for different sexes from 1990–2021

sexes combined. There was a significant increase from 1990 to 2003 (APC = 1.71%, p < 0.001). A nonsignificant decrease was noted from 2003 to 2006 (APC = -1.12%, 95% CI: -1.69, 0.28; p = 0.092), followed by an increase from 2006 to 2011 (APC = 1.72%, p = 0.025). A significant rise was observed from 2011 to 2015 (APC = 5.11%, p < 0.001). Similar to the overall and female trends, the rate plateaued from 2015 to 2019 (APC = -0.10%, 95% CI: -0.65, 1.32; p = 0.839). Finally, a significant decline was observed from 2019 to 2021 (APC = -3.91%, p < 0.001). The overall AAPC for males throughout the study period was 1.26% (p < 0.001). Figure 1 provides a comprehensive visualization of the log-transformed joinpoint trends of ASDR, ASMR, and ASIR for LOCC, stratified by sex and analyzed by ASRs across Iranian provinces.

Geographic variations in ASDR, ASMR, and ASIR for lip and oral cavity across Iranian provinces

Analysis of ASDR, ASMR, and ASIR revealed consistent upward trends across most provinces for both sexes. ASDR exhibited geographical variations, with a significant increase observed in females for all provinces except Tehran, which showed a decrease. Similarly, males displayed increasing ASDR in most provinces, with exceptions in Markazi, Semnan, Tehran, Yazd, and Kerman, where a decreasing trend was observed. These findings are further supported by Fig. 2, which shows a widespread and significant increase in ASMR for both females and males across most provinces throughout the study period. Notably, all provinces except Tehran exhibited increasing trends in mortality among females. Conversely, males showed a consistent increase in ASMR within 26 provinces, while a decrease was observed in Kerman, Kermanshah, Markazi, Semnan, and Tehran. Interestingly, ASIR analysis revealed a pervasive increase for both sexes across all provinces, with no exceptions.

Projected burden of lip and oral cavity in Iran and provinces from 1990 to 2040

The projected burden of disease in Iran from 1990 to 2040 is analyzed through DALYs, deaths, and incidence using a hybrid forecasting model integrating ARIMA, ETS, and neural networks. Figure 3 shows an decreasing trend in DALYs, a generally stable but fluctuating pattern in deaths, and a continuous increase in incidence. Table 3 presents projections for 2040, where the total burden in Iran is estimated at 247.45 DALYs, 11.70 deaths, and 23.84 incidence per 100,000 population. Provinces such as Tehran, Alborz, Qom, Sistan and Baluchistan, Chahar Mahaal and Bakhtiari, and Markazi show a higher disease burden compared to others. Full province-specific forecasts from 2022 to 2040 are available in the Additional file 2 as Excel sheets and Figures.

Spatial shift in lip and oral cavity burden distribution in Iran

Figure 4 illustrates the spatial distribution of LOOC burden in Iran, showing that the global Moran's I statistic was not statistically significant in 2021, indicating no strong spatial autocorrelation at the national level. However, local hotspot analysis revealed significant clustering in specific provinces. In 1990, Qom and Alborz were hotspots for DALYs, deaths, and incidence, while Mazandaran and Isfahan were coldspots. By 2021, Qom and Alborz lost their hotspot status for DALYs and deaths, though Qom remained a hotspot for incidence, while Alborz lost significance entirely.

Discussion

Our study revealed a significant and increasing burden of LOCC in Iran over the past three decades, as indicated by trends in DALYs, mortality rates, and incidence rates from 1990 to 2021. Specifically, the DALYs increased from 9.63 to 10.79 per 100,000 person-years, and mortality rates climbed from 0.40 to 0.46 per 100,000 person-years. The incidence of these cancers has increased markedly from 0.61 to 0.94 per 100,000 person-years, highlighting a substantial public health challenge. Sex-specific analyses showed that both males and females experienced rising trends, with females exhibiting a slightly more pronounced increase in these criteria. The log-transformed joinpoint analysis further revealed significant AAPC in age-standardized rates (ASDR, ASMR, and ASIR) for both sexes combined and separately. Notably, geographical variations were observed across Iranian provinces, with most showing upward trends in the ASDR and ASMR, except for some decreasing trends in specific regions such as Tehran. In addition, there were consistent upward trends in the ASIR across all provinces for both sexes. Projection analysis suggests that while DALYs may follow a declining trend, mortality rates are expected to remain relatively stable with fluctuations, and incidence rates are projected to rise further. By both 1990 and 2021, the LOCC burden showed no strong geographic clustering at the national level, indicating a dispersed distribution. Over time, some provinces lost their hotspot status, while new high-burden areas emerged. Qom remained a persistent hotspot for incidence, whereas Alborz, once a high-burden region, declined in significance.

The current study revealed a significant upward trend in the ASDR, ASMR, and ASIR of LOCC in both sexes in Iran from 1990 to 2021. These findings align with global observations reported by the GBD Study. The GBD study reported substantial global increases in LOCC, particularly in low- and middle-socioeconomic development index (SDI) regions, attributing a significant portion to

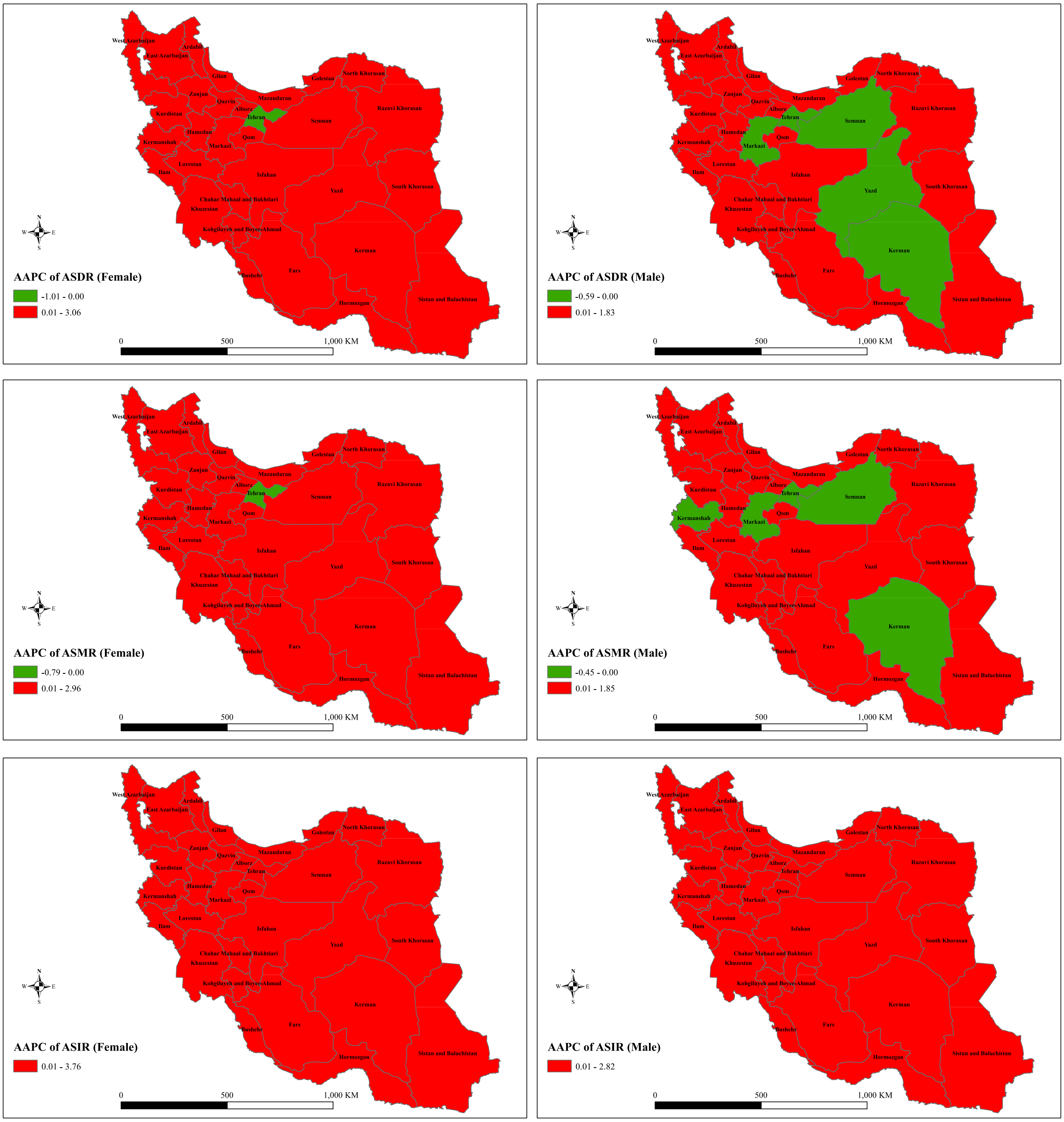

Fig. 2 AAPC of ASDR, ASMR, and ASIR of lip and oral cavity cancers from 1990–2021 in Iran

smoking, alcohol use, and tobacco chewing [21]. Similarly, Hernandez et al. (2023) reported positive correlations between the incidence and mortality of LOCC and tobacco use prevalence worldwide [7]. Wang et al. (2023) further supported this, demonstrating that smoking remains a major global risk factor [6]. However, regional variations exist. Sun (2023) observed a decrease in the ASIR within high-SDI regions [22], and similar to our findings, Jokar (2023) reported a lower pooled ASR in Iran [23]. These discrepancies may be due to variations in the SDI and regional health policies. Additionally, factors such as regional healthcare access, early detection rates, and cultural practices regarding tobacco and alcohol use could explain potential differences in cancer trends across studies. The increasing burden observed in Iran, contrasted with decreasing trends in some high-SDI

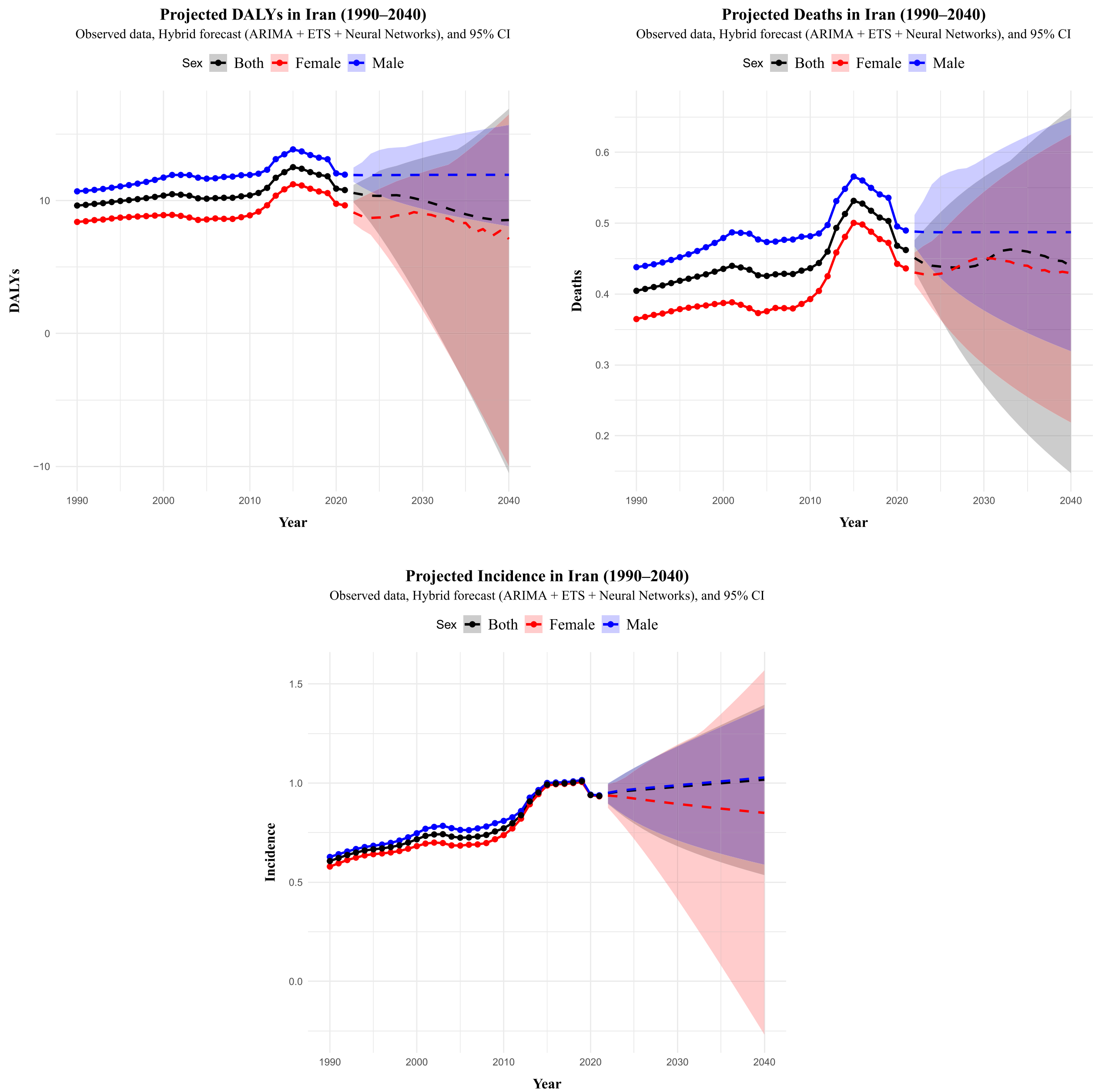

Fig. 3 Projected burden of lip and oral cavity cancers in Iran 1990–2040 using hybrid forecasting of deaths, DALYs, and incidence

regions, highlights the critical need for targeted public health interventions and policy adjustments tailored to the specific characteristics of each region.

Our analysis revealed a concerning increase in ASDR, ASMR, and ASIR of LOCC for both sexes, with a steeper rise in females, despite a greater overall incidence in males. This aligns with Jokar et al. (2023) report on gender disparities in Iranian cancer rates [23]. Shamloo et al. (2022) further supported this trend, documenting a high prevalence of male squamous cell carcinoma in Iran [24]. Najafi (2018) and Rezapour (2018) strengthened the evidence for sex disparities in Iran, with Rezapour (2018) highlighting the economic burden of oral cancers [25, 26]. Similarly, Zhang et al. (2022) projected a rise in LOCC incidence in China, particularly among men and the elderly individuals [3]. However, global trends appear more nuanced. Gangane et al. (2019) reported a higher (2.4-fold) incidence and mortality of oral cavity cancer (OCC) in Indian males, likely due to tobacco use [27]. Conversely, Duran-Romero et al.

Table 3 Projected burden of disease in Iran by province in 2040 based on forecasted DALYs deaths and incidence using hybrid models

Country/Province	DALYs			Death			Incidence		
	Female	Male	Both	Female	Male	Both	Female	Male	Both
Iran	214.44	297.87	247.45	10.69	13.07	11.70	23.12	25.08	23.84
Alborz	11.00	9.64	10.47	0.63	0.48	0.52	1.23	0.95	1.11
Ardebil	8.29	10.66	9.63	0.38	0.46	0.40	0.74	0.90	0.81
Bushehr	5.55	8.98	6.33	0.30	0.32	0.31	0.63	0.78	0.69
Chahar Mahaal and Bakhtiari	9.20	14.93	11.64	0.40	0.60	0.52	1.00	1.25	1.12
East Azarbayejan	7.08	9.27	8.52	0.36	0.51	0.42	0.71	0.95	0.86
Fars	6.46	8.22	6.86	0.28	0.33	0.28	0.52	0.64	0.61
Gilan	5.65	7.61	6.68	0.27	0.36	0.32	0.80	0.68	0.61
Golestan	8.22	9.39	7.31	0.33	0.37	0.41	0.69	0.65	0.63
Hamadan	6.69	7.08	5.93	0.31	0.32	0.29	0.61	0.58	0.56
Hormozgan	5.38	10.44	7.03	0.28	0.41	0.32	0.48	0.66	0.58
Ilam	6.91	6.48	7.12	0.33	0.37	0.35	0.69	0.68	0.70
Iran	7.11	11.94	8.54	0.43	0.49	0.44	0.85	1.03	1.02
Isfahan	6.58	7.52	6.98	0.32	0.32	0.34	0.66	0.71	0.74
Kerman	4.17	7.26	6.84	0.21	0.34	0.28	0.48	0.59	0.57
Kermanshah	4.47	7.49	5.19	0.25	0.31	0.27	0.53	0.53	0.45
Khorasan-e-Razavi	6.98	10.07	7.41	0.32	0.41	0.39	0.65	0.74	0.67
Khuzestan	7.44	7.43	7.29	0.38	0.29	0.33	0.70	0.67	0.62
Kohgiluyeh and Boyer-Ahmad	6.07	9.25	7.66	0.27	0.34	0.29	0.61	0.74	0.68
Kurdistan	6.30	12.48	8.23	0.29	0.48	0.41	0.62	0.80	0.71
Lorestan	3.36	5.16	4.01	0.17	0.27	0.18	0.40	0.52	0.38
Markazi	8.01	13.51	11.02	0.42	0.52	0.41	0.80	0.89	0.92
Mazandaran	5.93	5.84	5.72	0.28	0.23	0.30	0.74	0.56	0.56
North Khorasan	3.05	6.33	4.63	0.14	0.25	0.18	0.29	0.48	0.36
Qazvin	5.10	8.16	6.61	0.31	0.45	0.30	0.59	0.79	0.66
Qom	8.48	13.53	11.39	0.48	0.54	0.51	0.99	1.02	1.05
Semnan	3.28	4.56	3.85	0.19	0.45	0.30	0.42	0.73	0.65
Sistan and Baluchistan	16.72	20.91	18.73	0.74	0.78	0.75	1.37	1.37	1.30
South Khorasan	4.49	7.32	5.79	0.21	0.30	0.24	0.41	0.53	0.50
Tehran	10.46	7.81	9.97	0.54	0.43	0.48	1.73	1.26	1.52
West Azarbayejan	7.20	11.52	8.74	0.38	0.48	0.46	0.80	0.82	0.84
Yazd	5.13	5.89	5.11	0.29	0.40	0.40	0.95	0.67	0.69
Zanjan	3.70	11.18	6.25	0.20	0.48	0.29	0.43	0.90	0.67

Note: The projected burden of disease in 2040 across different provinces in Iran includes Disability-Adjusted Life Years (DALYs), deaths, and incidence rates, categorized by gender (female, male, both). These projections are based on a hybrid forecasting model that integrates ARIMA (AutoRegressive Integrated Moving Average), ETS (Error, Trend, Seasonality), and neural networks, ensuring robust predictions with 95% confidence intervals. DALYs measure the overall disease burden by combining years of life lost due to premature mortality and years lived with disability, while deaths represent the forecasted mortality rates, and incidence refers to the estimated number of new cases expected in 2040

(2022) observed a decline in OCC mortality, particularly in males, potentially reflecting successful sun protection campaigns, which aligns with global trends reported by Miranda-Filho & Bray (2020) [28, 29]. Joinpoint analysis by Duran-Romero et al. (2022) suggested shared risk factors for OCC, but their analysis of age, period, and cohort effects revealed a significant decrease in OCC mortality for males born after the 1950s, indicating a likely future decline. Conversely, female OCC mortality remained high throughout the study period [28]. These findings suggest potential sex-specific differences in risk factor exposure patterns and warrant further investigation. Furthermore, the rising trends observed in specific demographics and regions emphasize the critical need for targeted prevention and early intervention strategies.

In our study, we analyzed the provincial trends in the ASDR, ASMR, and ASIR of LOCC in Iran from 1990 to 2021 using the AAPC. Our findings revealed a consistent

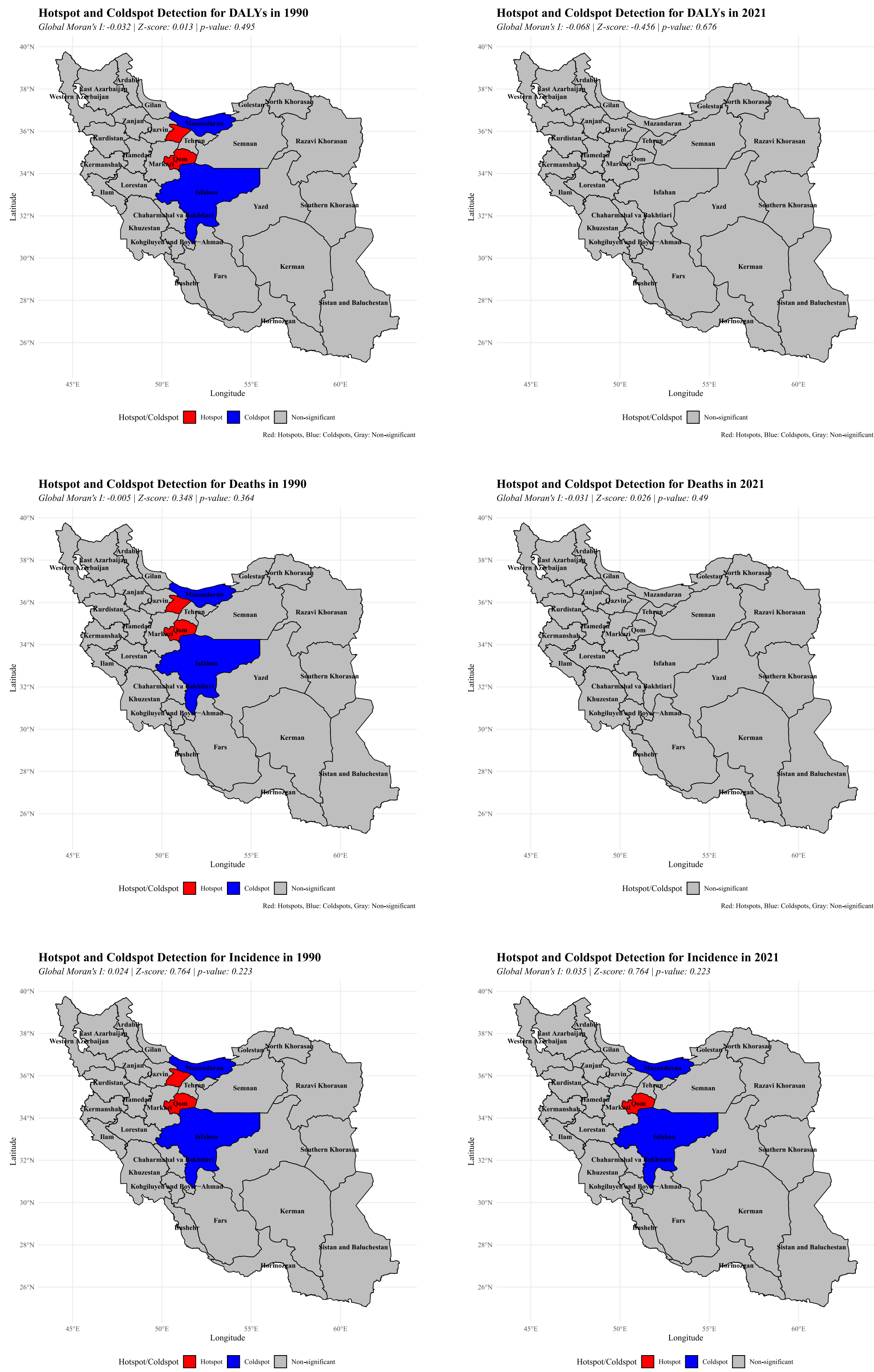

Fig. 4 Spatial distribution of hotspots and coldspots in lip and oral cavity cancers burden across Iran – 1990 and 2021

increase in the ASIR across all provinces. Tobacco and alcohol consumption are significant risk factors for these cancers [30]; however, despite the GBD report indicating a decline in alcohol consumption in Iran, no corresponding decrease in LOCC incidence has been observed. This discrepancy might be explained by the prevalent use of opioids in Iran, which has been increasing over the past thirty years [31]. Opium consumption is known to contribute to the initiation of cancers in the lip and oral cavity [32]. While the reasons behind the greater increase in the ASIR for LOCC among women compared to men are unclear, Luna-Ortiz et al. noted that women are more likely to have lesions on their upper lips, which could partially account for the increased incidence in females [33]. Additionally, our results indicated an increase in the AAPC in ASDR and ASMR for LOCC in Iran, except in specific provinces such as Tehran. This increase was more pronounced in women than in men. Several factors could be driving the upward trend in AAPC of ASDR, ASMR, and ASIR for LOCC in Iran. Firstly, lifestyle changes and greater exposure to risk factors, such as human papillomavirus infection (HPV) infections, have likely contributed to the overall rise in LOCC rates. Rezaee Azhar et al. (2022) documented an increase in HPV infections over the past decade in Iran [34]. Socioeconomic and environmental factors, such as poor diet and poor air quality, may also play significant roles [35, 36]. The higher AAPC in women compared to men might be due to lower baseline rates of such cancers in women historically, leading to a steeper percentage increase when exposed to similar risk factors. Changes in social norms and behaviors, such as increased smoking rates among women in recent decades, might be accelerating the incidence and mortality rates. Improved healthcare access and better cancer detection among women could also be contributing to these trends, identifying cases that previously went undiagnosed or untreated. In some provinces such as Tehran, where the AAPC in these criteria for LOCC has shown a negative trend, factors such as better healthcare infrastructure, increased public awareness, and effective cancer prevention and control programs could lead to earlier detection, more effective treatment, and reduced exposure to risk factors. These targeted health interventions and public health policies might successfully curb the growth of LOCC incidence and mortality in these areas.

Joinpoint regression analysis revealed distinct temporal trends in ASDR, ASMR, and ASIR of LOCC in Iran. The data show an increasing trend until 2015, followed by a period of relative stability from 2015 to 2019 and lastly, a decreasing trend from 2019 to 2021. Several factors could contribute to this observed pattern. The introduction of the HPV vaccine, Gardasil, in Iran's private sector between 2011 and 2015 coincides with the observed plateau and subsequent decline in LOCC rates [37]. While data on widespread vaccine uptake are limited, the significant increase in Gardasil vial sales suggests a growing awareness and potential for a delayed impact on HPV-related cancer rates. This period might have also seen improvements in public health initiatives and screening programs, potentially influencing the trends. Therefore, a combination of factors, including increased awareness of risk factors, enhanced cancer screening and treatment efforts, and potentially, HPV vaccination in the private sector, could collectively explain the observed changes in LOCC trends in Iran. Further research with more comprehensive data on HPV vaccination rates is needed to definitively assess its contribution.

Shield et al. (2016) projected a 62% increase in LOCC incidence, reaching 856,000 cases by 2035 [8], primarily driven by demographic shifts and lifestyle factors such as smoking and alcohol consumption [38]. In line with these global projections, our study revealed a continuous upward trend in LOCC incidence in Iran until 2040, emphasizing the growing public health burden. This rising incidence inevitably influences mortality trends, yet its impact varies by demographic factors. Dai et al. (2024) reported an increase in ASMR among males but stability among females for risk-related early-onset oral cavity cancers [39], while Infante-Cossio et al. (2022) identified higher female mortality rates for OCC between 2040 and 2044. Despite these projections [28], our study suggests that mortality rates in Iran will remain relatively stable with fluctuations, potentially due to advancements in early detection and treatment, which may mitigate the fatal consequences of increasing incidence. This stabilization in mortality aligns with our findings on DALY trends, which also exhibit a relatively steady trajectory, reflecting a balance between rising incidence and potential improvements in survival rates and healthcare accessibility. Despite this apparent stability, the continued rise in LOCC incidence necessitates sustained preventive strategies to avoid future strain on healthcare resources. Notably, our study is the first to provide DALY projections for LOCC in Iran and globally, underscoring its unique contribution.

Limitations

Although the GBD study offers a comprehensive assessment of the LOCC burden in Iran, limitations exist. Data quality can vary across regions due to the reliance on secondary sources such as surveys and vital registries. Additionally, the GBD's focus on aggregated data, rather than individual participants, may introduce biases. However, the GBD employs robust statistical methods to account for these limitations, enhancing the reliability of its estimates. Importantly, the GBD study design is observational and cannot establish causal links between risk factors and

LOCC trends. Joinpoint analysis, used to identify temporal trends, can be sensitive to change point placement, potentially affecting interpretation. Nevertheless, the GBD's methodological strengths and extensive data integration provide valuable insights into regional and temporal variations in LOCC burden, informing public health strategies.

Conclusion and further directions

Our study revealed a concerning and significant increase in LOCC burden in Iran over the past three decades, reflected in rising age-standardized rates (ASDR, ASMR, and ASIR) across the country. While our projections suggest that mortality and DALY rates will remain relatively stable with fluctuations, incidence is expected to continue rising until 2040, highlighting a persistent public health challenge. This trend highlights the need for multipronged public health interventions tailored to address regional variations and potential sex-specific risk factors. While traditional risk factors such as tobacco and alcohol consumption remain crucial areas for focus, the observed increase in HPV incidence and the plateauing/decline in LOCC rates following the private sector introduction of the HPV vaccine warrant further investigation. Incorporating routine HPV vaccination for both sexes at the recommended age of 11–12 years [36], alongside continued efforts to reduce tobacco, alcohol, and opioid consumption, improve early detection programs, and enhance public awareness, could be a crucial preventive strategy. Future research with more comprehensive HPV vaccination data and long-term impact analysis is vital to definitively assess its effectiveness in the Iranian context.

Abbreviations

ARIMA	Autoregressive Integrated Moving Average
ASDR	Age-standardized DALYs rate
ASIR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
BIC	Bayesian Information Criterion
CI	Confidence interval
DALYs	Disability-adjusted life years
GBD	Global Burden of Disease
UI	Uncertainty interval
WHO	World Health Organization
YLDs	Years lived with disability
YLLs	Years of life lost
LOCC	Lip and oral cavity cancer
APC	Annual percent change
AAPC	Average annual percent change

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22202-8.

Additional file 1.

Additional file 2.

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Authors' contributions

Conceptualization: F.N., S.E.B.B., M.A.L., A.S., A.B., G.M. Data curation: F.N., S.E.B.B., M.A.L., A.S. Formal analysis: M.A.L. Methodology: F.N., S.E.B.B., M.A.L. Project administration: S.E.B.B. Software: M.A.L. Supervision: S.E.B.B., M.A.L. Validation: S.E.B.B. A.S. Visualization: M.A.L. Writing – original draft: F.N., S.E.B.B., M.A.L. G.M. Writing – review & editing: F.N., S.E.B.B., M.A.L. A.S., G.M.

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Data availability

Data can be obtained from the following website: http://ghdx.healthdata.org/gbd-results-tool.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer J Clin. 2024;74(3):229–263.
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer; 2024. Available from: https://gco.iarc.fr/. Accessed 12 Mar 2025.
3. Zhang J, Lu Y, Li H, Zhang N, He R, Zhang R, Mao Y, Zhu B. Lip and Oral Cavity Cancer Burden and Related Risk Factors in China: Estimates and Forecasts from 1990 to 2049. Healthcare (Basel). 2022;10(9):1611.
4. O'Sullivan A, Kabir Z, Harding M. Lip, Oral Cavity and Pharyngeal Cancer Burden in the European Union from 1990–2019 Using the 2019 Global Burden of Disease Study. Int J Environ Res Public Health. 2022;19(11):6532.
5. Romagna DV, Oliveira MM, Abreu LG, Stein C, Hugo FN, Teixeira R, Malta DC, Naghavi M, Iser BPM. Incidence and mortality rates of lip, oral cavity, and pharynx cancers in Brazil: time-trend and age-period-cohort analysis from the last 30 years, Global Burden of Disease Study. Rev Soc Bras Med Trop. 2022;55(suppl 1):e0286.

6. Wang Y, Zhuo L, Yang S, Dong C, Hu X. The worldwide epidemiology of lip and oral cavity cancer attributable to smoking based on the Global Burden of Disease Study 2019. J Public Health. 2023. https://doi.org/10.1007/s10389-023-02081-2.
7. Hernández-Morales A, González-López BS, Scougall-Vilchis RJ, Bermeo-Escalona JR, Velázquez-Enríquez U, Islas-Zarazúa R, Márquez-Rodríguez S, Sosa-Velasco TA, Medina-Solís CE, Maupomé G. Lip and Oral Cavity Cancer Incidence and Mortality Rates Associated with Smoking and Chewing Tobacco Use and the Human Development Index in 172 Countries Worldwide: An Ecological Study 2019–2020. Healthcare (Basel). 2023;11(8):1063.
8. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, Soerjomataram I. The Global Incidence of Lip, Oral Cavity, and Pharyngeal Cancers by Subsite in 2012. CA Cancer J Clin. 2016;67(1):51–64.
9. Huang J, Chan SC, Ko S, Lok V, Zhang L, Xu L, Lucero-Prisno DE, Xu W, Zheng ZJ, Elcarte E, et al. Disease Burden, Risk Factors, and Trends of Lip, Oral Cavity, Pharyngeal Cancers: A Global Analysis. Cancer Med. 2023;12(17):18153–64.
10. Ferrari AJ, Santomauro DF, Aali A, Abate YH, Abbafati C, Abbastabar H, Abd ElHafeez S, Abdelmasseh M, Abd-Elsalam S, Abdollahi A, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 2024;403(10440):2133–61.
11. Murray CJ: Findings from the global burden of disease study 2021. Lancet. 2024;403(10440):2259–62.
12. Global Burden of Disease. The Lancet. 2024. Available from: https://www.thelancet.com/gbd. Accessed 3 Mar 2025.
13. Naghavi M, Ong KL, Aali A, Ababneh HS, Abate YH, Abbafati C, Abbasgholizadeh R, Abbasian M, Abbasi-Kangevari M, Abbastabar H, et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 2024;403(10440):2100–32.
14. Kim H-J, Fay MP, Yu B, Barrett MJ, Feuer EJ. Comparability of segmented line regression models. Biometrics. 2004;60(4):1005–14.
15. National Cancer Institute. Joinpoint Trend Analysis Software, Version 5.3.0. Division of Cancer Control & Population Sciences. 2024. Available from: https://surveillance.cancer.gov/joinpoint/. Accessed 3 Mar 2025.
16. Hyndman RJ, Khandakar Y. Automatic Time Series Forecasting: The forecast Package for R. J Stat Softw. 2008;27(3):1–22.
17. Hyndman R, Koehler AB, Ord JK, Snyder RD: Forecasting with exponential smoothing: the state space approach: Springer Science & Business Media; 2008.
18. Zhang GP. Time series forecasting using a hybrid ARIMA and neural network model. Neurocomputing. 2003;50:159–75.
19. Brunsdon C, Comber L. An Introduction to R for Spatial Analysis and Mapping. London: SAGE Publications Ltd; 2015.
20. Kaya E, Agca M, Adiguzel F, Cetin M. Spatial data analysis with R programming for environment. Hum Ecol Risk Assess Int J. 2019;25(6):1521–30.
21. Cunha ARD, Compton K, Xu R, Mishra R, Drangsholt MT, Antunes JLF, Kerr AR, Acheson AR, Lu D, Wallace LE, et al. The Global, Regional, and National Burden of Adult Lip, Oral, and Pharyngeal Cancer in 204 Countries and Territories: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2023;9(10):1401–16.
22. Sun R, Dou W, Liu W, Li J, Han X, Li S, Wu X, Wang F, Xu X, Li J. Global, regional, and national burden of oral cancer and its attributable risk factors from 1990 to 2019. Cancer Med. 2023;12(12):13811–20.
23. Jokar M, Namavari N, Moshiri SA, Jahromi HK, Rahmanian V. The incidence of oral cavity cancer in Iran: A systematic review and meta-analysis. Cancer Rep (Hoboken). 2023;6(6):e1836.
24. Shamloo N, Ghannadan A, Safarpour R. Epidemiological study of lip cancer between 2004 and 2016 in public hospitals of Tehran, Iran: Squamous cell carcinoma as the most common cancer. J Oral Health Oral Epidemiol. 2022;11(4):202–6.
25. Najafi S, Khayamzadeh M, Jafari Ghavamabad A, Moradi F, Bafrouii SD. A 5 year Epidemiological Study on Oral and Pharyngeal Cancers from Cancer Registration Centers in Tehran. J Iranian Med Council. 2018;1(2):63–8.
26. Rezapour A, Jahangiri R, Olyaeemanesh A, Kalaghchi B, Nouhi M, Nahvijou A. The economic burden of oral cancer in Iran. PLoS ONE. 2018;13(9):e0203059.
27. Greinert R, de Vries E, Erdmann F, Espina C, Auvinen A, Kesminiene A, Schüz J. European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. Cancer Epidemiol. 2015;39:S75–83.
28. Duran-Romero AJ, Infante-Cossio P, Pereyra-Rodriguez JJ. Trends in mortality rates for oral and oropharyngeal cancer in Spain, 1979–2018. Oral Dis. 2022;28(2):336–44.
29. Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue and mouth. Oral Oncol. 2020;102:104551.
30. Hashibe M, Sturgis EM, Ferlay J, Winn DM: Oral cavity, oropharynx, lip, and salivary glands. In: Schottenfeld and Fraumeni Cancer Epidemiology and Prevention, Fourth Edition. edn.: Oxford University Press; 2017: 543–578.
31. Institute for Health Metrics and Evaluation (IHME). GBD Results. 2024. Available from: https://vizhub.healthdata.org/gbd-results. Accessed 3 Mar 2025.
32. Mohebbi E, Alimoradi Z, Rozek LS, Mohebbi A, Jafari E. Risk of head and neck cancer among opium users. Arch Oral Biol. 2024;157:105846.
33. Luna-Ortiz K. Güemes-Meza An, Villavicencio-Valencia V, Mosqueda-Taylor A: Lip cancer experience in Mexico. An 11-year retrospective study. Oral Oncol. 2004;40(10):992–9.
34. Rezaee Azhar I, Yaghoobi M, Mossalaeie MM, Kollaee Darabi A, Nejadeh AH, Jamshidi M, Ahani A, Karkhane Mahmoodi M, Ghalichi L, Shabanzadeh A, et al. Prevalence of human papilloma virus (HPV) genotypes between outpatients males and females referred to seven laboratories in Tehran. Iran Infect Agents Cancer. 2022;17(1):7.
35. Ochoa Scussiatto H, Stenson KM, Al-Khudari S, Jelinek MJ, Pinto JM, Bhayani MK. Air pollution is associated with increased incidence-rate of head and neck cancers: A nationally representative ecological study. Oral Oncol. 2024;150:106691.
36. Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. Med Sci (Basel). 2023;11(2):42.
37. Mohammadpour F, Mansouri A, Hadjibabaie M. Utilization Evaluation of Human Papilloma Virus Vaccine (GARDASIL®) in Iran; A Cross-Sectional Study. Iran J Pharm Res. 2020;19(1):68–76.
38. Louredo BV, Vargas PA, Pérez-de-Oliveira ME, Lopes MA, Kowalski LP, Curado MP. Epidemiology and Survival Outcomes of Lip, Oral Cavity, and Oropharyngeal Squamous Cell Carcinoma in a Southeast Brazilian Population. Med Oral Pat Oral Cir Bucal. 2022;27:e274–84.
39. Dai X, Liang Y. Tobacco- and alcohol-attributable burden of early-onset lip, oral cavity, and pharyngeal cancer in 204 countries and territories from 1990 to 2019, with projections to 2040. Front Oncol. 2024;14:1429972.

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