

# Epidemiology of Oral Cavity Malignancies in Adolescents and Young Adults in Jordan: A Population-Based Study

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## Abstract

**Background:** Oral cavity malignancies mostly affect older adults and the elderly. Adolescents and young adults (15–39 years) are less affected. However, there is a paucity of studies addressing the epidemiology of oral cavity malignancies in these age groups.

**Objectives:** To describe the epidemiology of oral cavity malignancies in adolescents and young adults in Jordan.

**Patients and methods:** The records of ordinarily resident patients in Jordan aged between 15 and 39 years, with histologically confirmed oral cavity malignancies, between the years 2000 and 2017, were analyzed. The frequency of each type of malignancy, incidence, annual percentage, site, age, sex, and trends were analyzed.

**Results:** Between the years 2000 and 2017, 406 adolescents and young adults fulfilled the inclusion criteria. This comprised 2.9% of all cancers in this age category during the same period. The mean age was  $28.5 \pm 7.6$  years. Some 59.4% were male and 40.6% female. Regarding marital status, 34.2% were single, 61.6% married, and 0.7% divorced, while the marital status of 3.4% was unknown. Most (98.3%) were Jordanian nationals. The number of cases increased from 4.7% in 2000 to 6.2% in 2017, with no statistically significant trend. The overall age-adjusted incidence rate was 7.8 per 1,000,000. It decreased from 9.4 in 2000 to 6.2 in 2017, with no statistically significant trend over the study period. Nasopharyngeal cancer was the most common (56.9%), followed by cancers of the salivary gland (16.7%), tongue (10.3%), gums (6.2%), lips (5.2%), hypopharynx (2.7%), other oral cavity and pharynx (1.0%), oropharynx (0.5%), floor of mouth (0.2%), and tonsils (0.2%). Overall, the incidence of cancers of the oral cavity and pharynx was higher in males. The incidence of cancers of the nasopharynx, tongue, and lips was higher in males, while salivary gland cancer was higher in females. The incidence of cancers of the gum, hypopharynx, and pharynx did not differ between the sexes.

**Conclusions:** The incidence of oral malignancies in adolescents and young adults in Jordan is relatively high compared to worldwide estimates but is not increasing. Risk factors for these malignancies should be the target of primary prevention interventions.

**Keywords:** Oral cavity malignancies, pharyngeal cancer, adolescents, young adults, Jordan

(J Med J 2024; Vol. 58(2): 138–146)

Received

Accepted

August 26, 2022

January 1, 2023

## INTRODUCTION

Cancer of the oral cavity is a common malignancy [1]. Annually, more than 250,000 cases of oral cavity cancer are diagnosed worldwide [2], with higher prevalence in developing countries [3]. Malignancies of the oral cavity may develop *de novo* or as an extension of pre-malignant lesions that present clinically as leukoplakia and erythroplakia [4]. Squamous cell carcinoma is the most common type of oral malignancy, but other tumors, including adenocarcinoma, adenoid cystic carcinoma of the

salivary gland, lymphoma, Kaposi's sarcoma, malignant melanoma, and metastatic cancers from other sites, may also occur [5, 6].

Oral squamous cell carcinomas are divided into well, moderate, and poorly differentiated carcinomas, depending on their histopathological features, which include the extent of cellular atypia, mitotic activity, nuclear pleomorphism, and keratinisation. Several histological subtypes may exist within squamous cell carcinomas exhibiting different prognoses, such as verrucous and basaloid carcinomas with varying prognosis [7].

The main etiological factor for oral malignancies is chronic exposure to carcinogens such as tobacco or alcohol [8, 9]. Carcinogenesis involves

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overexpression of oncogenes and inactivation of tumor suppressor genes. Tumor protein P53, also known as the p53 tumor suppressor gene, has been identified in oral cavity carcinomas of smokers. In addition, oral cavity carcinoma is more common in younger non-smoking subjects with the human papillomavirus, which expresses p16 oncoprotein [10].

Epidermal growth factor receptor plays a role in epithelial malignancies, as its activity enhances tumor growth, invasion, and metastasis. The role of epidermal growth factor receptors in oral cavity malignancies, however, remains unclear. Several histological subtypes exist within squamous cell carcinomas, with different prognoses, such as verrucous and basaloid carcinomas, with varying prognoses [7]. The diagnosis of squamous cell malignancies is relatively easy when patients attend early for consultation. In contrast, it is not unusual to come across advanced cases due to late presentation [8, 9].

The primary modality of therapy is surgical resection. Survival statistics demonstrated better results when surgery was combined with postoperative radiation or chemotherapy [8, 9]. Generally, verrucous squamous cell cancers are associated with better prognoses than basaloid carcinomas. Over expression of epidermal growth factor receptor in oral cavity carcinomas appears to be related to poor prognosis; however, it does not correlate with a response to targeted molecular therapies, in the form of epidermal growth factor receptor inhibitor medications, such as cetuximab, used for the treatment of various metastatic cancers, including those that involve the head and neck [7].

Various histopathological factors are of prognostic value, including tumor thickness, nodal extra-capsular spread, and invasion. Sampling error and heterogeneity of tumors affect their prognostic value [7]. Extra-capsular spread in cervical lymph nodes is associated with an increased risk of loco-regional metastasis, especially those cancers that have a non-cohesive invasive front or perineural invasion, with an associated decrease in survival rates [11]. Tongue squamous cell malignancy of greater than 4 mm thickness presents a high risk of cervical lymph node metastatic involvement [12].

In 2006, the National Cancer Institute and the Lance Armstrong Foundation initiated the Adolescent and Young Adult Oncology Progress Review Group. The group's report included the development of guidelines for the care of adolescents and young adults (AYAs) with cancer. The alliance included clinicians, researchers, and

advocates. The group defined AYAs as those diagnosed with cancer between the ages of 15 and 39 years [13]. Patients with cancer in this category are distinct from other categories in relation to site, distribution, risk factors, disease course, health consequences, and survival [14].

Despite the high incidence of invasive cancer among AYAs aged 15 to 39 years [15], they tend to fare worse in comparison to their older and younger counterparts [16]. Many issues unique to AYAs are relevant to their medical care; they need special modifications compared with other age groups. Developmental status, type of research, socioeconomic impact, access to care, and biologic differences of cancer types are examples of such factors [17–21].

The aim of this study was to review the contemporary incidence, type, annual percentage, site, age, survival, trend, and mortality of oral cavity malignancies in AYAs in Jordan.

## PATIENTS AND METHODS

The Jordanian Cancer Registry (JCR) was established in 1996. It collects data from all hospitals and is part of the international cancer database. Data on all patients aged between 15 and 39 years, with histologically confirmed oral cancers between January 2000 and December 2017, were collected and analyzed. Follow-up data on overall survival were available to allow for the computation of survival estimates. Survival data are curated by the JCR and supplemented by the national Civil Status and Passports Department.

The codes of the third revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-O-3) and a medical classification list by the World Health Organization (WHO), were converted to the codes of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), using the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) (version 2.13) tools.

For this project, to calculate frequencies, age-adjusted incidence rates (AAIRs), annual percentage changes (APCs) and trends, the following databases and applications were utilized:

- World Development Indicators (WDI) database. This provides access to hundreds of indicators for all countries, where information on various topics, including health and demographics, can be found. It allows users to discover how indicators were collected, and how they can be visualized to

analyze development trends. The WDI database was accessed to retrieve population estimates to allow for the computation of incidence rates.

- The Surveillance, Epidemiology, and End Results (SEER) Program. This provides information on cancer statistics. It is supported by the Surveillance Research Program (SRP) of the Division of Cancer Control and Population Sciences (DCCPS). The SEER\*Prep (version 2.5.8) software was used to curate and prepare the data for analysis, and the SEER\*Stat (version 8.3.8) software was used to calculate frequencies, AAIRs, and APCs. SEER\*Stat was also used to calculate sex differences.

- The joinpoint regression analysis application: This involves fitting a series of joined straight lines on a log scale to the trends in the annual age-adjusted cancer incidence and mortality rates. The application was used to assess temporal trends.

- Overall survival curves were computed in R (version 4.1.2) using the Kaplan–Meier method and compared using the log-rank test.

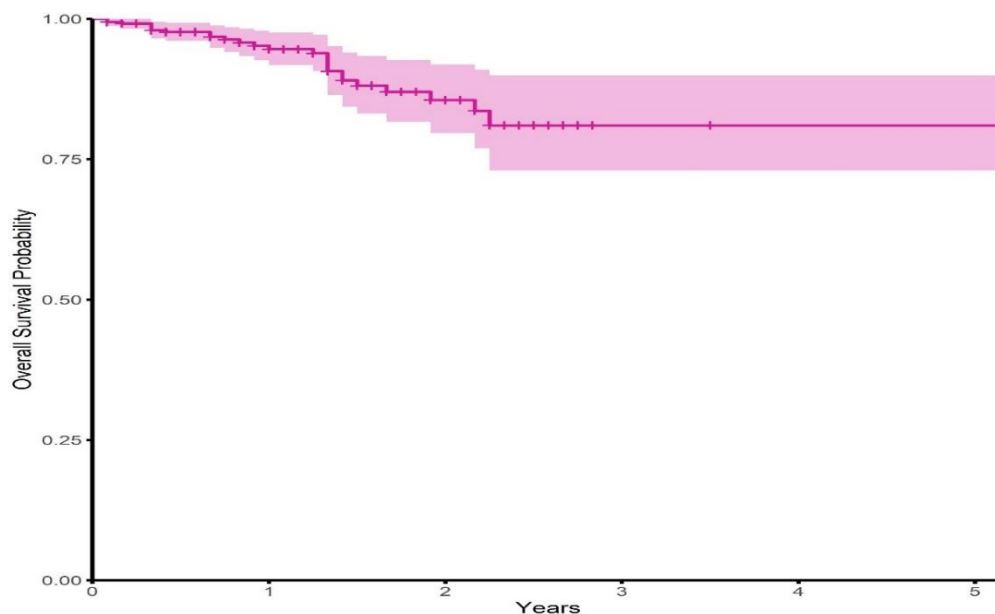
For all hypothesis tests, namely assessment of sex differences, temporal trends, and survival differences,  $p$ -values of  $<0.05$  were considered statistically significant.

## RESULTS

Between January 2000 and December 2017, 406 AYAs residing in Jordan were diagnosed with

cancers of the oral cavity and pharynx. These cases comprised 2.9% of all cancers diagnosed in the same age group during the same period. The demographic characteristics of the study population are summarized in Table 1. The mean age of the patients was  $28.5 \text{ years} \pm 7.6 \text{ years}$ . Males outnumbered females, 241 males (59.4%) vs. 165 females (40.6%), respectively. Of the total, 139 (34.2%) were single, 250 (61.6%) were married, three (0.7%) were divorced, and the marital status of 14 (3.4%) was unknown. The vast majority were Jordanian nationals ( $n=399$  [98.3%]). The number of cases increased from 19 (4.7%) in 2000 to 25 (6.2%) in 2017, but there was no statistically significant trend over the study period (APC, 2.3%; 95% CI,  $-0.2\%$  to  $4.8\%$ ). The overall AAIR was 7.8 (per 1,000,000 population). The AAIR decreased from 9.4 in 2000 to 6.2 in 2017, also with no statistically significant trend (APC:  $-1.8\%$ , 95% CI:  $-4.2\%$  to  $0.6\%$ ).

The cohort was followed for 4,893 individual months (median, eight months). During the follow-up period, 27 patients (6.7%) died. The one-year and five-year overall survival rates were 94.6% (95% CI: 91.8–97.5%) and 81.0% (95% CI: 73–90.0%), respectively. There was no statistically significant difference between the survival distributions of the sexes ( $p=0.40$ ). Figure 1 shows the overall survival curve for the full cohort.



**Figure 1.** Kaplan–Meier estimates of the overall survival probability of  $n=406$  adolescents and young adults with cancers of the oral cavity and pharynx (Jordan; 2000–2017)

The most common cancer was nasopharyngeal cancer (n=231 [56.9%]), followed by cancers of the salivary gland (n=68 [16.7%]), tongue (n=42 [10.3%]), gum and other mouth cancers (n=25 [6.2%]), lips (n=21 [5.2%]), hypopharynx (n=11 [2.7%]), other oral cavity and pharynx (n=4 [1.0%]), oropharynx (n=2 [0.5%]), floor of mouth (n=1 [0.2%]), and tonsil (n=1 [0.2%]). The corresponding AAIRs are listed in Table 2. The only cancer diagnosed at least once a year was nasopharyngeal cancer. There was no statistically significant trend in the incidence of nasopharyngeal cancer over the study period (APC: -2.0%; 95% CI: -5.0% to 1.1%). Overall, the incidence of cancers of

the oral cavity and pharynx was higher in male AYAs (female-to-male AAIR ratio was 0.73 [0.60 to 0.90];  $p<0.002$ ). However, site-specific sex differences were variable (Table 2). Briefly, the incidences of cancers of the nasopharynx, tongue, and lips were higher in male AYAs, while the incidence of salivary gland cancer was higher in female AYAs. The single cases of cancers of the floor of mouth and tonsil occurred in male AYAs, while the two cases of oropharyngeal cancer occurred in female AYAs. The incidence of cancers of the gum and other mouth, hypopharynx, and other oral cavity and pharynx did not differ between the sexes.

**Table 1. Demographic characteristics of adolescents and young adults diagnosed with cancers of the oral cavity and pharynx in Jordan, 2000–2017 (n=406)**

| Characteristic                  | No. (%)    |
|---------------------------------|------------|
| <i>Age at diagnosis</i>         |            |
| 15–19 years                     | 73 (18.0)  |
| 20–29 years                     | 123 (30.3) |
| 30–39 years                     | 210 (51.7) |
| <i>Sex</i>                      |            |
| Male                            | 241 (59.4) |
| Female                          | 165 (40.6) |
| <i>Nationality</i>              |            |
| Jordanian                       | 399 (98.3) |
| Non-Jordanian                   | 7 (1.7)    |
| <i>Governorate of residence</i> |            |
| Irbid                           | 76 (18.7)  |
| Ajloun                          | 8 (2.0)    |
| Jerash                          | 8 (2.0)    |
| Ma'raq                          | 18 (4.4)   |
| Balqa                           | 24 (5.9)   |
| Amman                           | 186 (45.8) |
| Zarqa                           | 50 (12.3)  |
| Madaba                          | 10 (2.5)   |
| Karak                           | 16 (3.9)   |
| Tafilah                         | 6 (1.5)    |
| Ma'an                           | 2 (0.5)    |
| Aqaba                           | 2 (0.5)    |

**Table 2. Age-adjusted incidence rates (AAIRs; per 1,000,000 population) and female-to-male AAIR ratios of cancers of the oral cavity and pharynx diagnosed in adolescents and young adults in Jordan, 2000–2017 (n=406)**

| Site                          | AAIR (95% CI) | AAIR Ratio (95% CI); <i>p</i> value |
|-------------------------------|---------------|-------------------------------------|
| Lip                           | 0.4 (0.3–0.6) | 0.25 (0.06–0.76); 0.010             |
| Tongue                        | 0.8 (0.6–1.1) | 0.41 (0.19–0.82); 0.010             |
| Salivary gland                | 1.3 (1.0–1.7) | 1.91 (1.14–3.26); 0.013             |
| Floor of mouth                | 0.0 (0.0–0.1) | NA                                  |
| Gum and other mouth           | 0.5 (0.3–0.7) | 0.82 (0.34–1.93); 0.75              |
| Nasopharynx                   | 4.3 (3.8–4.9) | 0.61 (0.46–0.81); < 0.001           |
| Tonsil                        | 0.0 (0.0–0.1) | NA                                  |
| Oropharynx                    | 0.0 (0.0–0.1) | NA                                  |
| Hypopharynx                   | 0.2 (0.1–0.4) | 1.41 (0.36–5.80); 0.78              |
| Other oral cavity and pharynx | 0.1 (0.0–0.2) | 1.20 (0.08–16.21); 1.00             |

## DISCUSSION

The global incidence of lip, oral cavity, and pharyngeal cancers has been estimated to be responsible for over half a million cases and about 300,000 deaths per annum, accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths [22, 23]. These figures correspond to the findings of this study, where the incidence was 2.9% of all cancers diagnosed in the same age group during the same period.

In this study of oral cancer in AYAs, the mean age of the patients was 28.5 years  $\pm$  7.6 years. Males outnumbered females with a percentage of 59.4% versus 40.6%, respectively. This rate was less than that reported in a study from India, where the male-female ratio was 2.3 to 1 [24]. These differences may be explained by the fact that the global burden of oral cavity and pharyngeal cancers varies according to geographic location, region, country, sex, and age [25, 26]. Other confounders include tobacco smoking [27], alcohol consumption [28], and high-risk human papillomavirus infection [29]. These have been shown to be major risk factors for oropharyngeal cancers, with tobacco smoking and alcohol consumption having synergistic effects [30, 31]. Compared to GLOBOCAN 2020 estimates, the overall AAIR in this study, which is historical, falls beyond the 90<sup>th</sup> percentile worldwide for AYAs, making the burden of oral cancer in Jordan disproportionately high [32]. This finding is not surprising given that the incidence rate of tobacco use in Jordan is among the highest regionally and worldwide [33].

In this study, the number of cases increased from 4.7% in 2000 to 6.2% in 2017, with an overall AAIR of 7.8 per 1,000,000 population, but no statistically significant trend. This is in contrast to the results of other studies that showed a high incidence of oral cancer among young adults with significant anatomic variation compared to older patients, with

failure to show any relation with the commonly implicated etiologic agents of oral cancer [34].

Cancer heterogeneity is due to its multiple levels of regulation. Although fundamental and clinical research has made noticeable advances in recent years, oral cancer incidence and mortality are expected to rise because of the accumulation of important risk factors in increasingly aged populations [35].

In this study, the most common cancer was nasopharyngeal cancer, followed by cancers of the salivary gland, tongue, gums, pharynx, floor of mouth, and tonsils. In a comparative study of demographic detail, frequency, location, and histologic grade between general patients and those occurring in patients less than 40 years of age, 5% occurred in this group of patients, with a statistically significant increase in oral squamous cell cancer over the study period. The mobile (oral) tongue was most common in young patients, with a statistically significant difference from those who were more than 40 years of age [36].

Overall, the incidence of cancers of the oral cavity and pharynx was higher in male AYAs, with a statistically significant female-to-male AAIR ratio, with variable site-specific sex differences. This is consistent with the findings of other studies [24, 37].

The higher incidence of oral cancer in males compared to females is probably due to differences in tobacco and alcohol exposure. Compared to the above studies [24, 37], there was a higher proportion of females without the risk factors of tobacco and alcohol, and patients older than 70 years of age [38].

The outcomes in patients treated for squamous carcinoma of the oral cavity in major series around the world vary according to clinical stage of disease and country. The five-year survival stood at 9.5% in India in the year 2000 for stage IV cancer and at 74% disease-specific survival in the United Kingdom in 2008 for all patients. This study found that the five-

year survival rate was 81%, which compares favorably with historical cohorts. This may be related to recent advances in the implementation of microvascular free flaps in the use of elective selective neck dissections, and the more effective postoperative adjuvant therapy [39].

There was no statistically significant difference between the survival distributions of the sexes in this study. This was in contrast to a recent study where death certification data for 61 countries provided by the World Health Organization in 2010–2015 were analyzed and showed that the male age-standardized death rates per 100,000 were 5.03 in the European Union, 8.33 in the Russian Federation, 2.53 in the United States, and 3.04 in Japan, while the respective rates in women were 1.23, 1.23, 0.82, and 0.76 [40]. These contrasting results, in addition to changes in tobacco and alcohol exposure, may be explained by genetic predisposition differences between the sexes, and the implication of human papillomavirus infection in oropharyngeal cancer.

Recent advances in reversing epigenetic features are gaining ground, where aberrant signatures can be

modified through the administration of exogenous inhibitors of certain DNA processes. The combination of epigenetic modulatory agents with conventional therapy could mark a new milestone in improving clinical outcomes [41].

## CONCLUSIONS

Oral cavity malignancies are diagnosed more often in male AYAs in Jordan, but the survival rates are comparable between the sexes. However, site-specific sex differences are variable and require further investigation. Modifiable risk factors for oral cavity malignancies are highly prevalent in Jordanian AYAs and should be targeted by primary prevention interventions.

**Funding:** This work is a report on a sabbatical project granted to the author by the University of Jordan, Office of the President. Document Number 1/5/2/459. Dated 26 January 2021.

**Competing interests:** None declared.

**Ethical approval:** Not required.

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## وبائيات الأورام الخبيثة في تجويف الفم لدى المراهقين والشباب في الأردن: دراسة سكانية

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### الملخص

**الخلفية:** تؤثر سرطانات الفم بشكل أساسي على كبار السن والمسنين. يتأثر المراهقون والشباب (15-39 عاماً) بشكل أقل. هناك نقص في الدراسات التي تتناول وبائيات سرطانات الفم لدى المراهقين والشباب.

**الأهداف:** وصف وبائيات سرطانات الفم لدى المراهقين والشباب في الأردن.

**المرضى والطرق:** تم تحليل سجلات المرضى المقيمين في الأردن والذين تتراوح أعمارهم بين 15 و 39 عاماً، والذين تم تأكيد إصابتهم بسرطانات الفم من خلال التحليل النسيجي، بين عامي 2000 و 2017. تم تحليل تواتر كل نوع من السرطانات، معدل الإصابة، النسب السنوية، الموقع، العمر، الجنس والاتجاهات.

**النتائج:** بين عامي 2000 و 2017، توافق 406 مراهق وشاب مع معايير الاختيار. وشكل ذلك 2.9% من جميع السرطانات في هذه الفئة العمرية خلال نفس الفترة. كان متوسط العمر  $28.5 \pm 7.6$  سنة، وكان 59.4% منهم ذكوراً، و 40.6% إناثاً، وكان 34.2% منهم أعزب، و 61.6% متزوجين، و 0.7% مطلّقين، وكان الوضع الاجتماعي لـ 3.4% غير معروف، وكان 98.3% منهم مواطنين أردنيين. ارتفع عدد الحالات من 4.7% في عام 2000 إلى 6.2% في عام 2017، دون اتجاه ذو دلالة إحصائية. كان معدل الإصابة المعدل للعمر العام 7.8 لكل مليون نسمة. انخفض من 9.4 في عام 2000 إلى 6.2 في عام 2017، دون اتجاه ذو دلالة إحصائية خلال فترة الدراسة. كان سرطان الأنف والبلعوم الأكثر شيوعاً (56.9%)، تليه سرطان الغدة اللعابية (16.7%)، ثم سرطان اللسان (10.3%)، اللثة (6.2%)، الشفة (5.2%)، البلعوم السفلي (2.7%)، غيرها من سرطانات الفم والبلعوم (1.0%)، البلعوم الأوسط (0.5%)، قاع الفم (0.2%)، واللوزتين (0.2%). بشكل عام، كانت معدلات الإصابة بسرطانات الفم والبلعوم أعلى في الذكور. كانت معدلات الإصابة بسرطانات الأنف والبلعوم واللسان والشفة أعلى في الذكور، في حين كانت معدلات الإصابة بسرطان الغدة اللعابية أعلى في الإناث. لم تكن هناك فروق في معدلات الإصابة بسرطانات اللثة والبلعوم السفلي والبلعوم بين الجنسين.

**الاستنتاجات:** معدل حدوث الأورام الخبيثة في الفم لدى المراهقين والشباب في الأردن مرتفع نسبياً مقارنة بالتقديرات العالمية، ولكن ليس في تزايد. يجب أن تكون عوامل الخطر لهذه الأورام الخبيثة هدفاً لتدخلات الوقاية الأولية.

**الكلمات الدالة:** الأورام الخبيثة في تجويف الفم، سرطان البلعوم، المراهقون، الشباب، الأردن.