ORAL CANCER IN HUNGARY: EPIDEMIOLOGICAL TRENDS, DIAGNOSTIC BEHAVIOR, AND CLINICAL CHALLENGES

PhD Thesis

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LIST OF PUBLICATIONS PROVIDING THE BASIS OF THE THESIS

1. Sonkodi I, Nagy J, **Novák P**, Braunitzer G, Virág K, Boda K, et al. A retrospective screening and epidemiological study of oncological and other diseases in the oral and maxillofacial region at the University of Szeged, Department of Oral Medicine (1960-2014). *Fogorv Sz* 2016;109(3):94-101

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2. **Novák P**, Szabó RM, Braunitzer G, Vereb I, Bágyi K, Nagy Á, et al. Diagnostic confidence and oral cancer screening: insights from a nationwide cross-sectional study in Hungary. *Int Dent J* 2025; In press.

SJR rank: Q1 (dentistry/miscellaneous, 2024)

IF: 3.2

3. **Novák P**, Sükösd F, Hamar S, Németh I, Tiszlavicz L, Szalay I, et al. Metachronous clear cell carcinoma of the tongue and kidney: a diagnostically challenging coincidence. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;114(4):e25-30.10.1016/j.oooo.2012.01.028

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ABBREVIATIONS

ASIR	Age-Standardized Incidence Rate
CCC	Clear Cell Carcinoma
HCCC	Hyalinizing Clear Cell Carcinoma
RCC	Renal Cell Carcinoma
VHL	von Hippel–Lindau
LOH	Loss of Heterozygosity
MS	Microsatellite
PCR	Polymerase Chain Reaction
PAS	Periodic Acid–Schiff
EMA	Epithelial Membrane Antigen
RCC	Renal Cell Carcinoma
KL-1	Pancytokeratin antibody clone KL-1
SMA	Smooth Muscle-specific Actin
S-100	S-100 Protein
GFAP	Glial Fibrillary Acidic Protein
EDTA	Ethylenediaminetetraacetic Acid
dNTP	Deoxynucleoside Triphosphate
DNA	Deoxyribonucleic Acid

I. INTRODUCTION

I.1. Oral Cancer: A Global and National Burden

Oral cancer, including malignancies of the lips, tongue, floor of the mouth, buccal mucosa, and other intraoral sites is a global public health concern. Globally, it ranks among the top 15 most common cancers, with hundreds of thousands of new cases and deaths recorded each year (1). While its occurrence varies by region, it is most frequent in parts of South Asia, Central and Eastern Europe, and South America, where smoking, alcohol use, and poor oral hygiene are common risk factors (2,3).

In Europe, oral and oropharyngeal cancer has shown a steady rise over recent decades. Hungary has received particular attention due to its unusually high rates of both incidence and mortality. Reports have repeatedly placed Hungary among the worst-affected countries in Europe and even globally (4,5). These trends are often linked to patterns of tobacco and alcohol consumption, socioeconomic inequalities, limited access to dental care, and delays in diagnosis (6,7).

Despite improvements in cancer care, early-stage detection of oral cancer remains a challenge in many settings. It is estimated that in Hungary, around 60% of cases are diagnosed at an advanced stage, often after spread to nearby lymph nodes has occurred (6). This has serious consequences for treatment and survival, since late-stage oral cancers are harder to manage and carry a worse prognosis.

Screening for oral cancer is technically simple: the oral cavity is easily accessible, and most suspicious lesions can be identified through basic visual and tactile examination. For this reason, many researchers have called for the integration of screening into routine dental or medical checkups (8,9). Opportunistic screening—where clinicians examine the mouth during unrelated visits—has been suggested as a practical approach, especially in countries where population-wide programs are not yet in place (10).

Several Hungarian policy documents have emphasized the role of dentists and physicians in early detection. Guidelines issued as early as the 1970s recommended that dentists perform oral examinations even when patients come for other problems, and refer suspicious findings to specialist centers (11). Still, despite these long-standing recommendations, screening is not uniformly practiced. This may be due to time pressures, lack of training, or low awareness of oral cancer signs among clinicians and the general population.

In summary, oral cancer remains a serious and growing concern, both globally and in Hungary. The high mortality seen in Hungary is likely the result of multiple factors, including risk behaviors, social conditions, and weaknesses in early detection. Expanding awareness and improving access to screening within routine care could help reduce this burden in the future.

I.2. Epidemiological Patterns in Hungary

Hungary exhibits a particularly concerning epidemiological profile regarding oral cancer, marked by consistently high incidence and mortality rates when compared to other European nations. International comparisons have repeatedly shown that Hungary ranks near the top in Europe in age-standardized rates for cancers of the oral cavity and pharynx (3,5). Although several Central and Eastern European countries face similar challenges, Hungary's trajectory has been among the steepest, especially in the latter half of the 20th century and into the early 2000s (4).

This elevated disease burden has been attributed to a combination of lifestyle risk factors—most notably, high rates of tobacco use and alcohol consumption—as well as delayed detection, gaps in public awareness, and systemic limitations in screening infrastructure (1,6). These contextual factors have made Hungary a subject of interest in regional cancer epidemiology, particularly in relation to the broader trends of non-communicable disease surveillance and prevention.

Hungary has had a structured system for recording cancer data for decades. The National Cancer Registry (NCR), which operates in close cooperation with the Central Statistical Office and the National Health Insurance Fund, serves as a comprehensive source of data for cancer surveillance and planning. The registry includes detailed records of all newly diagnosed malignant tumors, including oral and pharyngeal cancers (12). It supports national-level health policy and allows international comparisons. However, challenges remain in collecting complete data on histological types and tumor stage, especially in certain cancer categories.

Hungary was also among the first countries in the region to establish a network of oral surgery centers to manage oral tumors. In 1968, the health system created specialized units for diagnosis and treatment, followed in 1973 by national guidelines promoting opportunistic mucosal examination during dental visits and referral for suspicious lesions (11). While these efforts were significant at the time, screening is still not consistently practiced across the country. Differences in training, access to care, and professional engagement continue to affect implementation (13).

Large teaching clinics—particularly those in Szeged, Debrecen, and Budapest—have contributed to documenting oral cancer trends and have played a role in training the dental workforce.

However, in the absence of a dedicated oral cancer registry or a national screening program, it remains difficult to track early detection rates or the effectiveness of existing interventions (9,14).

In summary, Hungary's oral cancer statistics reflect both long-established risk factors and uneven progress in early detection. While institutional structures and data systems exist, their full potential has not yet been realized. Stronger implementation of screening practices and more complete data reporting would support more effective public health strategies in the years ahead.

I.3. Professional Knowledge and Diagnostic Behavior

The early detection of oral cancer depends heavily on the vigilance and diagnostic engagement of frontline healthcare professionals, particularly general dentists, dental hygienists, and primary care physicians. While numerous international studies emphasize the anatomical accessibility of the oral cavity as an advantage for screening, the actual clinical uptake of routine oral cancer examination remains highly variable. This variability is shaped not only by institutional factors but also by professional knowledge, self-efficacy, and prevailing attitudes toward screening responsibility (15,16).

Globally, studies have found that even when clinicians possess basic knowledge about the risk factors and clinical signs of oral malignancies, they may not engage in screening behaviors unless they feel sufficiently confident in their diagnostic abilities (17). This distinction between knowledge and diagnostic self-confidence has emerged as a critical factor in understanding professional behavior. While knowledge can be imparted through education, diagnostic confidence is often shaped by experience, perceived role responsibility, and opportunities for hands-on clinical training (18,19).

Educational exposure to oral oncology during undergraduate training varies widely between institutions and disciplines. Dental curricula typically include more structured and practice-oriented components on oral mucosal pathology compared to medical curricula, which often focus on systemic disease frameworks. As a result, medical professionals may be less equipped to recognize early-stage oral cancer or to integrate mucosal examinations into routine clinical workflows (14). Moreover, continuing education in this field is often sporadic and tends to favor passive learning modalities such as lectures or reading materials, despite evidence suggesting that interactive and practice-based formats are more effective in improving both knowledge and screening engagement (20,21).

Time constraints, competing clinical priorities, and the absence of standardized screening protocols further hinder routine implementation. In many settings, particularly those with fee-for-service models, clinicians may perceive oral cancer screening as time-consuming and insufficiently reimbursed—discouraging its consistent integration into daily practice (13). Additionally, some professionals express uncertainty about referral pathways or follow-up procedures after a suspicious lesion is identified, leading to diagnostic inertia despite clinical suspicion (15).

Addressing these barriers requires a multifaceted approach. Enhancing undergraduate education, investing in structured postgraduate training, and embedding oral cancer screening into national clinical guidelines are critical steps. Equally important is cultivating a professional culture that prioritizes early detection and empowers practitioners to act with diagnostic confidence. Without such systemic and educational reforms, opportunities for timely intervention are likely to remain underexploited.

I.4. Rare Cases: Challenges in Early Detection and Differential Diagnosis

The diagnosis of oral cancer can be particularly complex when faced with rare or atypical presentations. While the majority of malignant tumors in the oral cavity follow well-characterized clinical and histopathological patterns, a subset of cases defies early detection due to subtle signs, nonspecific symptoms, or overlapping histological features. This diagnostic ambiguity often delays treatment initiation and complicates therapeutic planning, thereby negatively impacting patient outcomes (22).

One major diagnostic challenge arises in distinguishing between primary tumors of the oral mucosa and metastatic lesions from distant primaries, especially when clear cell morphology is involved. Clear cell tumors may originate from minor salivary glands, as seen in hyalinizing clear cell carcinoma (HCCC), or may represent metastases from renal cell carcinoma (RCC) or other distant neoplasms (23,24). The tongue, though rare as a metastatic site, has been documented in cases of RCC metastasis, posing serious diagnostic challenges when patients present without a known cancer history or when lesions appear deceptively benign.

HCCC itself is an uncommon neoplasm, constituting approximately 1% of all salivary gland malignancies. It predominantly affects middle-aged women and tends to present as a slowly enlarging, painless submucosal mass—usually without mucosal ulceration. Histologically, HCCC is characterized by clear cells set in a hyalinized stroma and typically lacks myoepithelial markers, supporting its presumed origin from the intercalated ducts of salivary glands (25,26). However, distinguishing HCCC from other clear cell entities—such as epithelial-myoepithelial carcinoma or metastatic RCC—requires an integrated approach involving immunohistochemistry and, increasingly, molecular diagnostics such as identification of the EWSR1-ATF1 fusion gene.

In clinical practice, these cases underscore the limitations of relying solely on gross examination or routine histology. Rare tumors may lack pathognomonic features, and their true nature may only emerge after extensive multidisciplinary investigation. This challenge is magnified when the initial clinical impression does not strongly suggest malignancy, as is often the case with slowly enlarging, non-ulcerated lesions of the tongue or palate. Furthermore, the absence of regional lymphadenopathy or systemic symptoms can mislead clinicians into underestimating the severity of the lesion (24).

These diagnostic complexities highlight the importance of vigilance, comprehensive patient history taking, and access to advanced diagnostic tools. They also reinforce the need for enhanced training in differential diagnosis and pathology among clinicians who encounter oral lesions. While rare entities may not constitute a large fraction of the total oncological burden, they often demand disproportionate diagnostic effort—and their misclassification can have profound implications for patient care.

I.5. Rationale for the Present Thesis

Oral malignancies represent a persistent burden within the Hungarian healthcare system, both in terms of incidence and clinical outcomes. Despite improvements in therapeutic modalities, early detection remains limited, and national-level screening is still somewhat inconsistent. This thesis addresses the problem of delayed diagnosis and limited screening uptake by examining three interrelated aspects of oral cancer: long-term epidemiological trends, diagnostic behavior among healthcare professionals, and diagnostic uncertainty in a rare clinical context.

The first study to be presented in this thesis is an epidemiological one. It provides longitudinal data spanning over five decades, documenting a substantial increase in premalignant and malignant lesions in the oral and maxillofacial region. This rising incidence supports the need for systematic early detection strategies and reinforces the relevance of opportunistic screening in dental and medical practice.

The second study, based on a national cross-sectional survey, focuses on the diagnostic behavior of physicians, dentists, and students. It demonstrates that diagnostic self-confidence plays a more significant role in screening behavior than factual knowledge. These findings suggest that training programs should address not only knowledge gaps but also decision-making confidence and diagnostic competence.

Finally, in the third study, a diagnostically complex case of metachronous clear cell carcinoma of the tongue in a patient with a history of renal carcinoma is presented. Although rare, such cases highlight the importance of interdisciplinary diagnostic awareness and the potential for diagnostic error in atypical presentations.

Together, these three studies support a comprehensive investigation into the barriers and challenges of early oral cancer detection in Hungary. The integration of population-level data, behavioral insights, and clinical diagnostic analysis provides a basis for identifying areas for intervention at both systemic and professional levels.

II. OBJECTIVES

The present thesis is based on three published studies that address different aspects of oral cancer diagnosis and detection. The specific objectives of each study were as follows:

The first study (*Sonkodi et al., 2016*) aimed to explore long-term trends in the incidence and pathology of oral and maxillofacial tumors through a retrospective review of clinical data spanning more than five decades. The objectives were to determine the frequency and distribution of benign, premalignant, and malignant lesions in a large patient population treated at the University of Szeged, to assess changes in tumor characteristics over time, and to consider the implications of these trends for the development of organized or opportunistic screening strategies in Hungary.

The second study (*Novák et al., 2025*) investigated the behavioral and cognitive factors influencing oral cancer screening and preventive counseling practices among healthcare professionals and clinical-grade students in Hungary. The primary objectives were to assess the relative contribution of diagnostic self-confidence and objective knowledge to screening behavior; to analyze the effects of professional background, experience, and self-perceived knowledge sufficiency; and to identify educational preferences and perceived needs for further training in oral cancer detection and prevention.

The third study (*Novák et al., 2012*) presented a diagnostically challenging case of clear cell carcinoma of the tongue in a patient with a prior history of renal clear cell carcinoma. The objective was to distinguish, through histopathological, immunohistochemical, and molecular genetic analysis, whether the oral lesion represented a primary tumor or a late metastasis. This study aimed to highlight the diagnostic complexity posed by histologically similar but etiologically distinct tumors and to emphasize the need for careful differential diagnosis in patients with oncological histories. To our knowledge, this was the first report in the English-language literature to document two primary clear cell carcinomas occurring metachronously in the kidney and the tongue.

III. METHODS

III.1. Methods of the Retrospective Epidemiological Analysis

The Dental and Oral Surgery Clinic of the University of Szeged has been designated as a central stomato-oncological subcenter, responsible for three counties (Bács-Kiskun, Békés, and Csongrád) with an average population of 1.7 million (according to the Hungarian Central Statistical Office).

In our clinic, organized multiphasic screenings (caries, periodontal, and stomato-oncological) were conducted between 1970 and 1973 on selected risk groups (textile, hemp processing, and paprika factory workers), examining 2,124 individuals (27,28).

Our first retrospective stomato-oncological screening, conducted between 1960 and 1974 on selected and unselected individuals (29), involved 80,269 new outpatient cases at our clinic.

We have previously published data on retrospective screenings between 1960 and 1974 (30), conducted on both selected and unselected individuals, with particular focus on precancerous conditions. During this time, 80,269 new patients were registered in our outpatient records.

From 1960 to 2014, our clinic's total new outpatient turnover amounted to 338,200 patients, which included spontaneously presenting dental and oral surgery patients, those referred from primary care, and stomato-oncological patients sent from the three affiliated counties.

For the purposes of later descriptive and analytical epidemiological studies and the development of a clinically based cancer registry ("hospital-based cancer registry") emphasizing early detection, we have, since 1968, had all stomato-oncological patients fill out a custom-designed coded data sheet. This form was designed for digital processing and registration of epidemiologically relevant data (age, sex, location, etiology, treatment, histology, etc.). Computerized data processing began in 1974; initially, data were stored on punch cards and punched tape, later on hard drives.

In most cases, photographs were taken for documentation. When necessary, a biopsy was performed to establish the clinicopathological diagnosis needed to guide further treatment. All patients with histologically confirmed premalignant or malignant lesions were re-examined every 6 months. Patients who failed to return were contacted, and strict follow-up protocols were maintained.

Diseases of the oral mucosa and maxillofacial oncological and other oral conditions were classified primarily based on WHO nomenclature and classification systems, but we also considered the recommendations of the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC), and the European Union (EU) (14,31-34).

In this descriptive epidemiological study, we focused on the incidence of diseases categorized under oral medicine and compared our findings with those published in international literature (10,35,36), based on the classification of such diseases (37).

The incidence of oral cavity cancers and other oral diseases was calculated for the period between 1960 and 2014 based on 338,200 new patients seen at the Department of Oral Medicine. We analyzed the annual changes in the number of benign, precancerous, and malignant lesions over this time period to study trends in incidence. All incidence figures were calculated relative to the number of new patients seen each year. In addition to descriptive statistics, linear regression analysis was conducted to show changes in incidence. For statistical analysis, we used SPSS version 17.0 (IBM, USA), and graphs were created using SigmaPlot (Systat Software, Inc., USA). To characterize the tendencies, descriptive statistics and linear regression analysis were used.

III.2. Methods of the Study on Cancer Knowledge and Diagnostic Confidence

III.2.1. Sampling

A cross-sectional, questionnaire-based study was conducted among Hungarian dentists, physicians, dental students, and medical students. The survey was distributed through two channels: electronically to all registered members of the Hungarian Medical Chamber and manually to clinical-year students at the country's four medical and dental universities. Clinical years were defined as years 4 to 6 for medical students and years 3 to 5 for dental students. Participation was voluntary and anonymous. Data collection took place between April 2022 and December 2023. At that time, the Chamber's registry listed 49,683 active medical doctors and dentists, while national enrollment included 650 dental students and 2,571 medical students. It is noteworthy that the registry does not differentiate between dentists and physicians, as some specialties, such as maxillofacial surgery, encompass both qualifications. Inclusion criteria required participants to be active professionals or clinical-grade students, native Hungarian speakers, and capable of understanding the study materials. Exclusion criteria applied to those who did not meet these conditions. Informed consent was obtained from all participants, with forms stored separately to maintain anonymity. The study was approved by the Scientific and Research Ethical Committee of the Hungarian Medical Research Council (Approval number: IV/6905-1/2021/EKU).

III.2.2. Questionnaire Design and Content

The survey evaluated participants' knowledge, attitudes, behaviors, and perceived barriers concerning oral cancer prevention and screening, including the effects of the COVID-19 pandemic. It consisted of 18 questions (see Appendix I), which were either adapted from prior studies (38-40) or developed by the research team. Items taken from earlier sources were translated following published standardized procedures (41). The questionnaire covered demographic and professional background, regular screening practices, oral cancer knowledge, diagnostic confidence, referral patterns, educational needs, and pandemic-related changes.

Administered in Hungarian, the questionnaire was pilot-tested with 10 dentists and physicians of varying experience levels. Feedback regarding clarity, completion time, and content relevance was used to refine the final version.

The initial section collected data on sex, age, professional category (dentist, physician, dental or medical student), years of experience, specialization, and whether the respondent's workplace was in an urban or rural setting. Screening behavior was assessed through direct questions regarding routine oral mucosa examinations, including for patients at high risk.

Knowledge was evaluated with open-ended questions, such as listing primary oral cancer risk factors (Question 7) and clinical signs (Question 10), which were scored against standardized textbook-based reference lists (42-45).

Diagnostic confidence was measured on a four-point scale ranging from "very confident" to "very uncertain." Referral preferences for suspected cases were assessed with multiple-choice items. Respondents were also asked about their perception of knowledge sufficiency and their interest in further education, including preferred formats such as online courses and workshops.

The impact of COVID-19 on screening practices was addressed in a separate section; those results are reported elsewhere.

III.2.3. Outcomes and Data Analysis

The study focused on several main outcomes related to oral cancer detection and prevention practices. The primary outcomes were the regular performance of screenings and the provision of preventive advice, both measured as binary variables. Diagnostic self-confidence was assessed using a four-level scale ("very confident" to "very uncertain"), while objective knowledge was quantified as a continuous variable based on the number of accurately identified risk factors and clinical signs.

Participants' educational needs were evaluated by their expressed interest in additional training and by their preferences for learning formats, including information packages, workshops, seminars, and online courses. Demographic characteristics—such as age, professional affiliation, and years of experience—were collected to support interpretation of the findings.

All statistical analyses were performed using Jamovi (version 2.3.28) and G*Power (version 3.1.9.7). Descriptive statistics were used to summarize demographic characteristics, screening activity, and advisory behaviors. Binomial logistic regression models were applied to identify predictors of regular screening and preventive advice, including variables such as professional group, diagnostic self-confidence, perceived sufficiency of knowledge, and experience. To align clinical experience between students (based on academic year) and practitioners (based on years in practice), experience values were standardized using a z-transformation.

Post-hoc power calculations indicated that the sample size was sufficient for robust regression analysis. For the outcome of regular screening, 571 of 803 respondents reported engaging in the behavior, exceeding the recommended minimum of 10 events per predictor (at least 80 events total) (46). This yielded an estimated statistical power of approximately 98%. A similar power level was calculated for analyses related to preventive advice.

To investigate predictors of diagnostic self-confidence, a multinomial logistic regression model was used. Predictor variables included self-perceived knowledge sufficiency, objective knowledge, and professional group. Objective knowledge scores were calculated as the sum of correctly identified risk factors and clinical signs.

Sex was excluded from the regression models, as it showed no significant effects and has been reported in previous literature to be a less relevant factor in professional screening behavior (47,48).

III.3. Methods of the Case Report

III.3.1. Case Presentation

In 2008, a 63-year-old Caucasian woman presented with a gradually enlarging, painless mass that had been present for approximately two months on the right side of her tongue. Clinical examination identified a 2 × 2 cm elevated, non-ulcerated lesion located on the middle third of the right lateral tongue. No palpable cervical lymphadenopathy was detected (Figure 1).

Figure 1. The tumor on the right middle third of the tongue.

The lesion was firm and non-tender on palpation. The patient denied tobacco and alcohol use. Routine hematological and serum biochemical parameters were within normal limits. Panoramic radiographic imaging showed no signs of dental pathology or bony involvement. Of note, the patient had undergone radical nephrectomy and regional lymphadenectomy seven years earlier for clear cell carcinoma of the kidney.

Given this medical history, the differential diagnosis for the lingual mass included benign neoplasms such as fibroma, neuroma, lipoma, adenoma, and granular cell tumor, as well as the possibility of a delayed metastasis from the prior renal malignancy. Based on the clinical findings, the lesion was surgically removed. A biopsy was performed, and cryosurgical treatment was administered.

Following the histopathological confirmation of clear cell carcinoma of the tongue, additional investigations were initiated to assess for possible occult metastases originating from the renal carcinoma. Ultrasonography revealed no local recurrence, and no lymphadenopathy was noted on either side of the neck. Computed tomography scans demonstrated no significant cervical nodal enlargement, and chest radiography showed no evidence of pulmonary metastasis. Laboratory tests, including complete blood count, serum biochemistry, and urinalysis, remained within normal ranges. The patient received no further treatment but continued oncologic surveillance at two-month intervals. She remained disease-free—both locally and systemically—throughout a three-year follow-up period.

III.3.2. Histopathologic Evaluation

Both the renal and lingual tumor specimens were fixed in formalin and processed for paraffin embedding using standard histopathologic techniques. Immunohistochemical analyses were conducted on sections from both tumors utilizing antibodies against pancytokeratin (KL-1), epithelial membrane antigen (EMA), CD10, renal cell carcinoma (RCC) antigen, and vimentin.

In addition, the lingual tumor was subjected to special histochemical stains, including periodic acid–Schiff (PAS) both before and after diastase digestion, and PAS–alcian blue at pH 2.5. To assess for possible myoepithelial differentiation, the tumor was also evaluated with a panel of myoepithelial markers: calponin, p63, smooth muscle actin (SMA), S-100 protein, and glial fibrillary acidic protein (GFAP).

III.3.3. Molecular Pathology Evaluation

III.3.3.1.DNA Isolation

Regions with a high density of tumor cells, along with adjacent normal kidney tissue, were selectively sampled using needle microdissection. The proportion of tumor cells relative to normal cells exceeded 60%. Genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's protocol. DNA concentrations were standardized to approximately 10 ng/µL for each sample.

III.3.3.2. Loss of Heterozygosity (LOH) Analysis Using Microsatellite Markers

Microsatellite marker sequences and chromosomal locations—including D3S2450, D3S1038, D3S3651, D3S1289, D3S1582, D3S3672, D3S1613, and D3S1300—were obtained from the National Center for Biotechnology Information (http://ncbi.nlm.nih.gov). Paired normal and tumor DNA samples were amplified in 10 µL reaction volumes, each containing 50 ng of genomic DNA, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.5 mM $MgCl_2$, 200 µM of each dNTP, 10 pmol of Cy5-labeled forward primer, 5 pmol of reverse primer, and 0.5 units of Taq DNA polymerase (Fermentas).

Thermal cycling was initiated with a 2-minute denaturation at 94°C, followed by 28 cycles of 30 seconds at 94°C, 30 seconds at 61°C, and 40 seconds at 72°C, concluding with a 10-minute final extension at 72°C in a CG1-96 thermal cycler (Corbett Research). Prior to electrophoresis, 20 µL of stop solution—comprising 50 mM EDTA and 5 mg/mL dextran blue 2000 in 100% deionized formamide—was added. Samples were denatured at 95°C for 2 minutes and analyzed using an automated DNA sequencer (ALFexpress II; Amersham Pharmacia Biotech, Freiburg, Germany) on 6% denaturing polyacrylamide gels. Electrophoresis was conducted at 400 V, 55 mA, and 30 W in 1× Tris-borate EDTA buffer at a constant temperature of 55°C. Fragment data were analyzed using Fragment Manager software (version 1.2; Amersham Pharmacia Biotech).

III.3.3.3. VHL Gene Sequencing

PCR amplification for VHL exons was carried out in 15 µL reaction volumes containing 1× buffer (75 mM Tris-HCl [pH 8.8], 20 mM $(NH_4)_2SO_4$, 0.01% Tween 20), 3.75 mM $MgSO_4$, and 10 pmol of each forward and reverse primer. The following primers were used:

Exon 1a F: M13(–20)-AgCgCgTTCCATCCTCTAC

Exon 1a R: CTgCgATTgCAgAAgATgAC

Exon 1b F: M13(–20)-TACggCCCTgAAgAAgACgg

Exon 1b R: gggCTTCAgACCgTgCTATC

Exon 2 F: M13(–20)-AggACggTCTTgATCTC

Exon 2 R: gATTggATAACgTgCCTgAC

Exon 3 F: M13(–20)-gTTggCAAAgCCTCTTgTTC

Exon 3 R: gAAggAACCAgTCCTgTATC

The cycling conditions included an initial denaturation at 95°C for 20 seconds, annealing at 53°C for 20 seconds, and extension at 70°C for 30 seconds. Sequencing was performed in a single direction using the Megabace 1000 system (Amersham Biosciences, Uppsala, Sweden), and the results were evaluated with Sequence Analyzer version 4.0.

IV. RESULTS

IV.1. Results of the Retrospective Epidemiological Analysis

In our organized multiphasic (caries, periodontal, stomato-oncological) screening of selected risk groups (28), among 2,124 examined individuals, we identified 103 cases of stomato-oncological disease. Of these, 51 cases (2.4%) turned out to be precancerous lesions; no malignant tumors were found.

In our retrospective screening conducted between 1960 and 1974 on selected and unselected individuals (29,30), we examined a total of 80,269 new patients at our clinic, and among them, 1,372 stomato-oncological patients (1.70%) were identified. Of these: 575 cases (0.71%) were benign tumors, 239 cases (0.29%) were precancerous lesions, and 218 cases (0.27%) were malignant tumors. Thus, the combined occurrence rate of precancerous and malignant tumors in this sample was 0.569%.

In our current retrospective analysis of the period between 1960 and 2014, a total of 338,200 new outpatients visited our clinic. Among them: 20,065 patients (5.93%) suffered from benign, premalignant, or malignant conditions, and 14,446 patients (5.80%) were diagnosed with other oral mucosal diseases. Altogether, this represented 34,511 patients or 10.2% of all new patients. Within this group: 9,482 cases (2.80%) were benign tumors, 5,438 (1.60%) were precancerous lesions, and 5,145 (1.50%) were malignant tumors.

Altogether, we detected 10,579 patients with precancerous and cancerous conditions, corresponding to an incidence rate of 3.1%. Table 1 presents data on new patient cases recorded at the clinic, with a distinction made between overall figures starting from 1960 and more detailed records on oral diseases available from 1974 onward. Information on patients returning for follow-up visits has been systematically collected since 1970. In this context, "new patient" refers to individuals who either sought care on their own or were referred for evaluation or treatment of dental, oral surgical, stomato-oncological, or oral mucosal conditions. The current table focuses specifically on those new cases that involved tumors and other oral diseases, excluding unrelated dental pathologies or procedural visits.

When examining the data broken down by decades (Table 2), it is clear that until 1969, our clinic primarily received and treated patients with benign maxillofacial tumors, and only a small number of precancerous and malignant tumors. For example: 341 benign tumors (0.61%), 88 precancerous lesions (0.15%),65 malignant tumors (0.12%).

Table 1. Incidence of oral and maxillofacial oncological and oral diseases, 1960–2014.

Year	New patients (n)	Follow-up visits (n)	Benign tumors (n)	Precancerous lesions (n)	Malignant tumors (n)	Total tumors (% of new)	Oral diseases (% of new)
1960	5338	–	19	4	4	27 (0.51%)	–
1961	5227	–	27	5	3	35 (0.67%)	–
1962	5402	–	39	7	1	47 (0.87%)	–
1963	6023	–	34	6	4	44 (0.73%)	–
1964	5972	–	33	6	3	42 (0.70%)	–
1965	5318	–	26	11	6	43 (0.81%)	–
1966	5721	–	35	8	5	48 (0.84%)	–
1967	6112	–	30	12	7	49 (0.80%)	–
1968	5416	–	52	15	12	79 (1.46%)	–
1969	5318	–	46	14	20	80 (1.50%)	–
1970	6014	16	45	16	9	70 (1.16%)	–
1971	6268	81	29	8	19	56 (0.89%)	–
1972	5743	715	44	36	20	100 (1.74%)	–
1973	5777	2167	74	41	41	156 (2.70%)	–
1974	5052	2062	42	50	64	156 (3.09%)	33 (0.65%)
1975	4602	887	46	64	87	197 (4.28%)	61 (1.33%)
1976	5371	1620	98	62	107	267 (4.97%)	166 (3.09%)
1977	6287	4982	105	94	94	293 (4.66%)	220 (3.50%)
1978	6325	1965	113	76	136	325 (5.14%)	193 (3.05%)
1979	5974	2162	82	83	108	273 (4.57%)	162 (2.71%)
1980	5439	2483	107	74	108	289 (5.31%)	171 (3.14%)
1981	4859	2290	113	81	115	309 (6.36%)	175 (3.60%)
1982	5275	2842	131	85	147	363 (6.88%)	206 (3.91%)
1983	5081	2663	136	90	171	397 (7.81%)	192 (3.78%)
1984	5060	2676	196	113	182	491 (9.70%)	182 (3.60%)
1985	4751	2767	149	115	177	441 (9.28%)	196 (4.13%)
1986	4678	2951	179	132	223	534 (11.42%)	254 (5.43%)
1987	4614	2002	136	144	218	498 (10.79%)	243 (5.27%)
1988	4943	2585	228	178	212	618 (12.50%)	301 (6.09%)
1989	4458	2520	210	166	186	562 (12.61%)	341 (7.65%)
1990	3944	2552	213	168	189	570 (14.45%)	278 (7.05%)
1991	5348	3217	220	190	190	600 (11.22%)	308 (5.76%)
1992	3974	3274	190	191	164	545 (13.71%)	283 (7.12%)
1993	4143	2974	214	176	166	556 (13.42%)	309 (7.46%)
1994	3991	2992	238	134	151	523 (13.10%)	340 (8.52%)
1995	2879	2866	251	109	163	523 (18.17%)	335 (11.46%)
1996	1799	3062	227	113	156	496 (27.57%)	406 (22.57%)
1997	1815	3218	238	92	146	476 (26.23%)	437 (24.08%)
1998	2037	2859	213	110	156	479 (23.51%)	432 (21.21%)
1999	2024	2455	230	141	130	501 (24.75%)	369 (18.23%)
2000	1846	2355	224	158	126	508 (27.52%)	360 (19.50%)
2001	2083	2197	244	129	129	502 (24.10%)	393 (18.87%)
2002	2709	2515	284	119	128	531 (19.60%)	427 (15.76%)
2003	5525	2454	282	116	104	502 (9.09%)	443 (8.02%)
2004	7368	2629	281	119	99	499 (6.77%)	468 (6.35%)
2005	5678	2932	351	144	80	575 (10.13%)	486 (8.56%)
2006	11747	3294	274	148	59	481 (4.09%)	445 (3.79%)
2007	12678	3054	307	163	93	563 (4.44%)	455 (3.59%)
2008	15230	3372	353	165	70	588 (3.86%)	625 (4.10%)
2009	12245	3698	395	161	33	589 (4.81%)	619 (5.06%)
2010	10754	3687	340	169	29	538 (5.00%)	693 (6.44%)
2011	10049	3480	338	167	26	531 (5.28%)	574 (5.71%)
2012	9828	3430	323	181	31	535 (5.44%)	598 (6.08%)
2013	9960	2993	333	151	22	506 (5.08%)	604 (6.06%)
2014	18748	3273	315	128	16	459 (2.45%)	663 (3.54%)
Total 1960-	338200	–	9482 (2,8%)	5438(1,6%)	5145(1,5%)	20065(5.9%)	–
Total 1974-	251171	117268 (1970-)	9141(3,6%)	5350(2,1%)	5080(2,0%)	19571 (7.8%)	14446 (5.8%)

Between 2000 and 2009, we registered a total of 5,338 new tumor cases. Among these: 2,995 were benign tumors (3.88%),1,422 were precancerous lesions (1.84%), 921 were malignant tumors (1.19%).

The peak incidence of tumor and premalignant diseases occurred between 1986 and 2002. In 1986, for the first time, tumor patients made up more than 10% of the clinic's new patient population. Within this interval, the years 1995–2002 were particularly notable, during which the proportion of new tumor cases remained around 20% of all new cases.

The years 1996 and 2000 may be considered extreme outliers. In these two years, the combined incidence of tumor and premalignant conditions approached 30%. However, in 1996, as already noted, the total number of new patients was significantly lower than in other years, so it is likely that this year represents a relative increase rather than an absolute one.

Table 2: Incidence data broken down by decade (percentages in parentheses relative to the total number of new patients)

Decade	All new patients (n)	All tumors (n(%))	Benign tumors (n(%))	Precancerous lesions (n,(%))	Malignant tumors (n,(%))
1960-1969	55847	494 (0.88%)	341 (0.61%)	88 (0.16%)	65 (0.12%)
1970-1979	57413	1893 (3.29%)	678 (1.18%)	530 (0.92%)	685 (1.19%)
1980-1989	49158	4502 (9.16%)	1585 (3.22%)	1178 (2.40%)	1739 (3.54%)
1990-1999	31954	4768 (14.92%)	2234 (6.99%)	1424 (4.46%)	1611 (5.04%)
2000-2009	77109	5338 (6.92%)	2995 (3.88%)	1422 (1.84%)	921 (1.19%)

Linear regression analysis of the dataset revealed two main patterns. First, the incidence of all three lesion categories—benign tumors, premalignant lesions, and malignant tumors—increased steadily and significantly over the course of the 52-year study period. The strongest upward trend was observed in benign tumors ($\beta = 0.97$, $t(51) = 28.21$, $p < 0.001$), followed by premalignant lesions ($\beta = 0.87$, $t(51) = 12.43$, $p < 0.001$), and malignant tumors ($\beta = 0.44$, $t(51) = 3.45$, $p < 0.001$). When considering all tumor types together, the combined incidence also showed a significant positive trend ($\beta = 0.91$, $t(51) = 15.03$, $p < 0.001$). Despite these increases in absolute numbers, the relative distribution among the three lesion categories remained stable throughout the study period, indicating no significant shift in their proportional representation. These trends are clearly illustrated in Figure 2.

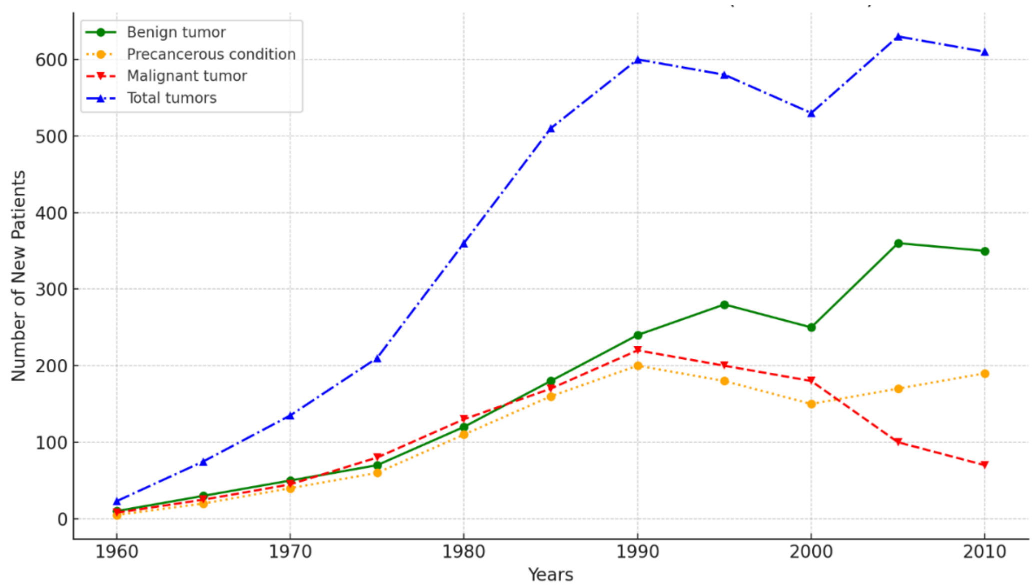

Figure 2: Incidence trends of benign, precancerous, malignant, and total oral and maxillofacial tumors between 1960 and 2010. Data points represent five-year intervals, but only decade labels (e.g., 1960, 1970, etc.) are shown on the x-axis for readability.

From the data, it can be concluded that between 1960 and 2014, the incidence of all three lesion types—benign, premalignant, and malignant—showed steady growth, even when taking into account that after 2004 our clinic was only partially responsible for managing malignant conditions.

Between 1960 and 2004, the total number of tumor and premalignant cases showed a clear upward trend. In the 1960s, growth was moderate, with 27 new cases recorded in 1960 and 80 by the end of the decade. This pattern changed significantly in the 1970s, when annual case numbers rose sharply. From that decade onward, it became increasingly uncommon for fewer than 100 new tumor cases to be registered in a given year. The increase continued over the following decades and reached its peak in the 1990s, during which the clinic recorded as many as 600 new cases in a single year. Across the full period from 1960 to 2004, all major lesion categories experienced substantial increases. The number of benign tumors grew approximately 15-fold, while precancerous lesions increased thirtyfold. Malignant tumors also rose dramatically, showing a 25-fold increase over the study period. In addition to primary diagnoses, the clinic provided ongoing care for a large number of patients. A total of 117,268 individuals returned for follow-up examinations, representing 76.97% of the clinic's total outpatient activity during this time. These figures show the long-term engagement of patients in the institution's screening and monitoring system, and reflect the central role the clinic played in stomato-oncological care at the regional level.

IV.2. Results of the Study on Cancer Knowledge and Diagnostic Confidence

IV.2.1. Demography

The final sample consisted of 803 respondents, comprising 184 physicians (22.9%), 127 medical students (15.8%), 164 dentists (20.4%), and 328 dental students (40.8%). Response rates were 14.1% among students and 0.7% among practicing professionals. Demographic characteristics are summarized in Table 3.

Table 3. Demographic characteristics of the groups. Age is given in years (± SD), sex is shown as N (% within group). D: dentist, DS: dental student, MD: physician, MS: medical student.

	Age	**Sex**
D N=164	39.5 (±13.2)	M: 84 (51.2%) F: 80 (48.8%)
DS N=328	23.7 (±1.8)	M: 119 (36.3%) F: 209 (63.7%)
MD N=184	46.6 (±14.3)	M: 84 (45.7%) F: 100 (54.3%)
MS N=127	24.3(±3.05)	M: 32 (25.2%) F: 95 (74.8%)

Dentists had a mean age of 39.5 years (±13.2), and physicians 46.6 years (±14.3). Among students, dental students averaged 23.7 years (±1.8), and medical students 24.3 years (±3.05). The sex distribution was relatively balanced across groups, as shown in Table 1.

Among practicing professionals, dentists reported a median of 10.5 years in practice (range: 0–53), while physicians reported a median of 19.0 years (range: 0–62). A majority of professionals held at least one specialist qualification: 62.8% of dentists and 77.0% of physicians. The most common dental specialties were restorative dentistry (27.0%), dento-alveolar surgery (25.5%), and dental/oral diseases (23.4%). Among physicians, the most frequent specialties were family medicine (32.5%) and occupational medicine (12.4%).

Most respondents (85.7%) were based in urban environments, including county seats and the capital.

IV.2.2. Cancer Knowledge

Oral cancer knowledge was evaluated based on the number of correctly identified clinical signs and risk factors. Table 4 presents the results across groups. On average, participants listed approximately three correct items in each category, and fewer than 10% in any group failed to provide at least one accurate answer.

Table 4. The number of correctly identified clinical signs and risk factors (mean, minimum-maximum), and the percentage of respondents who failed to provide a correct answer in each group.

	Correctly identified clinical signs	No correct identification
D (N=164)	3.01 (0-8)	1.8 %
DS (N=328)	2.71 (0-7)	7.0 %
MD (N=184)	2.73 (0-8)	4.9 %
MS (N=127)	3.52 (0-7)	8.7 %
	Correctly identified risk factors	**No correct identification**
D (N=164)	3.22 (0-9)	3.7 %
DS (N=328)	2.80 (0-7)	6.4 %
MD (N=184)	2.48 (0-8)	7.1 %
MS (N=127)	2.81 (0-6)	3.9 %

Qualitative analysis revealed that the most commonly recognized clinical signs included ulceration, exophytic or endophytic growth, and white lesions—each named by over 50% of respondents in at least two groups. Regarding risk factors, smoking and alcohol use were cited most frequently, with recognition rates ranging from 70% to 96%. Other risk factors were identified far less often, with proportions between 3.6% and 36%. Detailed percentages for each group and item are provided in Tables 5 and 6.

Table 5. Risk factors associated with oral cancer identified by the respondents. Percentages of respondents who identified the given item by group. D: dentist, DS: dental student, MD: physician, MS: medical student.

Risk factor	**D**	**DS**	**MD**	**MS**
smoking	96.34%	93.29%	93.48%	92.91%
alcohol abuse	87.80%	81.10%	69.02%	80.31%
chronic irritation	35.98%	20.43%	7.61%	5.51%
poor oral hygiene	34.76%	18.90%	34.24%	32.28%
viral infection	20.12%	25.00%	12.50%	30.71%
genetic predisposition	11.59%	11.28%	13.59%	8.66%
sunlight (UV radiation)	10.37%	8.23%	1.63%	3.15%
hot, spicy food	6.71%	6.71%	4.89%	14.17%
chemical agents	6.10%	4.57%	4.35%	3.94%
immunocompromised states	4.88%	3.66%	3.26%	7.09%
vitamin deficiency	3.66%	1.52%	1.09%	N/A
fungal infection	2.44%	4.88%	1.09%	0.79%
failed to provide acceptable response	3.66%	6.40%	7.07%	3.94%

Table 6. Clinical signs associated with oral cancer identified by the respondents. Percentages of respondents who identified the given item by group. D: dentist, DS: dental student, MD: physician, MS: medical student.

Clinical sign	D	DS	MD	MS
ulceration	75.00%	60.67%	66.30%	58.27%
exo- or endophytic growth	69.51%	52.74%	55.98%	43.31%
white lesions	45.73%	58.23%	51.09%	40.16%
red lesions	34.15%	39.63%	23.91%	27.56%
bleeding	18.90%	17.99%	21.74%	25.98%
other discoloration	17.68%	18.29%	17.39%	12.60%
pain	17.68%	10.37%	16.30%	18.11%
difficulty with swallowing	13.41%	5.79%	13.59%	16.54%
lymph node enlargement	6.10%	5.18%	7.07%	N/A
difficulty with speech	3.05%	2.13%	0.54%	7.87%
failed to provide acceptable response	1.83%	7.01%	4.89%	8.66%

IV.2.3. Screening and Advisory Activity

An overview of screening and preventive behaviors is provided in Table 7. Routine oral cancer screening was most commonly reported by dentists (97.6%) and dental students (85.4%), while lower rates were observed among physicians (40.8%) and medical students (44.1%). The regular provision of preventive advice was less frequent overall but followed a similar pattern, with dentists again reporting the highest rate (64.0%). A small percentage of respondents indicated that they conducted screenings only for high-risk patients: 1.3% of dentists, 6.6% of dental students, 11.8% of physicians, and 12.7% of medical students.

Table 7. The percentages of those dentists (D), dental students (DS), physicians (MD), and medical students (MS) who reported doing regular oral cancer screening and give preventive advice regularly.

	Does screening as a routine	Gives preventive advice regularly
D (N=164)	97.6%	64.0%
DS (N=328)	85.4%	34.5%
MD (N=184)	40.8%	31.5%
MS (N=127)	44.1%	32.3%

Binomial logistic regression analysis identified professional group, diagnostic self-confidence, and perceived sufficiency of knowledge as significant predictors of routine screening behavior (Table 5). The model accounted for 32.8% of the variance ($R^2 = 0.328$). Compared to physicians, the odds of regular screening were significantly higher for dentists (OR = 48.2) and dental students

(OR = 15.3). Higher levels of diagnostic self-confidence and perceiving one's knowledge as sufficient were also associated with greater likelihood of screening. Dentists reported the highest levels of confidence and self-perceived knowledge sufficiency, followed by the other professional groups.

Table 8. Results of the binomial logistic regression analysis for regular screening. Asterisk (*) indicates the reference category or level. D: dentist, DS: dental student, MD: physician, MS: medical student.

Predictor	Estimate	SE	Z	p	OR
Experience					
z-score	0.193	0.133	1.45	0.147	1.213
Group					
DS– MD*	2.727	0.306	8.92	< .001	15.294
D-MD	3.875	0.552	7.02	< .001	48.198
MS-MD	0.509	0.321	1.59	0.112	1.664
Diagnostic self-confidence					
Confident – Very uncertain*	1.948	0.398	4.89	< .001	7.016
Uncertain – Very uncertain	0.760	0.325	2.34	0.019	2.138
Very confident – Very uncertain	1.859	0.686	2.71	0.007	6.418
Self-perceived sufficiency of knowledge					
Yes-No*	1.063	0.290	3.67	< .001	2.896

*indicates the reference category

Figure 3 shows the estimated probability of regular screening across groups and confidence levels.

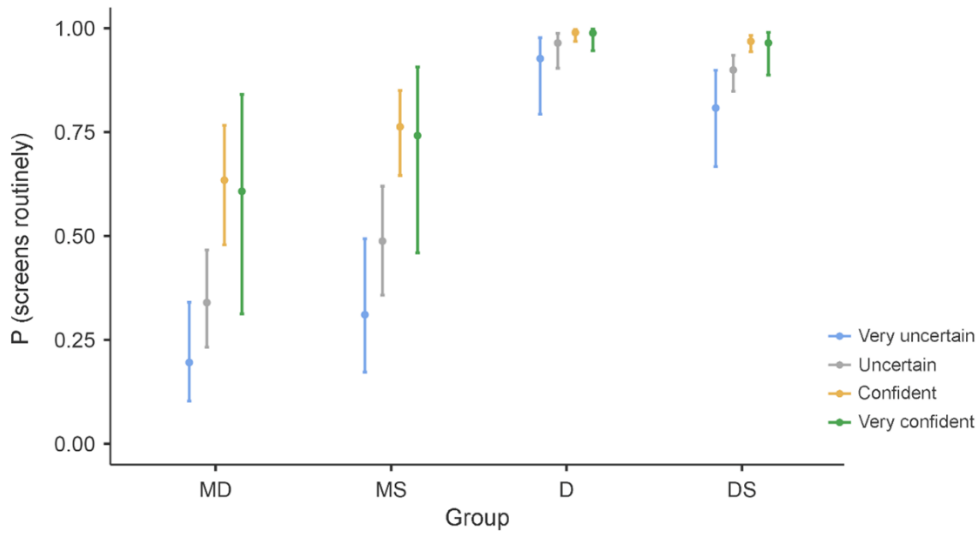

Figure 3. The probability of regular screening as determined by group affiliation and diagnostic self-confidence. D: dentist, DS: dental student, MD: physician, MS: medical student.

To further explore the factors influencing whether respondents engaged in preventive counseling, a separate binomial logistic regression analysis was performed. This analysis aimed to identify which variables could predict the likelihood of professionals advising patients on oral cancer prevention. The model revealed several significant predictors: years of professional experience, type of healthcare profession, level of diagnostic confidence, perceived sufficiency of professional knowledge, and whether the respondent regularly performed screening examinations. Together, these factors accounted for 18.1% of the variance in preventive advice behavior ($R^2 = 0.181$).

Dentists and dental students were both significantly more likely to provide preventive advice than physicians, with odds ratios of 2.63 and 2.14, respectively. Higher levels of diagnostic confidence and the belief that one's knowledge was sufficient were also positively associated with giving advice. Notably, unlike the screening behavior model, professional experience emerged as a significant contributor in this case, indicating that more experienced respondents were more likely to engage in counseling.

Although medical students appeared somewhat more likely than physicians to offer preventive advice, this difference did not reach statistical significance. The findings are presented in full in Table 9.

Table 9. Results of the binomial logistic regression analysis for offering preventive advice on a regular basis. Asterisk (*) indicates the reference category or level. D: dentist, DS: dental student, MD: physician, MS: medical student.

Predictor	Estimate	SE	Z	p	OR
Experience					
z-score	0.292	0.111	2.64	0.008	1.3394
Group					
DS-MD*	0.763	0.285	2.68	0.007	2.1444
D-MD	0.965	0.276	3.49	< .001	2.6255
MS-MD	0.579	0.327	1.77	0.077	1.7849
Diagnostic self-confidence					
Confident – Very uncertain*	2.435	0.465	5.24	< .001	11.4139
Uncertain – Very uncertain	1.111	0.446	2.49	0.013	3.0387
Very confident – Very uncertain	2.918	0.627	4.65	< .001	18.5103
Self-perceived sufficiency of knowledge					
Yes-No*	0.662	0.195	3.40	< .001	1.9392

*indicates the reference category

Figure 4 shows the probability of giving regular preventive advice as a function of group affiliation and diagnostic confidence.

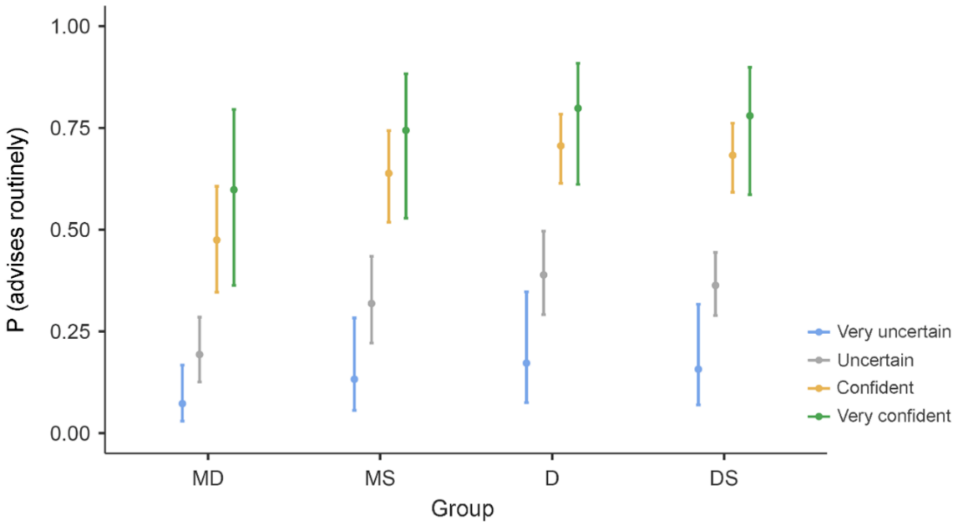

Figure 4. The probability of regular regular cancer prevention advisory activity as determined by group affiliation and diagnostic self-confidence. D: dentist, DS: dental student, MD: physician, MS: medical student.

IV.2.4. Effects on diagnostic self-confidence

The results showed that self-perceived sufficiency of knowledge was the most significant and consistent predictor of confidence across all levels. Respondents who perceived their knowledge as sufficient were 4.93 times more likely to report being "Uncertain" rather than "very uncertain" ($\beta = 1.60$, $p=0.03$). This grew substantially for higher confidence levels: those with sufficient self-perceived knowledge were 35.28 times more likely to identify as "confident" ($\beta = 3.56$, $p<0.001$) and 74.87 times more likely to report being "very confident" ($\beta = 4.32$, $p<0.001$).

Objective knowledge also had a significant, though more moderate, impact on confidence. For each one-unit increase in objective knowledge, respondents were 1.19 times more likely to report being "uncertain" ($\beta = 0.17$, $p=0.006$), 1.26 times more likely to identify as "confident" ($\beta = 0.23$, $p<0.001$), and 1.23 times more likely to describe themselves as "very confident" ($\beta = 0.21$, $p=0.037$) compared to "very uncertain." While the effect of objective knowledge was consistent and statistically significant, it was notably smaller than that of self-perceived sufficiency.

Group affiliation further differentiated confidence levels. Dentists were more likely than physicians to report higher levels of confidence, being 3.43 times more likely to report being "uncertain" rather than "very uncertain" ($\beta = 1.23$, $p=0.054$), 9.79 times more likely to identify as "confident" ($\beta = 2.28$, $p<0.001$), and 6.15 times more likely to describe themselves as "very confident" ($\beta = 1.82$, $p=0.018$). In contrast, medical students and dental students showed smaller or nonsignificant differences compared to physicians. Due to space constraints, the tabular form of the analysis is not shown.

IV.2.5. Self-perceived need for cancer education and education preferences

A majority of participants reported that their knowledge of oral cancer was insufficient. This perception was most prevalent among medical students (79.5%) and dental students (77.4%), followed by physicians (75.0%) and dentists (54.9%) (Table 6). Despite this, the proportion of respondents expressing interest in further training was relatively low across all groups: 12.1% among medical students, 18.3% among dentists, 18.8% among physicians, and 38.5% among dental students indicated a desire for additional education.

When asked about preferred learning formats, most respondents favored online courses and written information packages. In contrast, fewer participants preferred in-person options such as seminars or workshops (Table 7).

Table 10. Preferred forms of further education regarding oral cancer across the groups. D: dentist, DS: dental student, MD: physician, MS: medical student.

Format	D	DS	MD	MS
an online course	67.68	71.34	67.93	63.78
information pack	34.15	51.83	40.22	47.24
lunchtime meeting	23.17	28.05	27.17	33.07
evening seminar	5.49	6.71	11.96	14.17
a whole-day seminar	10.37	10.06	9.24	4.72

IV.3. Results of the Case Study

IV.3.1. Pathologic Features of the Renal Tumor

Gross examination revealed a predominantly bright-yellow, spherical neoplasm measuring 95 × 60 × 45 mm, with areas of focal hemorrhage and cystic degeneration. The tumor extended into the renal sinus, pelvis, and renal vein. Histologically, it was composed of polygonal cells with clear cytoplasm and exhibited Fuhrman nuclear grades I to II. Architectural patterns included solid, acinar, and microcystic arrangements (Figure 5 left). Immunohistochemical staining demonstrated diffuse positivity for pancytokeratin and epithelial membrane antigen (EMA), with focal positivity for vimentin, CD10 (Figure 5 right), and RCC antigen. The tumor stroma was scant but rich in capillaries. Surgical margins were clear, and no metastatic deposits were found in the adrenal gland or in the three examined lymph nodes. The final diagnosis was low-grade clear cell renal cell carcinoma, staged as pT3aN0.

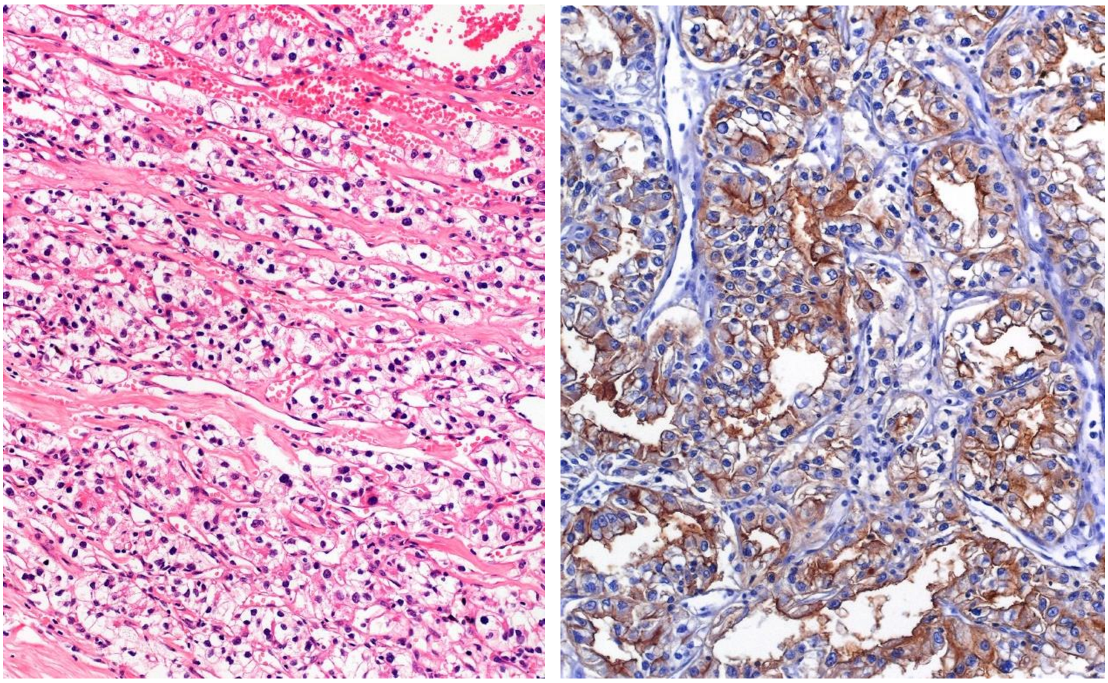

Figure 5. Renal cell carcinoma. Left: Solid and microcystic nests of clear cells with a fine capillary vascular background and Fuhrman grade II nuclear pleiomorphism. Hematoxylin-eosin, ×20. Right: CD10 positivity of tumor cells. The architecture was tubular in this visual field, ×20.

IV.3.2. Pathologic Features of the Lingual Tumor

Macroscopically, the excised specimen measured 10 × 15 × 10 mm and retained an intact mucosal surface. Microscopically, the lesion was situated beneath a layer of nondysplastic stratified squamous epithelium and appeared as a relatively well-demarcated, nonencapsulated, infiltrative tumor (Figure 6 left). The tumor cells were characterized by clear cytoplasm, well-defined cell borders, small nuclei, and inconspicuous nucleoli. These cells were arranged in small solid nests (Figure 6 right). The amount of stroma was variable, with thin bands of hyalinized collagen seen in several fields. No evidence of lymphovascular invasion was found.

Special histochemical staining demonstrated glycogen accumulation in approximately 20% of tumor cells. The lesion was negative for mucin. Immunohistochemistry showed diffuse expression of pancytokeratin and EMA. The tumor cells were negative for CD10, RCC antigen, vimentin, and all myoepithelial markers assessed.

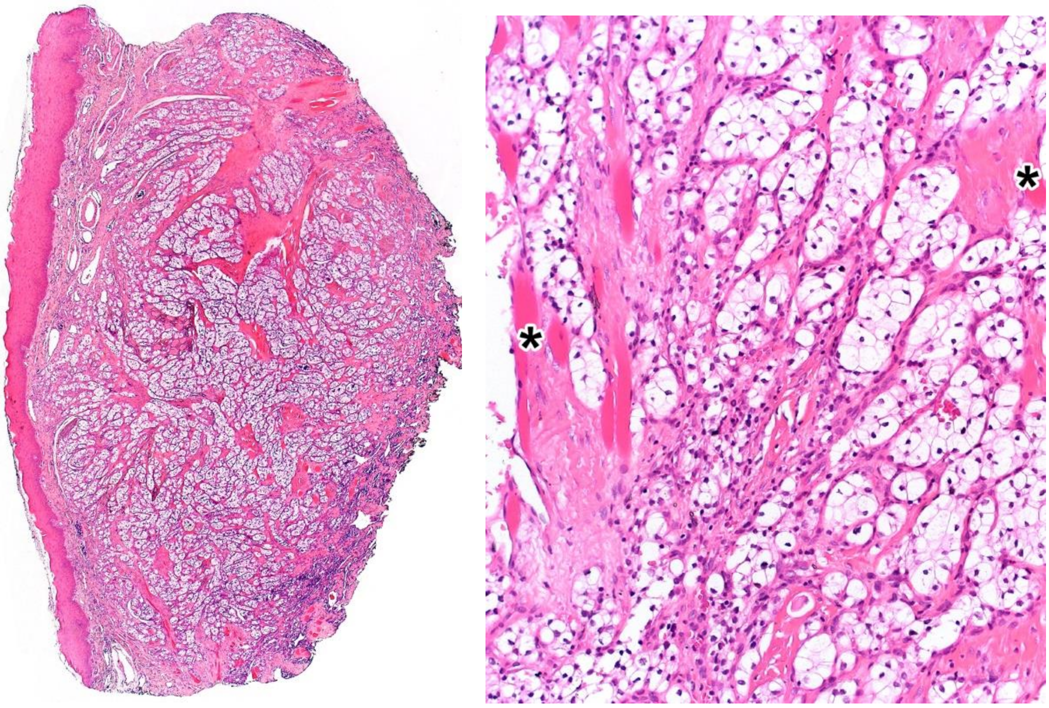

Figure 6. Left: Hyalinizing clear cell carcinoma of the tongue. Low power showing fascicles of clear cells and stromal bands of hyalinized collagen beneath the mucosal squamous epithelial layer. The tumor is uncapsulated and infiltrative. Hematoxylin-eosin, ×5. Right: a monomorphous population of tumor cells with clear cytoplasm and very mild nuclear atypia, arrangement into solid nests, and invasion of the lingual striated muscle (*). Hematoxylin-eosin, ×20.

IV.3.3. Molecular Pathology Results

Loss of heterozygosity (LOH) analysis revealed allelic imbalance at the D3S2450 microsatellite locus in the renal tumor. This locus is situated upstream of the VHL gene, suggesting a potential genomic alteration in this region specific to the kidney lesion. In contrast, no allelic imbalance was observed at this site in the lingual tumor, indicating a difference in the genetic profiles of the two lesions. For all loci located downstream of the VHL gene that were informative, allelic retention was observed in both tumors, supporting the absence of deletion events in that region (Figure 7).

Three additional microsatellite markers—D3S1289, D3S1582, and D3S1613—were included in the analysis but proved uninformative due to the presence of identical allele lengths, which made LOH determination impossible at those sites. Complementary sequencing of the VHL gene did not identify any pathogenic variants in either the renal or lingual tumors. These findings suggest that, despite some genomic alteration upstream of VHL in the renal tumor, there was no clear evidence of biallelic inactivation or mutation of the VHL gene in either lesion.

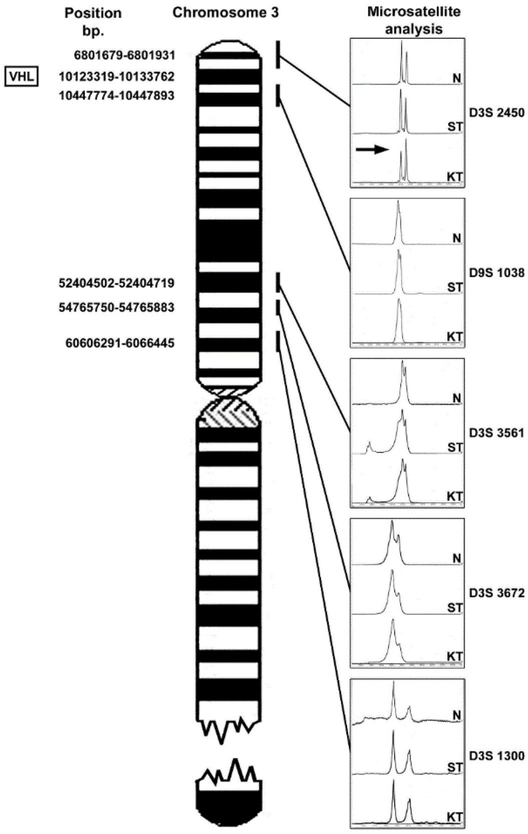

Figure 7. Microsatellite markers and their approximate location on chromosome 3p. The D3S2450 marker shows an allelic imbalance in the renal tumor (arrow). N, Normal kidney; ST, salivary tumor; KT, kidney tumor.

V. DISCUSSION

V.1. Epidemiology of Oral Diseases at the Szeged University Clinic, 1960-2014

Until 1968, the Dental and Oral Surgery Clinic of the University of Szeged primarily treated patients with benign tumors, and only a few precancerous and malignant tumors were managed, due to the lack of sufficient personnel and infrastructure.

In Hungarian studies conducted on risk groups (27,28,49,50), the average incidence of oral precancerous and cancerous lesions was higher (7.96%) than in previously reported data from the general population (29,30,51-55) and in the present study, where the rate was only 3.1%. In a selective screening among homeless individuals, Szabó et al. (50) reported a high rate of 19.33%, confirming the priority of targeted screenings in high-risk groups.

Our Hungarian data from risk group screenings are approximately in line with international studies of a similar nature (56,57) as well as general population results (3,5,58,59), since among risk groups the prevalence of oral precancerous and cancerous lesions usually ranges from 6% to 25%, while in non-risk populations it mostly varies between 1% and 6%. Our clinical cancer registry database may serve as a foundation for future analytical studies that can help identify screening target groups and contribute to the decision-making regarding the implementation of population-level screening programs.

We must note that we do not consider the 1.70% stomato-oncological morbidity rate found in our clinic's 1960–1974 patient population (29) to be representative or suitable for comparative purposes, as those data reflect a period when these diseases did not yet receive the focused attention they later did. Nonetheless, even those figures underline the importance of stomato-oncology and highlight the essential role of dentists and physicians in cancer prevention and in validating the importance of screening.

Our current 3.1% incidence rate, derived from over fifty years of data on oral precancerous and cancerous lesions, is not significantly different from the 4.2% frequency reported by Lim et al. (2003), which was based on a prospective opportunistic screening. However, the main difference is that their data came from a prospective setting, while ours are based on a retrospective analysis. Also, our own study included 5,145 carcinoma patients (1.55%), whereas their prospective screening detected only 2 carcinoma cases (0.08%).

Because the oral and maxillofacial regions are anatomically accessible, early-stage oncological diseases here can be detected easily, using non-invasive methods without the need for complex or expensive equipment. Early detection significantly improves treatment outcomes and survival rates. This circumstance validates and clearly confirms the importance and justification for secondary prevention—in other words, screening. Our results from prospective screenings in general dental practice (10) and our own retrospective opportunistic screenings confirm that this method offers a realistic opportunity in stomato-oncology for conducting population-level screenings and for contributing to the fight against oral cancers.

Both the international prospective (10) and our present retrospective screenings—performed in general dental care settings and involving patients detected opportunistically—can be considered representative, as they reflect the types and frequency of oral oncological conditions that occur in the general population. Thus, opportunistic screening could be a realistic alternative to mass population screening, the implementation of which in Hungary should be seriously considered. This, despite the existence of both international (9,60,61) and domestic (62) publications that do not yet deem oral cancer mass screening to be warranted.

In our over 50-year screening and epidemiological study, we observed one or more types of oral mucosal lesions in 35,247 screened and examined patients, corresponding to a 12.06% prevalence. This figure is comparable to the 10.3% reported by Bouquot (35) and the 14.1% by Lim et al. (10). However, the literature also contains prevalence values ranging from 3% up to 81% (63), indicating the difficulty of comparison, which is largely due to differences in screening methods, population sampling, and classification systems.

One publication (3) argues that opportunistic mass screening is the only viable pathway for the early detection of oral precancerous and cancerous lesions and for achieving high survival rates. Given that our study includes epidemiological data on patients screened and referred to our clinic by practicing dentists and physicians in the three counties mentioned earlier, we believe that our large retrospective study qualifies both as organized and opportunistic mass screening and as a representative study, reinforcing our own view of the advantages and primary applicability of this screening method.

These findings underline the value of long-term, clinic-based screening programs and suggest that opportunistic approaches may play a meaningful role in population-level cancer prevention. However, the success of any screening initiative ultimately depends on the attitudes, knowledge, and daily practices of healthcare professionals. For this reason, we also examined how medical and dental practitioners in Hungary approach oral cancer screening and preventive counseling in their routine care. The following section continues the discussion by presenting and interpreting the results of this nationwide study.

V.2. Oral Cancer Screening and Advisory Behavior Among Hungarian Professionals

In this nationwide study, we explored the factors associated with oral cancer screening and preventive practices among dentists, physicians, and clinical-grade students in Hungary. The central finding is that diagnostic self-confidence emerged as the most influential predictor of both screening and advisory behavior, outweighing the effect of objective knowledge. Dentists and dental students exhibited greater confidence and higher screening rates than their medical counterparts, likely reflecting differing emphases in their educational training.

While objective knowledge had a measurable impact on confidence, the influence of perceived knowledge sufficiency was notably stronger. This indicates that increasing healthcare professionals' confidence may be more effective in promoting screening behavior than focusing solely on enhancing factual knowledge. Although this is consistent with earlier findings, our results highlight important distinctions related to methodology and participant composition.

Diagnostic self-confidence and perceived sufficiency of knowledge were strong predictors of screening engagement. Even moderate gains in confidence were linked to significantly higher odds of performing routine screenings and offering preventive advice; for instance, participants who identified as "very confident" were 6.4 times more likely to engage in regular screening than those who reported being "very uncertain." This aligns with the findings of Mariño et al. (16), who also observed a relationship between self-reported confidence and screening rates among Australian oral health professionals, though their reported odds ratios and screening frequencies were considerably lower. The exceptionally high screening rate observed among Hungarian dentists (97.6%) may be influenced by national differences in clinical training or professional expectations.

Our observation that perceived knowledge sufficiency had a more substantial effect on confidence than objective knowledge is consistent with findings from Hassona et al. (15) , who identified only weak correlations between factual knowledge and diagnostic skills among Jordanian primary care providers. The use of multinomial logistic regression in our study allowed for a clearer distinction between the effects of knowledge and self-perception, suggesting that subjective confidence plays a more decisive role in shaping behavior than factual knowledge alone.

Tax et al. (17) also highlighted a disconnect between knowledge and practice among dental hygienists, which contrasts with the high screening rates we observed among dentists and dental students. In our sample, 97.6% of dentists and 85.4% of dental students reported routinely performing screenings, whereas only 40.8% of physicians and 44.1% of medical students did so. The pattern was similar for preventive advice, with dentists again reporting the highest rate (64%).

Diagnostic confidence mirrored these trends: 67.7% of dentists rated themselves as “confident” or “very confident,” compared to only 21.0–31.5% in the other groups.

These outcomes are in line with the findings of Langton et al. (64), who reported that dentists were more likely than physicians to detect oral cancers early, often during asymptomatic visits. Although that study did not measure confidence directly, the qualitative data support the conclusion that perceived competence is a key factor in promoting both screening and advisory behaviors.

Professional experience did not significantly predict engagement in screening, but it did show a positive association with the likelihood of giving preventive advice. This distinction is similar to observations by Mariño et al. (16), who found that screening behavior was more closely linked to confidence and communication skills than to years in practice. It may indicate that while screening can be standardized and procedural, effective advisory communication relies more on interpersonal competencies, which tend to improve over time. However, our study design did not allow for direct testing of this hypothesis.

In addition to the central role of confidence, other patterns emerged. Although a majority of participants—especially students—considered their oral cancer knowledge insufficient, only a minority expressed interest in further education. Leuci et al. (19) observed a similar tendency among Italian dental hygienists, attributing low demand for continuing education to time constraints, reliance on supervising dentists, and a discrepancy between perceived and actual knowledge. While our study did not directly assess these factors, they likely contribute to the low levels of interest seen in our sample. For example, Trifunovic-Koenig et al. (18) reported that heavy workloads were a major barrier to participation in infection control training, suggesting that time limitations may similarly discourage involvement in oral cancer education.

Preferences for online learning formats and written information materials likely reflect these time constraints and the need for flexible access, a trend that has accelerated during the COVID-19 pandemic. However, while online education offers greater convenience, it may not effectively build the practical skills and diagnostic confidence necessary for performing screening and advisory tasks in real-world settings.

This concern is supported by previous research. Tax et al. (17) emphasized that knowledge acquisition on its own is insufficient to produce behavioral change. Continuing education programs that include interactive components such as hands-on sessions, gamified elements, or confidence-based learning approaches have demonstrated greater effectiveness in enhancing diagnostic performance and increasing screening participation (20,65). Training methods that focus on communication—such as role-playing, standardized patient encounters, and workshops—can also improve practical skills, although their impact may vary depending on how they are delivered and to whom they are targeted (66-70).

This study has several limitations. First, the response rate among practicing professionals was very low (0.7%), especially among physicians, which limits the generalizability of the findings and introduces the possibility of non-response bias. Although the total sample size was adequate for statistical analysis—and exceeded that of comparable studies (15-17) —future research should aim to improve participation rates, possibly through the use of incentives, institutional collaboration, or mixed-methods approaches.

Second, the use of self-reported data may have introduced biases such as social desirability and recall inaccuracies. Incorporating objective measures, such as simulated clinical cases or direct observation, would enhance data validity in future investigations.

Third, while many respondents acknowledged a lack of knowledge, only a few expressed interest in additional education. Future qualitative studies could explore underlying motivational and systemic barriers that limit engagement in continuing professional development. Including open-ended questions alongside structured items in future surveys may help capture more nuanced insights into participants' perspectives and behaviors.

Fourth, diagnostic confidence was assessed using self-report measures. Combining these with external evaluations of diagnostic performance would provide a more accurate picture of actual competence.

Finally, since the data were collected in Hungary—a country with high oral cancer incidence and mortality—the applicability of findings to other healthcare settings may be limited. Repeating this research in different countries would help clarify how generalizable these results are.

V.3. Metachronous Clear Cell Carcinoma of the Tongue and Kidney

Between 1970 and 2008, a total of 203,389 patients were treated at our Department of Oral Surgery. Of these, 172 individuals (0.08%) were diagnosed with malignant salivary gland tumors, and only two cases (1%) were identified as hyalinizing clear cell carcinoma (HCCC). One of these cases involved the parotid gland, while the other is the subject of this report.

In 2001, the patient underwent radical nephrectomy for a low-grade renal cell carcinoma (RCC) characterized by invasion into the renal vein. During the subsequent follow-up period, neither local recurrence nor distant metastasis was observed. Seven years later, the patient presented with a slowly enlarging lingual mass, and the histopathologic finding of low-grade clear cell morphology raised the suspicion of a delayed RCC metastasis.

However, a detailed comparative evaluation of the histologic and immunohistochemical features of the renal and lingual tumors revealed clear distinctions. The renal tumor exhibited solid, acinar, and microcystic growth patterns with a prominent capillary network, and Fuhrman grade II nuclear atypia was frequently observed. Immunohistochemically, the RCC cells showed positivity for vimentin, CD10, and RCC antigen—markers typically associated with clear cell RCC.

In contrast, the lingual tumor lacked a microcystic architecture and instead exhibited stromal hyalinization, a less prominent vascular network, and minimal nuclear atypia. The tumor was focally positive for glycogen, negative for mucin, and lacked immunoreactivity for vimentin, CD10, RCC antigen, and myoepithelial markers. These findings were consistent with the diagnosis of HCCC. Other primary clear cell salivary gland neoplasms, such as clear cell mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, and myoepithelial carcinoma, were excluded based on these features.

Regarding VHL gene status, LOH analysis showed an allelic imbalance at the D3S2450 microsatellite locus—upstream of the VHL gene—in the renal tumor but not in the lingual lesion. All informative downstream markers exhibited allelic retention. Although mosaicism or contamination with non-tumorous parenchyma could not be entirely ruled out, sequence analysis revealed a wild-type VHL gene in both tumors. These findings suggest that VHL gene deletion contributed to the pathogenesis of the renal tumor but was not involved in the development of the lingual lesion, further supporting its classification as a primary neoplasm.

Taken together—clinical course, histopathologic features, immunophenotype, and molecular findings—these data indicate that the patient had achieved remission from renal cancer and later developed a primary metachronous HCCC of the tongue. The patient remained free of disease at the 3-year follow-up.

Clear cell tumors of the salivary glands were first described in the German-language literature by Kleinsasser et al. in 1968 (71). In 1977, Batsakis et al. proposed a unified category of “clear cell” neoplasms, excluding acinic cell carcinoma and mucoepidermoid carcinoma, and concluded that these tumors are generally of low-grade malignancy (72). Subsequently, in 1983, Chen (25) distinguished between dimorphic and monomorphic variants of clear cell carcinoma—the former characterized by a bilayered pattern of clear and eosinophilic cells, correlating with epithelial-myoepithelial carcinoma.

In 1994, Milchgrub et al. reported a series of 11 cases, which they classified as hyalinizing clear cell carcinoma (HCCC) (23). The current World Health Organization classification uses the term "clear cell carcinoma, not otherwise specified" to describe HCCC, acknowledging that some cases may lack the characteristic stromal hyalinization (73).

HCCC is a rare neoplasm of the salivary glands, with an estimated incidence of 1% (24,74). Its clinical behavior, presentation, and histologic features in this case are consistent with those previously described. HCCC predominantly affects middle-aged adults and demonstrates a female predilection. While the palate is the most commonly affected site, the tongue represents the second most frequent location. Clinically, the tumor usually manifests as a slowly enlarging, painless submucosal mass, often without mucosal ulceration. Approximately 25% of patients may present with regional lymph node metastases, although hematogenous dissemination, particularly to the lungs, is infrequent (24).

The histogenesis of HCCC remains uncertain. Given the consistent absence of myoepithelial marker expression, it is hypothesized that the tumor originates from the intercalated ducts. Recent studies have identified the EWSR1-ATF1 fusion gene in a cohort of 23 HCCC cases, but not in cases of mucoepidermoid carcinoma or epithelial-myoepithelial carcinoma, suggesting a potential molecular signature for HCCC (26). Unfortunately, analysis for this fusion gene could not be performed in our case due to the complete utilization of the archived lingual tumor tissue for VHL gene testing.

Among malignant epithelial tumors, RCC, breast carcinoma, and lung carcinoma are known—albeit rarely—to metastasize to the head and neck region. Metastasis of RCC to the tongue is exceedingly uncommon. Between 1973 and 2011, only 33 cases of lingual metastases from primary renal tumors were reported in the English-language literature (75-79). In five of these cases, lingual metastasis was the initial manifestation of an undiagnosed RCC. The metastatic pathway to the tongue remains unclear, although most lesions are located at the base of the tongue and the prognosis in such cases is generally poor, with median survival often under six months.

In our case, although the clinical appearance of the lingual lesion did not strongly suggest metastasis, the patient's history of RCC necessitated comprehensive diagnostic workup, including advanced histologic, immunohistochemical, and molecular studies.

VI. CONCLUSIONS

Based on the presented studies, we draw the following conclusions, which we consider as the new scientific findings of the thesis:

From the analysis of long-term institutional data (Sonkodi et al., 2016), it was established that the incidence of premalignant and malignant oral lesions has significantly increased over the past five decades in the Southern Hungarian region. This trend highlights the need for structured secondary prevention strategies and justifies the implementation of opportunistic screening, particularly in high-risk populations.

From the results of the national cross-sectional survey (Novák et al., 2025), it was demonstrated that diagnostic self-confidence is a stronger predictor of oral cancer screening and preventive advisory behavior than objective knowledge. The findings show that while most healthcare professionals and students acknowledge their knowledge deficits, relatively few express interest in further education. Moreover, preferred educational formats (e.g., online courses) may be poorly suited to strengthening the diagnostic competence needed for effective screening. These results support the need for educational interventions that go beyond knowledge transmission and specifically aim to enhance clinical confidence and decision-making capacity.

From the case study on clear cell carcinoma of the tongue (Novák et al., 2012), it was confirmed—through histopathological, immunohistochemical, and molecular genetic methods—that the oral lesion represented a primary tumor, not a metastasis from the previously treated renal carcinoma. To the authors' knowledge, this was the first reported case in the English-language literature of two histologically similar but independent clear cell carcinomas occurring metachronously in the kidney and the tongue. This case illustrates the diagnostic complexity of rare salivary gland neoplasms and underscores the importance of multidisciplinary diagnostic approaches in patients with prior oncological histories.

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REFERENCES

1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*. 2009;45(4-5):309-316.

2. Sankaranarayanan R, Ramadas K, Thomas G, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet*. 2005;365(9475):1927-1933.

3. La Vecchia C, Lucchini F, Negri E, Levi F. Trends in oral cancer mortality in Europe. *Oral Oncol*. 2004;40(4):433-439.

4. Ottó S, Kásler M. Rákmortalitás és -incidencia hazánkban, az európai adatok tükrében. *Magyar Onkológia*. 2002;46:111-117.

5. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol*. 2005;16(3):481-488.

6. Remenár E. [Proposal for screening of oral and oropharyngeal cancer in the population at risk]. *Magyar Onkológia*. 2001;45(2):149-151.

7. Nemes J, Redl P, Boda R, Kiss C, Márton I. Oral Cancer Report from Northeastern Hungary. *Path Onc Res*. 2008;14

8. Speight P, Epstein J, Kujan O, et al. Screening for oral cancer: a perspective from the Global Oral Cancer Forum. *Oral Surg Oral Med Oral Path Oral Radiol*. 2017;123(6)

9. Kujan O, Glenny AM, Oliver RJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev.*2006;2006(3):CD004150-CD004150.

10. Lim K, Moles DR, Downer MC, Speight PM. Opportunistic screening for oral cancer and precancer in general dental practice: results of a demonstration study. *Br Dent J*. 2003;194(9):497-502.

11. Kásler M, Ottó S. [Secondary prevention and early detection (screening) of malignant tumors]. *Orv Hetil*. 1993;134(9):473-480.

12. Kenessey I, Szilágyi I, Dobozi M, Nagy P, Polgár C. [The role of National Cancer Registry in the assessment of Hungarian cancer epidemiology]. *Orv Hetil*. Jun 16 2024;165(24-25):925-932.

13. Downer MC, Moles DR, Palmer S, Speight PM. A systematic review of measures of effectiveness in screening for oral cancer and precancer. *Oral Oncol*. 2006;42(6):551-560.

14. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Path Med*. 2007;36(10):575-580.

15. Hassona Y, Scully C, Shahin A, Maayta W, Sawair F. Factors Influencing Early Detection of Oral Cancer by Primary Health-Care Professionals. *J Cancer Ed*. Jun 2016;31(2):285-91.

16. Marino R, Haresaku S, McGrath R, et al. Oral cancer screening practices of oral health professionals in Australia. *BMC Oral Health*. Dec 15 2017;17(1):151.

17. Tax C, Haslam S, Brillant M, Doucette H, Cameron J, Wade S. Oral cancer screening: knowledge is not enough. *Int J Dent Hyg*. 2017;15

18. Trifunovic-Koenig M, Bushuven S, Gerber B, et al. Correlation between Overconfidence and Learning Motivation in Postgraduate Infection Prevention and Control Training. *Int J Environ Res Public Health*. May 9 2022;19(9)

19. Leuci S, Coppola N, Viglione AP, et al. Knowledge, attitude and practice in oral cancer: a national survey on 150 dental hygienists. *Oral Diseases*. 2022.

20. Scavone J, Robinson K, Scully E, Cooper S, Esgro R, Klein E. Coupling gamified continuing education with confidence-based assessment to address knowledge gaps and assess attitudes towards liquid biopsy for cancer screening among primary care providers. *J Clin Oncol*. 2022.

21. Walsh T, Warnakulasuriya S, Lingen M, et al. Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database Syst Rev*. 2021;12

22. Chakraborty D, Natarajan C, Mukherjee A. Advances in oral cancer detection. *Adv Clin Chem*. 2019;91

23. Milchgrub S, Gnepp DR, Vuitch F, Delgado R, Albores-Saavedra J. Hyalinizing clear cell carcinoma of salivary gland. *Am J Surg Pathol*. 1994;18:74-82.

24. Solar AA, Schmidt BL, Jordan RC. Hyalinizing clear cell carcinoma: case series and comprehensive review of the literature. *Cancer*. 2009;115:75-83.

25. Chen KT. Clear cell carcinoma of the salivary gland. *Hum Pathol*. 1983;14:91-93.

26. Antonescu CR, Katabi N, Zhang L, et al. EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. *Genes Chromosomes Cancer*. 2011;50:559-570.

27. Sonkodi I, Tóth K. A szegedi textilipari munkások stomato-onkológiai vizsgálata. *Fogorv Szle*. 1972;65:560-569.

28. Sonkodi I, Tóth K. Újabb adatok szegedi ipari munkások stomato-onkológiai vizsgálatáról. *Népegészségügy*. 1975;56:282-284.

29. Sonkodi I, Gorzó I, Borbély L, Tátrai J, Boda K. A Szegedi Fogászati és Szájsebészeti Klinika sztomato-onkológiai beteganyagának számítógépes feldolgozása 1960-1974 között. *Árkövy Kongresszus*. 1977.

30. Sonkodi I, Boda K. [Precancerous lesions of the oral cavity with special reference to white lesions]. *Fogorv Szle*. 1977;70(9):257-262.

31. Barnes L, Reichart PA, Sidransky D. World Health Organisation Classification of Tumors. Pathology and Genetics. Head and neck Tumors. *World Health Organization, IARC*. 2005.

32. World Health O. Application of international classification of diseases to dentistry and stomatology. *World Health Organization*. 1978.

33. World Health O. Cancer prevention and control. *World Health Assembly*. 2005.

34. World Health O. Oral health: action plan for promotion and integrated disease prevention. *World Health Organization*. 2007.

35. Bouquot JE. Common oral lesions found during a mass screening examination. *J Am Dent Ass*. 1986;112(1):50-57.

36. Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. *Comm Dent Oral Epidemiol*. 2000;28(5):390-398.

37. Carpenter WM, Jacobsen PL, Eversole LR. Two approaches to the diagnosis of lesions of the oral mucosa. *J Calif Dent Ass*. 1999;27(8):619-624.

38. Razavi M, Zolfaghari B, Foroohandeh M, Doost M, Tahani B. Dentists' Knowledge, Attitude, and Practice Regarding Oral Cancer in Iran. *J Cancer Ed*. 03/19 2013;28

39. Giuseppe C, Gaeta G, Moscariello A, Angelillo I. Oral cancer and dentists: Knowledge, attitudes, and practices in Italy. *Oral Oncol*. 05/01 2008;44:393-9.

40. Ahmed NHM, Naidoo S. Oral Cancer Knowledge, Attitudes, and Practices among Dentists in Khartoum State, Sudan. *J Cancer Ed*. 2019/04/01 2019;34(2):291-296.

41. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)*. Dec 15 2000;25(24):3186-91.

42. Silverman S, Jr., Eversole LR, Truelove EL. *Essentials of Oral Medicine*. BC Decker Inc.; 2001.

43. Scully C. *Oral and Maxillofacial Medicine: The Basis of Diagnosis and Treatment*. Churchill Livingstone; 2013.

44. Odell EW. *Cawson's Essentials of Oral Pathology and Oral Medicine*. Churchill Livingstone; 2017.

45. Sonkodi I. *Orális és maxillofaciális medicina*. Semmelweis Kiadó; 2017.

46. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. Dec 1996;49(12):1373-9.

47. Davis JL, Buchanan KL, Katz RV, Green BL. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. *Am J Mens Health*. May 2012;6(3):211-7.

48. Konda M, Verma R. Chapter 5 - Cancer screening and prevention: Sex and gender evidence in lung, breast, and colorectal cancer. In: Jenkins MR, Newman CB, eds. *How Sex and Gender Impact Clinical Practice*. Academic Press; 2021:75-99.

49. Dombi C, Vörös-Balog T, Czeglédy A, Hermann P, Vincze N, Bánóczy J. Risk group assessment of oral precancer attached to X-ray lung-screening examinations. *Comm Dent Oral Epid*. 2001;29(1):9-13.

50. Szabó G, Klenk G, Veér A. [Correlation between the combination of alcohol consumption and smoking in oral cancer (screening of the population at risk)]. *Orv Hetil*. 1997;138(52):3297-3299.

51. Bakó A, Kósa Z. Szűrővizsgálati modellprogram a szájüregi daganatok korai felismerésére Szabolcs-Szatmár-Bereg megyében. *Magyar Fogorvos*. 2001;2001/4:197-201.

52. Bánóczy J, Radnai T, Reményi I. [Our methodologic experience in the stomatologic-oncologic mass screening of the population of Dunakeszi and Felsogod]. *Fogorv Szle*. 1969;62(4):118-122.

53. Bruszt P. [Stomato-oncological screening tests in 7 villages of the Baja and Bacsalmas district]. *Magyar Onkológia*. 1962;6:28-33.

54. Dombi CS, Vörös-Balog T, Vincze N, Bánóczy J. A Budapest III. kerületében végzett stomato-onkológiai szűrővizsgálat tapasztalatai. *Lege Artis Medicinae*. 1996;6:728-733.

55. Kardos L, Pácz M, Reményi I, Nemes I. [Stomato-oncological screening test of volunteers]. *Magyar Onkológia*. 2000;44(2):145-147.

56. Mehta FS, Gupta PC, Daftary DK, Pindborg JJ, Choksi SK. An epidemiologic study of oral cancer and precancerous conditions among 101,761 villagers in Maharashtra, India. *Int J Cancer*. 1972;10(1):134-141.

57. Pearson N, Croucher R, Marcenes W, O'Farrell M. Prevalence of oral lesions among a sample of Bangladeshi medical users aged 40 years and over living in Tower Hamlets, UK. *Int Dent J*. 2001;51(1):30-34.

58. Silverman S, Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. *J Amer Dent Ass*. 2001;132:7S-11S.

59. Speight PM, Zakrzewska J, Downer MC. Screening for oral cancer and precancer. *Eur J Cancer Part B: Oral Oncology*. 1992;28B(1):45-48.

60. Speight PM, Zakrzewska J. Screening for oral cancer and precancer. A report of the UK working group on screening for oral cancer and precancer. *Commun Dent Health*. 1993;10:1-89.

61. Warnakulasuriya KA, Johnson NW. Strengths and weaknesses of screening programmes for oral malignancies and potentially malignant lesions. *Eur J Cancer Prev*. 1996;5(2):93-98.

62. Döbrössy L. A szájüregi daganatok epidemiológiája: a probléma jelentősége. *Magyar Onkológia*. 2001;45:99-105.

63. Campisi G, Margiotta V. Oral mucosal lesions and risk habits among men in an Italian study population. *J Oral Path Med*. 2001;30(1):22-28.

64. Langton S, Cousin GCS, Plüddemann A, Bankhead CR. Comparison of primary care doctors and dentists in the referral of oral cancer: a systematic review. *Br J Oral Maxillofac Surg*. Oct 2020;58(8):898-917.

65. Rankin K, Jones DL, McDaniel R. Oral cancer education in dental schools: survey of Texas dental students. *J Cancer Ed*. 1996;11(2):80-83.

66. Price-Haywood E, Harden-Barrios J, Cooper L. Comparative Effectiveness of Audit-Feedback Versus Additional Physician Communication Training to Improve Cancer Screening for Patients with Limited Health Literacy. *J Gener Int Med*. 2014;29:1113-1121.

67. Price-Haywood E, Roth K, Shelby K, Cooper L. Cancer Risk Communication with Low Health Literacy Patients: A Continuing Medical Education Program. *J Gener Int Med*. 2010;25:126-129.

68. Carney P, Dietrich A, Freeman D, Mott L. A standardized-patient assessment of a continuing medical education program to improve physicians' cancer-control clinical skills. *Acad Med*. 1995;70:52-58.

69. Dietrich A, Barrett J, Levy D, Carney-Gersten P. Impact of an educational program on physician cancer control knowledge and activities. *Am J Prev Med*. 1990;6(6):346-352.

70. McPhee SJ, Bird JA, Jenkins CNH, Fordham D. Promoting Cancer Screening: A Randomized, Controlled Trial of Three Interventions. *Arch Intern Med*. 1989;149(8):1866-1872.

71. Kleinsasser O, Klein HJ, Hübner G. Salivary duct carcinoma. A group of salivary gland tumors analogous to mammary duct carcinoma. *Arch Klin Exp Ohren Nasen Kehlkopfheilkd*. 1968;192:100-105.

72. Batsakis JG, Regezi JA. Selected controversial lesions of salivary tissues. *Otolaryngol Clin North Am*. 1977;10:309-328.

73. Ellis G. Clear cell carcinoma, not otherwise specified. *WHO Classification of Tumours Pathology and Genetics of Head and Neck Tumours*. 2005:227-228.

74. Kauzman A, Tabet JC, Stiharu TI. Hyalinizing clear cell carcinoma: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2011;112:e26-e34.

75. Marioni G, Gaio E, Poletti A, Derosas F, Staffieri A. Uncommon metastatic site of renal adenocarcinoma: the oral tongue. *Acta Otolaryngol*. 2004;124:197-201.

76. Azam F, Abubakerr M, Gollins S. Tongue metastasis as an initial presentation of renal cell carcinoma: a case report and literature review. *J Med Case Reports*. 2008;2:249.

77. Morvan JB, Veyrières JB, Mimouni O, Cathelinaud O, Allali L, Verdalle P. Clear-cell renal carcinoma metastasis to the base of the tongue and sphenoid sinus: two very rare atypical ENT locations. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2011;128:91-94.

78. Basely M, Bonnel S, Maszelin P, Verdalle P, Bussy E, de Jaureguiberry JP. A rare presentation of metastatic renal clear cell carcinoma to the tongue seen on FDG PET. *Clin Nucl Med*. 2009;34:566-569.

79. Yoshitomi I, Kawasaki G, Mizuno A, et al. Lingual metastasis as an initial presentation of renal cell carcinoma. *Med Oncol*. 2011;28:1389-1394.

APPENDICES

NOTE: This version of the thesis does not include the appendices, in accordance with the regulations of the Doctoral School of Clinical Medicine at the University of Szeged.