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Review Article

Possibilities for the Early Diagnosis of Head and Neck Squamous Cell Carcinoma

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Abstract

Head and neck cancers (including cancers of the oral cavity, oropharynx, hypopharynx, and larynx) are the sixth most common type of cancer worldwide. Almost all of these cancers are squamous cell carcinomas that develop from the mucosal lining. Due to the lack of specificity of the symptoms and inadequate screening methods, less than half of these tumors are currently discovered, albeit at an early stage. These cancers, therefore, constitute a real public health problem. Smoking, alcohol consumption, certain HPV infections, and chronic betel nut consumption are the main risk factors for developing squamous cell carcinoma of the upper aerodigestive tract. Early diagnosis depends on performing a complete and systematic physical examination of the oral cavity, pharynx, and larynx with a nasofibroscope in populations at risk. However, there are no strict criteria, in terms of alcohol and tobacco consumption, to trigger a physical examination by an ENT specialist, and there are no indications concerning the frequency with which such "screening" should be performed in at-risk populations. Even if such "screening strategies" are used in the absence of an alternative, different approaches are used in practice, depending on the medical system and country, and their efficacy and ideal modes of implementation remain unknown.

Introduction

Head and neck squamous cell carcinoma (HNSCC), including cancers of the oral cavity, oropharynx, hypopharynx, and larynx, is the sixth most frequent type of cancer worldwide. The two principal risk factors for developing these cancers are chronic alcohol intoxication and tobacco consumption. In addition to alcohol and tobacco consumption, chronic betel nut consumption (a risk factor for oral cancer) in Central and South Asia explains that these cancers are the 3rd most frequent cancers in these countries, constituting a real public health problem.[1]

Despite the therapeutic progress of the last 10 to 15 years, too many cases of HNSCC are still diagnosed at an advanced stage and are associated with a poorer prognosis and quality of life. Diagnosing HNSCC is, therefore, a real public health issue and of considerable importance for the patients themselves. In early cancer detection, it is essential to distinguish between "screening" (testing for the presence of the disease in asymptomatic individuals) and "case detection" (application of a procedure to patients with an identified lesion). In 1968, Wilson and Jungner outlined the key principles of screening in agreement with the WHO:[2] screening is performed for public health problems; it provides access to diagnosis and treatment at an early stage. Its feasibility, the "invasiveness" of the screening tools, and the cost must be acceptable. Its fundamental objective is to improve overall survival through early detection, thereby increasing the likelihood of a curative intervention. Its disadvantages are its cost, the risk of false negatives, the inability to prevent cancer, and the risk of developing cancer between screening sessions.[3] Because of their high morbidity and mortality in the context of an often-late diagnosis, certain HNSCCs may be suitable for screening, as defined above. The relevance of such screening is likely to increase over time, as the incidence and mortality of these cancers may double by 2050 due, in particular, to the aging of the population and increases in the use of tobacco and alcohol, especially among women.[4]

This literature review was designed to provide an update on current practices for the early diagnosis of HNSCC.

Method

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) system (https://en.wikipedia.org/wiki/Preferred_Reporting_Items_for_Systematic_Reviews_and_Meta-Analyses).

Keywords: Head and Neck squamous cell carcinoma; Premalignant lesion; Tobacco; Alcohol; HPV; Screening.

Abbreviations: DNA, Deoxyribose Nucleic Acid; ENT, Ear Nose Throat; HNSCC, Head and Neck squamous cell carcinoma; HPV, Human Papilloma Virus; OC(s), Oral cancer(s); OPC(s), Oropharyngeal cancer(s).

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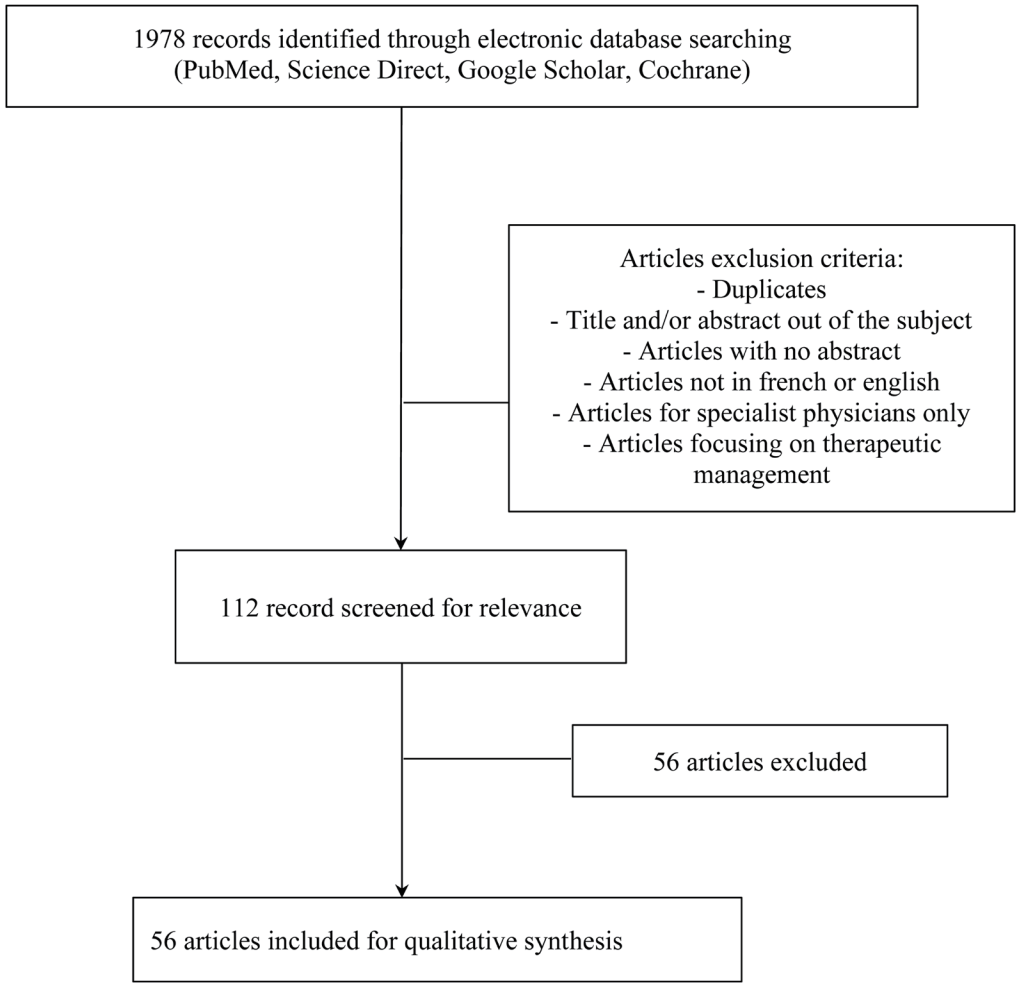

Fig. 1. Flow diagram of the study.

The flow diagram of the study is reported in Figure 1. Apart from the article by Wilson and Jungner,[2] this review was based on articles listed in international databases, including PubMed, Science Direct, Google Scholar, and the Cochrane Register, published between 2006 and 2022. The keywords used to search for these articles were: "prevention," "screening," "early diagnosis," "head and neck cancer," and "general practitioner." Articles focusing on specialized management of HNSCC (diagnosis, therapy, prognosis, outcomes, readaptation, quality of life, etc.) were excluded, as this study aimed to propose simplified methods and "popularize" screening, particularly among non-specialist physicians.

Oral cancers (OCs)

In 2018, Conway *et al*.[5] proposed a compromise for differentiating squamous cell carcinomas of the oral cavity from those of the oropharynx, which was accepted in the code of the International Classification of Diseases for Oncology. Oral cancers are defined as cancers of the inner part of the lips, the dorsal surface of the tongue, the gums, the hard palate, the soft palate, the oral mucosa, the floor of the mouth, and other unspecified parts of the oral cavity. According to the epidemiological data for 2020, OCs will account for 2% of all new cancers at any site and 1.8% of cancer deaths worldwide[4] The geographic areas most affected by these cancers are India, Sri Lanka, Pakistan, Bangladesh, and Papua New Guinea, with the highest incidence globally. The incidence of oral cancers is also high in Eastern and Western Europe, Australia, and New Zealand. However, the risk factors for developing OC differ between geographic regions. In Asian countries, the leading risk factors are chewing Areca nuts (betel nuts) and pan masala.[6] In the countries of Europe and Oceania, the principal risk factors are tobacco consumption (smoking or chewing tobacco), alcohol, poor dental hygiene,[7] and certain diseases linked to genetic alterations (xeroderma pigmentosum, Fanconi anemia, congenital dyskeratosis, familial oral squamous cell carcinoma).[8,9]

Clinically, patients might have precancerous lesions, which are usually asymptomatic. The lesions observed include leukoplakia, erythroleukoplakia, erythroplakia, verrucous hyperplasia, oral submucosal fibrosis, and lichen planus.[10,11] Many screening and early diagnosis methods have been described in published articles.

Conventional examination of the oral cavity

Conventional examination of the oral cavity consists of a visual physical examination and palpation.[12–14] It is simple, rapid, and non-invasive; it is easily accessible, and many healthcare professionals can perform it. Its implementation as a component of a

population screening program could potentially reduce mortality and result in a change in the stage at which OC is detected in high-risk populations.[13] However, not all mucosal abnormalities are malignant. This examination cannot accurately identify precancerous lesions; some precancerous lesions do not modify the mucosa, and others require a biopsy for pathological confirmation.

Self-examination of the mouth by the patient

There is insufficient evidence to determine the accuracy of diagnostic tests based on self-examination of the mouth in the context of organized screening programs.[15]

Toluidine blue staining

Toluidine blue is basic and preferentially stains acidic tissues rich in nucleic acids. These properties are typical of cancerous tissues, hyperplasia, and inflammatory lesions. A computerized analysis of the staining can help observers to identify oral lesions, thereby promoting early cancer detection by advancing the performance of biopsies and guiding the choice of biopsy site.[12] According to Seoane Lestón,[16] toluidine blue staining[12,15,16] has a sensitivity of between 78 and 100% for detecting OCs, but its specificity is highly variable, ranging from 31 to 100%. This technique also has the drawback that it also stains benign inflammatory lesions but does not stain some cancerous lesions, and test performance depends on the procedure used.[15]

Exfoliative cytology

Exfoliative cytology is based on collecting cell samples from the mucosal surfaces by scraping, brushing, or rinsing to detect any cytological alterations. According to Chamoli,[12] the sensitivity and specificity of traditional exfoliative cytology range between 76.8 and 88.9%.

Salivary biomarkers

Saliva is a liquid enriched in DNA and proteins that can be used as a source of diagnostic biomarkers. Such tests are non-invasive, but they are subject to several limitations, including the timing of sample collection, the lack of standardized protocols for sample collection and processing, and our currently incomplete understanding of salivary biomarkers of disease. In several clinical domains, promising biomarker tests have ultimately proved disappointing. Further studies are required.[12,15]

Blood biomarkers

Serum tumor markers for OCs have proved only moderately sensitive for diagnosis. Serum concentrations of carcinoembryonic antigen (CEA), squamous cell carcinoma-associated antigen (SCCAA), an inhibitor of apoptosis (IAP), and cytokeratin fragments (CYFRA) have a sensitivity of 81% for OC detection. Annexin A1 was recently identified in peripheral blood by real-time PCR and has been proposed as a potential diagnostic biomarker.[16]

Cell-free DNA biomarkers

Circulating tumor DNA is released from tumor cells by pathogenic and physiological mechanisms (apoptosis, necrosis, phagocytosis, and exocytosis). Its concentration may depend on the size and stage of the cancer, hence its potential value for detecting the disease at an early stage and as a potential source of biomarkers for OC detection.[12,15]

Autofluorescence imaging

In autofluorescence imaging, fluorophores absorb light of a specific wavelength and emit at a greater wavelength. Nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) fluorophores are present in normal healthy cells, resulting in a green color for healthy tissues. The metabolic changes occurring in malignant tumors lead to a change in the distribution of fluorophores in tissues, causing the tumor tissue to appear as a black area.[12]

Light-based detection systems

Many light-based detection systems have been developed based on chemiluminescence, tissue fluorescence imaging, and spectroscopy.[14–16] Such systems are based on the assumption that structural and metabolic changes in the mucosa during carcinogenesis give rise to distinctive patterns of absorption and refraction following exposure to different types of light or energy. Few reliable studies were performed on these systems before their release onto the market for clinical use, and several factors have hindered their use. These factors include the lack of demonstration of clear superiority over conventional oral examination and significant interobserver variability, limiting their use to clinicians with experience in oral pathology. More extensive studies are required in the future. These techniques are simple to use and provide results in real time. However, they are expensive, cannot be indexed, and their interpretation is relatively subjective.

Oropharyngeal cancers (OPCs)

According to Conway *et al*.,[5] oropharyngeal cancers affect the base of the tongue, the lingual and palatine tonsils, the anterior surface of the epiglottis, and the lateral and posterior walls of the lateral oropharynx. In 2020, squamous cell carcinoma of the oropharynx will account for 0.5% of all new cancers at all sites and 1% of cancer deaths worldwide.[4] This cancer has an exceptionally high incidence in the United States and Western Europe. In developed countries, the incidence of HPV-positive OPC is increasing, whereas that of HPV-negative OPC decreases.[17,18] The risk factors for OPCs are well known: consumption of alcohol, tobacco, or betel nuts,[6] papillomavirus infection (due to the HPV 16 and 18 oncogenes in particular), mostly in men, and lifetime number of sexual partners.[7,19] Physical examination of this anatomic region is less straightforward for non-specialists. As with OCs, patients generally have precancerous lesions, such as leukoplakia or soft palate erythroplakia. However, papilloma lesions are not precancerous. There are also generally no precancerous lesions in HPV^+ OPCs, whereas HPV^- OPCs begin with dysphagia, odynophagia, and reflex otalgia. HPV^+ OPCs rapidly metastasize to the cervical area, with adenomegaly as the first symptom, while the primary tumor remains asymptomatic for an extended period. The measures for the screening or early diagnosis of OPCs described in published studies are identical to those proposed for OCs, with specific features for HPV^+ OPCs not shown to be significant:[20]

- Tonsillar swabs for detecting tumor HPV DNA have been proposed for cervical cancer screening but are ineffective and invalid.
- Serological tests have also been proposed targeting E2, E6, and E7 antibodies. However, not all HPV^+ cancers lead to seropositivity, and not all seropositive patients have HPV^+ cancers.

Laryngeal cancer

Laryngeal cancer accounts for 3.5% of all malignant tumors around the world. In 2020, 184,615 new cases were diagnosed

worldwide, and 99,840 deaths were recorded.[21] Laryngeal cancers account for 1% of all new cancers at all sites and 1% of cancer deaths worldwide.[4]

The two main risk factors for laryngeal cancer are a high cumulative level of tobacco exposure and a history of excessive alcohol consumption.[22–24] However, no threshold level of alcohol or tobacco consumption likely to promote the development of laryngeal cancer has been proposed. Some cases are due to papillomavirus infection, with HPV 16 in particular, but this etiology is rarer than for oropharyngeal cancer.[25,26]

The early stages of vocal fold cancer ("glottic cancer") are defined as follows, according to the 8th edition of the American Joint Committee on Cancer and the Union for International Cancer Control (AJCC/UICC) TNM classification for head and neck cancer: T1aN0M0, T1bN0M0 (stage I), and T2N0M0 (stage II).[26]

The principal and earliest clinical sign is dysphonia for cancers of the glottic plane, particularly if it persists for more than four weeks. Vocal cord cancers often develop from precancerous lesions (epithelial hyperplasia, squamous metaplasia, acanthosis, keratosis, dyskeratosis, pachydermia, etc.), which are often the underlying cause of dysphonia. The diagnosis is based on a biopsy performed under general anesthesia.[27]

By contrast, cancers of the supraglottic larynx (particularly those of the laryngeal margin) behave like cancers of the hypopharynx in that they are often asymptomatic and discovered at an already advanced stage when the first symptoms appear. Dysphonia in any patient who smokes should therefore lead to laryngoscopy to facilitate the early diagnosis of laryngeal cancer. ENT specialists are the most likely to be involved in screening and early diagnosis for laryngeal cancers, as they have access to indirect laryngoscopy techniques (mostly nasofibroscopy) that are not generally accessible to non-specialists.

Laryngoscopy with magnification by Narrow Band Imaging (NBI)

This imaging method facilitates visual analyses of biopsy specimens by providing a better contrast of superficial vessels than standard white light endoscopy based on the *de novo* vascularization occurring during the cancer process, which may be invisible to the naked eye.[28–33]

High-speed, computerized video laryngeal endoscopy

Dysphonia is caused by alterations to the vibration of the vocal mucosa. Thus, evaluations of the abnormal laryngeal dynamics properties induced by infiltration of the deep submucosal structures of the vocal folds can serve as a predictor of vocal fold cancer.[34,35]

Video stroboscopy

By contrast, the goal of video stroboscopy is to analyze the movement of the vocal cords in slow motion with a stroboscope integrated into the optics.[35,36]

Storz Professional image enhancement system light filters

This system can be used for the video-digital processing of endoscopic recordings based on the spectral separation of the recording with a high-definition camera system.[28,33,34] It improves visualization of the mucosal surface and the vascular architecture, facilitating the detection and classification of tumor neoangiogenesis.

Contact endoscopy with methylene blue application

This technique enables the surgeon to visualize cellular details *in vivo*. The magnifying endoscope is placed in direct contact with the mucosa.[28,31] It delivers images at a magnification of 60 to 150 times the normal size.

Raman spectroscopy, a non-invasive diagnostic method

This approach can be used for molecular analysis.[31,35] It involves using a monochromatic laser to analyze the chemical and morphological structures of tissues.

Other systems have been described but are not used in routine practice (videokymography, optical coherence tomography).[31]

Hypopharyngeal cancers

Cancers of the hypopharynx are rarer, accounting for 0.4% of all new cancers worldwide and 0.4% of all cancer-related deaths.[4] The incidence of hypopharyngeal cancer varies by region, with the highest incidence in South-Central Asia, followed by Central and Eastern Europe, Western Europe, and North America.[37] Prolonged alcohol and tobacco consumption are the main risk factors, but other less frequent risk factors have also been identified: Plummer-Vinson syndrome,[38] gastroesophageal reflux disease (GERD),[39] chewing betel nuts,[40] and ALDH2 polymorphism, which modifies alcohol metabolism.[41] The warning signs for hypopharyngeal cancer are pharyngeal discomfort, odynophagia, and reflex otalgia. These signs are followed by dysphagia and dysphonia due to invasion of the pharyngolaryngeal wall.[42]

Hypopharyngeal tumors are characterized by strong lymph-node involvement from the outset, with 70% of patients presenting lymph-node involvement at the time of diagnosis. The screening and early diagnosis methods of hypopharyngeal cancer largely overlap with those for laryngeal cancers. General practitioners are advised to question their at-risk patients carefully concerning swallowing disorders and to refer patients to a specialist for nasofibroscopy if these problems become chronic (> 3 weeks).

In summary, factors of risk and possibilities of early diagnosis of HNSCC are reported in Table 1.

Discussion

Primary prevention

Primary prevention lies slightly outside the scope of this review but is nevertheless worthy of mention here. The main approaches used for primary prevention are:

- Public health campaigns focusing on preventing the consumption of the agents implicated in these diseases (tobacco, alcohol, betel nuts), the legal age for their consumption, and a ban on advertising.[43–45]
- Investigating the genetic mechanisms involved and proposing appropriate follow-up for the patients identified.[45]

In the context of HPV infection:

- Campaigns to raise awareness about the need for protection during sex, including oral sex in particular, as it has been shown that individuals practicing oral sex for a prolonged period with a person with genital HPV infection are at greater risk of developing HPV^+ HNSCC.
- Vaccination campaigns.[20,21]

Secondary protection

Here we enter the framework of early detection in patients who have the disease without knowing it. Numerous studies have been performed, and actions have been proposed to promote changes in

Table 1. Factors of risk and possibilities of early diagnosis of HNSCC

HNSCC location	Principal risk factors	Self examination	Non-Specialist examination	ENT Specialist-examination	Possible screening methods
Oral Cavity	Tobacco, Alcohol, Betel nut	Yes	Yes	Yes	Precancerous lesions, Toluidine blue, Salivary and Blood tests, Exfoliative cytology, Imaging techniques
Oropharynx	Tobacco, Alcohol, HPV	+/− Yes	+/− Yes	Yes	Precancerous lesions, Toluidine blue, Salivary and Blood tests, Exfoliative cytology, Imaging techniques, HPV detection (blood and/or Tonsil)
Larynx	Tobacco, Alcohol	No	No	Yes	Precancerous lesions, Imaging techniques
Hypopharynx	Tobacco, Alcohol	No	No	Yes	Imaging techniques

ENT, Ear Nose Throat; HNSCC, Head and Neck squamous cell carcinoma.

practice in this context. These studies have shown that conventional oral examinations dominate early detection methods. It would therefore appear necessary to focus early screening on this clinical examination while extending its practice to as many medical and paramedical fields as possible (general practitioners, addiction specialists, and dentists),[46–49] but focusing on target populations, which would most likely need to be defined more precisely than simply as "alcohol or tobacco users" or "daily users of betel nuts." One major difficulty is identifying and accessing the target population. For example, it is common practice in France to offer a systematic ENT examination to patients at risk (alcohol and tobacco users) hospitalized for any reason. Baert *et al*. demonstrated the utility of this practice for the more-or-less early diagnosis of squamous cell carcinoma in such patients presenting at least one symptom (16 cases of cancer among the 159 patients).[48] The American Dental Association (ADA) issued recommendations in 2017 regarding oral cavity cancer screening.[50] The ADA specified that these recommendations are also "guidelines" for general practitioners, dentists, and nurses and proposed the following measures:

- Conventional oral examination and systematic palpation. A biopsy can be performed in the chair before referral to a specialist if there is any doubt about a suspicious accessible lesion.
- If a biopsy is not possible, the patient should undergo a cytological test, and even if this test is negative, the patient should undergo clinical re-evaluation.
- In the context of low-quality evidence, the committee does not recommend autofluorescence, vital stains, tissue reflectance, or saliva adjuvant testing.

The Make Sense Campaign was set up in Europe in 2013 (https://makesensecampaign.eu/). It brings together the various medical disciplines involved in head and neck oncology to raise awareness for education, prevention, and the early diagnosis of head and neck cancers in a broad sense (but giving priority to HNSCC) through "awareness weeks," during which various events are organized, and through social networks, podcasts, and videos for the public, as well as through healthcare professionals in hospitals, clinics, and private practice. This campaign currently operates in 18 European countries and Brazil. Unfortunately, the "Make Sense" campaign does not give detailed information or results on available screening programs. In 2010, Shuman *et al*. proposed free clinical screening annually for volunteer patients followed up for 14 years. It was found that only a minority of the patients screened had a suspicious lesion. Given these findings, future head and neck cancer screening clinics should focus on patients with identifiable risk factors to maximize potential benefits and make the most of education and prevention opportunities.[51] The literature reviews performed by Brocklehurst *et al*. in 2013[13] and Gogarty *et al*. in 2016[3] revealed that screening for HNSCC would require prior identification of populations at risk. The "gold standard" was based on physical examination (conventional oral cavity examination). In 2015, Dakpé *et al*. proposed a project to encourage oral cavity cancer screening in which tobacconists were asked to give tobacco users warning leaflets encouraging them to consult their general practitioner.[52] This project could be extended to other actors, such as pharmacists, doctors at healthcare centers, and voluntary workers at social centers. However, it was difficult to draw conclusions about the number of patients sensitized to this issue and/or diagnosed. In 2022, Kozak and Achim studied volunteers screened with a questionnaire. This study provided an excellent opportunity to educate at-risk populations about the risk factors for developing HNSCC. However, it was concluded that this was not a cost-effective use of doctors' time because this generalized screening did not increase detection rates, even in high-risk subsets of the general population.[53] In 2018, Zhang *et al*. focused on biomarkers involved in the catabolism of phospholipids and showed significant variations in the levels of three of these biomarkers (LysoPC 16:0, PAF, and DPPC) in laryngeal cancer.[36] Along similar lines, Falco *et al*.[54] focused on circulating extracellular miRNAs (blood, serum, and saliva) that could be assayed by "liquid biopsy." Many recent studies have concluded that miRNAs are of interest for detecting and monitoring laryngeal cancers at early stages due to their rapid modulation[36,54–56] Past, present, and future? At the moment, early detection of HNSCC is challenging. As previously presented, several methods (tissue colorations, salivary or blood tests, imaging methods like NBI, etc.) have been described. Although globally minimally invasive, these methods are either experimental or not easily accessible globally for most physicians (and patients!) and possibly expensive. The reported diagnostic accuracy of tests of this type tends to decline as studies progress. As a result, the possibility of early diagnosis of HNSCC in patients at risk must still rely on systematic ENT physical examination when possible. In particular, an ENT examination is mandatory in cases of symptoms lasting more than three weeks (even if only one symptom among dysphonia, dysphagia, otalgia, odynophagia, cervical tumefaction, or dyspnea exists). Furthermore, non-specialist physicians (particularly dentists, general practitioners, addiction specialists, anesthesiologists, pulmonologists, etc.) should be aware of the presence of precancerous lesions in the oral cavity and larynx (for example, incidental pickup of vocal cord lesions during intubation under general anesthesia or laryngeal lesions seen at the start of a bronchoscopy) and refer patients accordingly. Otherwise, one possible way to improve early diagnosis of HNSCC requires making high-risk

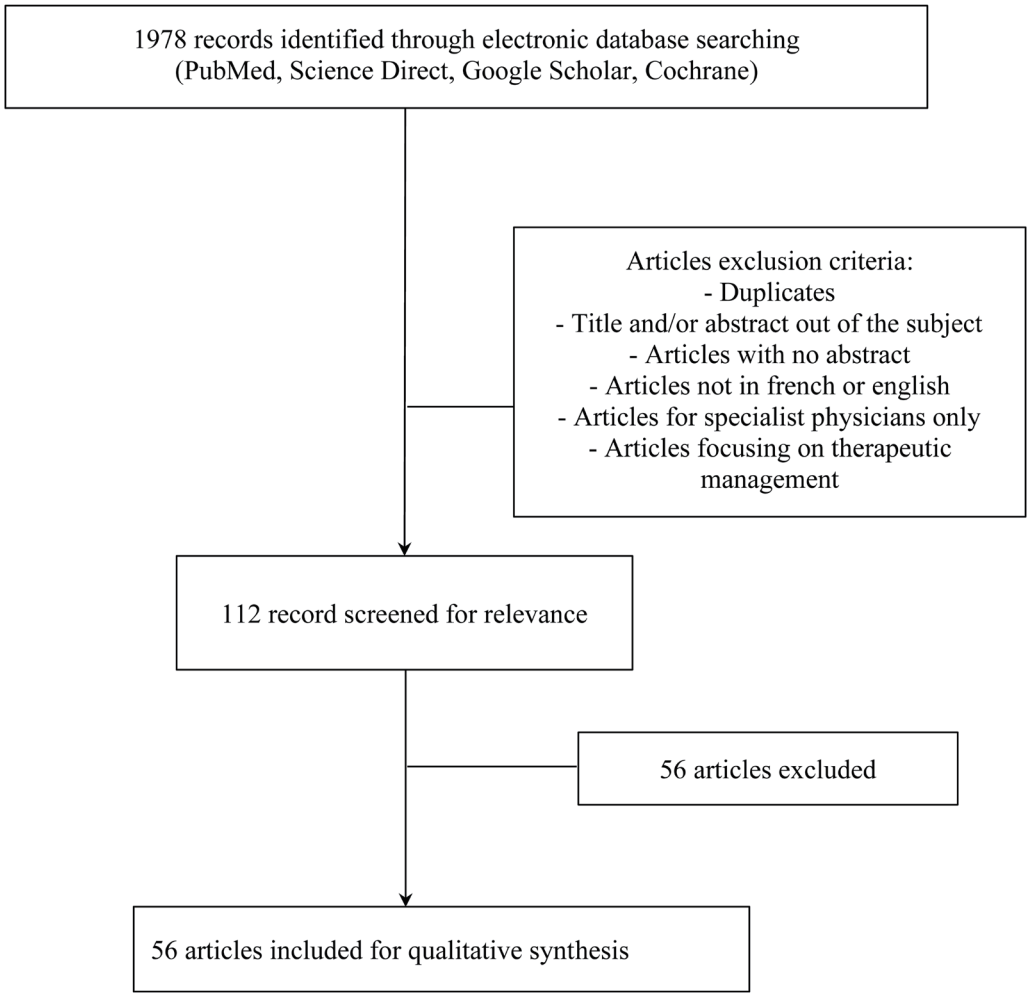

Fig. 2. Possible patient pathways for early diagnosis of HNSCC. (*) Persistent symptoms among dysphonia, dysphagia, odynophagia, dyspnea, otalgia, cervical pain, and cervical swelling. ENT, Ear Nose Throat; HNSCC, Head and Neck squamous cell carcinoma.

patients aware that they must visit a professional if they notice any symptoms to shorten the patient delay (Fig. 2).[48]

Conclusion

In conclusion, there are currently no well-defined national or international screening protocols for HNSCC and no validated criteria for quantifying the level of alcohol, tobacco, or betel intoxication that may justify an ENT examination. There are no guidelines on the optimal frequency of this type of examination in a high-risk population. However, we hypothesized that when possible, a systematic ENT examination on all high-risk patients would be the only way to allow for early detection of HNSCC.

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Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

Contributed to study concept and design (CP and JJ), acquisition of the data (JJ), assay performance and data analysis (JJ), drafting of the manuscript (JJ), critical revision of the manuscript (CP), and supervision (CP).

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