Review Article

Early identification of people at high risk of oral cancer—A review of existing risk prediction models

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Abstract

Prediction plays a ubiquitous role in cancer care. At every stage of the illness, the patient, the physician, and the family must make numerous decisions. Utilizing epidemiological, clinical, biological, lifestyle, and genetic factors, a cancer-specific risk assessment model calculates the likelihood of developing cancer. In India, oral cancer ranks as the fourth most common cancer, affecting nearly 3,000,00 individuals annually. Because it is in the premalignant stage, oral cancer is easily detectable in the oral cavity. Prompt identification of this lesion can result in better outcomes and a higher standard of living. Advanced statistical techniques have been used to develop prediction algorithms or risk scores that identify individuals with a high risk of developing oral cancer. With the aid of these risk assessment models, specific individuals can be screened to aid in the early detection of the disease, which may result in better outcomes and lifestyle modifications. Finding the best model among the current risk models for oral cancer may be aided by a thorough examination of all these models. Finding and assessing the risk model that primary care physicians can use and easily apply in clinical practice will be made easier with a succinct and straightforward comparison of the models. This review compares the current models to determine which has the best performance metrics, which could lead to a better understanding of the advantages and disadvantages of various risk prediction models of oral cancer.

Keywords: Oral cancer, oral health, risk factors, risk prediction, tobacco

Background

Cancer is a major cause of death and shortening of life expectancy in most of the countries around the world. According to the Global Health Organization's 2020 GLOBOCAN report, the number of new cancer cases and deaths in 2020 was estimated to be 19.3 million and 10.0 million, respectively. The report also predicts a 47% increase in cancer cases by 2040 compared to the current statistics.[1]

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Oral cancer is a malignant tumor of the lips and oral cavity, according to ICD-10 codes C00 - C06. Oral cancer is a heterogeneous group of cancers originating from different areas of the oral cavity. The incidence of oral cancer varies greatly from region to region in the world.[2]

India has the highest number of cases of oral cancer and one-third of the overall burden of oral cancer in the world. According to the Global Organisation for the Development of Vocational Training (GLOBOCAN 2020), oral cancer is the second most common cancer in the Indian subcontinent and the third most common cancer-causing mortality. A total of 70% of the cases of oral cancer in India are found in the late stages of the disease, which results in a very low 5-year survival rate, apart from putting a lot of strain on the health system in India.[3]

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One of the main advantages of oral cancer is that it is one of the rare cancers in the body that has a pre-cancerous stage and can be detected early.[3] Poor knowledge of warning signs, lack of staff, dental negligence, and lack of access to dental care are some of the reasons why oral cancer is being diagnosed late. Previous studies have shown that screening patients at high risk for developing oral cancer can reduce mortality and improve quality of life.[4] In the past, risk factor models have been developed to identify individuals at high risk for oral cancer. Risk factor models assign each person a risk score based on certain variables identified with a simple questionnaire that primary health workers can use.[5] Patients identified as high-risk can then be referred to oral health professionals.

The present review attempts to appraise the available risk factor models for oral cancer in terms of the various risk factors identified and understand the methods used to evaluate these models. Evaluating the existing models will help in the development of newer models that might be able to overcome the shortcomings of the existing models and incorporate the advantages of these risk assessment models.

Risk Factor

The most common types of cancer in the head and neck area are cancer in the mouth and the throat. About 90% of all oral cancer is squamous cell carcinoma, which means it starts in the lining of the mouth.[6] Risk factors for oral cancer include genetic factors, exposure to physical carcinogens such as sun and ionizing radiation, exposure to chemical carcinogens such as tobacco smoke, or biological carcinogens like infection from certain viruses and bacteria.[3] The presence or absence of a risk factor cannot guarantee that a disease will occur, but it can be very helpful in understanding the etiology of the disease and reducing its prevalence.[7]

The main risk factor for oral cancer is exposure to tobacco smoke produced by cigarettes, cigars, pipes, etc. Additionally, using smokeless tobacco or chewing tobacco has been linked to the development of cancer of the cheek, gums, and inner surface of the lips. In South Asian countries, the consumption of betel quid, areca nut, or tobacco leaves is a major risk factor for oral cavity cancer.[7] A total of 80% of oral cavity cancers are linked to a history of tobacco use. Additionally, the consumption of alcohol has been shown to increase the risk of oral cancer by many times.[8] Furthermore, the diet, particularly processed meat and spicy food, has been linked to an increased risk of oral cancer, while fruits and vegetables have a protective effect.[9] Finally, there are some other risks associated with oral cancer, such as family history of cancer and poor oral hygiene, recurrent oral ulcers and long-term usage of mouthwashes.[8]

Risk Assessment

Oral cancer is one of the most easily preventable types of cancer, and because the risk factors for oral cancer are modifiable, reducing risky behaviors can reduce the risk of oral cancer, reduce the economic burden of oral cancer, and reduce the mortality associated with oral cancer.[5] Risk assessment is the utilization of a tool to gain an understanding of an individual's risk level and the associated risk factors for a particular oral disease from the patient's clinical, demographic, and behavioral information.[10] Risk scores are mathematical equations that investigate the relationship between various exposures. Risk assessments based on model-based scores may help in the identification of patients at an increased risk of developing an illness in the future and thus aid in the early identification of diseases. Additionally, risk assessment tools can be used to motivate and inform patients.[11]

Based on their intended use, risk prediction models for oral cancer can be categorized into different groups.[12] Among them are:

1. Using screening algorithms to identify people at high risk without taking genetic variables
2. Using genetic factors and screening methods to identify patients at high risk
3. Predictive models for the likelihood of developing malignancy.
4. Oral cancer prognosis prediction models.

Only the first class of risk prediction models, which is helpful in identifying patients at high risk, with the help of risk scores will be covered in this review. Many attempts have been made in the past to create risk prediction models that could reliably identify or screen individuals who are at a high risk of oral cancer. All these risk prediction models were developed with the primary hypothesis that using a prediction model to screen could prevent unnecessary testing for individuals who could have a lower risk while identifying those who are at a higher risk and thus require further testing.[13] Primary care physicians have the unique opportunity to utilize risk prediction tools that identify individuals at high risk without requiring extensive biomarkers or invasive and expensive clinical procedures.[14] These models can help identify a target population who are most likely to benefit from an oral cancer screening program. A straightforward and trustworthy risk stratification tool, that could sub-stratify those exposed to carcinogenic elements may allow us to separate those who are most likely to develop oral cancer.[15]

Rationale for the Review

Since risk prediction is still a relatively new discipline, it is hard to say how much advancements have affected different areas of healthcare. Though systematic reviews and scoping reviews exist on risk prediction models for various types of cancers, there are neither scoping reviews nor full systematic reviews available on the use of risk assessment tools to predict oral cancer risk in those who do not exhibit symptoms. This led us to conduct a review of research to predict the likelihood of acquiring oral cancer in an asymptomatic adult population (≥18 years) using clinical, demographic, and behavioral histories that are probably easily accessible in a primary care setting.

Methodology

Articles that met the following requirements were included: (1) Exclusively oral cancer prediction models developed in a general adult population (≥18 years old), regardless of sex (2) any study that used statistical techniques to create predictive models for future cancer risk based on clinical, demographic, behavioral or dental history and (3) original studies carried out in all settings and in any part of the world. The following were the exclusion criteria: Risk models for head and neck cancer or oropharyngeal cancer, machine learning models, studies not written in English, prediction models developed using specialized tests like genetic profiling or imaging tests not widely available in the community, and any risk prediction model used to predict future events in patients with pre-existing conditions or cancer symptoms or survival outcomes.

Using the following search string in all fields, the PubMed database and Science Direct were searched from its creation until December 31, 2022, to find pertinent studies: ("oral cancer" OR "oral potentially malignant disorders") AND ("risk prediction model" OR "risk assessment" OR "risk calculator" OR "risk factor model" OR "risk tool").

A manual search of the citations and references of earlier research publications was added to this search. Every abstract found during the first search was vetted for inclusion and accuracy. The data for the studies that were included were taken from complete papers. The complete text of the article was obtained and evaluated in accordance with the eligibility requirements in cases where additional details were needed to decide on inclusion.

Results

Considering the title and abstract of 338 results found with the search strategy in PubMed and 266 articles in ScienceDirect, 56 reports were assessed for eligibility [Figure 1].[16] After these 56 studies were reviewed, only four of the studies that satisfied the inclusion requirements were added to the review. From citation searching of these studies, 6 more reports were assessed for eligibility of which two more risk models for oral cancer were identified and added to the present review making it a total of 6 risk models for oral cancer.

The risk factors in these oral cancer risk prediction models have been highly varied, and may generally be divided into four categories: sociodemographic history, medical history, which includes dental health, behavioral history, which includes alcohol and tobacco use, and diet history. Table 1 presents a summary of the prediction models included in this review along with the model performance and key findings.

Before being suggested as a tool for individualized decision-making in a population that was not included in the model-building process, risk prediction models must undergo a rigorous validation process.[21]

It is possible to evaluate the effectiveness of the oral cancer risk prediction model by looking at a few key attributes. Model fit can be used to evaluate a model's reliability, or its capacity to forecast the frequency of events in a population. The model's calibration is tested using the Hosmer Lemmeshow goodness of fit test.[22] Additionally, a risk prediction model must be able to distinguish between individuals who have a higher likelihood of contracting a certain disease and those who have a lower likelihood of contracting the same disease. The Net Reclassification Index (NRI) or Concordance Statistic (c-Statist) are used to quantify this discriminating ability.[23] The risk prediction models created to identify patients with a high risk of oral cancer had a level of discrimination ability between those with the disease and those without it that ranged from Acceptable (0.7–0.8) to Excellent (0.8–0.9).

Accurate classification of persons with a higher likelihood of developing a disease is a goal of risk prediction models. A risk factor model's sensitivity and specificity can be measured to aid in determining its correctness. The Area Under the Curve and cutoff scores are established using ROC curves. This aids in figuring out the risk factor model's false positivity and false negativity rates as well.[24] The risk prediction models created to identify patients with a high risk of oral cancer had a level of discrimination ability between those with the disease and those without it, that ranged from Acceptable (0.7–0.8) to Excellent (0.8–0.9). A key metric for gauging a screening test's accuracy is sensitivity, or the test's capacity to identify a diseased person as positive.[21] Few disease cases are overlooked when using a test that is extremely sensitive. The prediction models for oral cancer exhibited a good positive predictive value and a sensitivity ranging from 74% to 94%. A test's specificity is its capacity to identify a healthy person as negative and is another crucial component of accuracy. The prediction models' specificity for oral cancer varied from 68% to 85%.

When evaluating the effectiveness of any risk prediction model, validation is a crucial component. Even if the model does well on the sample used for development, it is not sufficient.[25] To be considered generalizable, the model must also be able to reproduce its results in a sample of people who are comparable to but distinct from the population from which it was developed.[26] Most of the oral cancer risk models have solely included internal validation using bootstrap sampling. When the datasets used for model development and validation are compared, the AUC is found to be quite good in these models.

Discussion

Risk factor models could identify patients who are at a high risk of getting oral cancer. They can also help with focused screening, which can lead to early detection and treatment of oral cancer, improving quality of life and prognosis.[27] The risk prediction techniques available for oral cancer are designed to either predict the absolute possibility of acquiring oral cancer or screen patients at high risk who require additional examination by an oral health expert.[28]

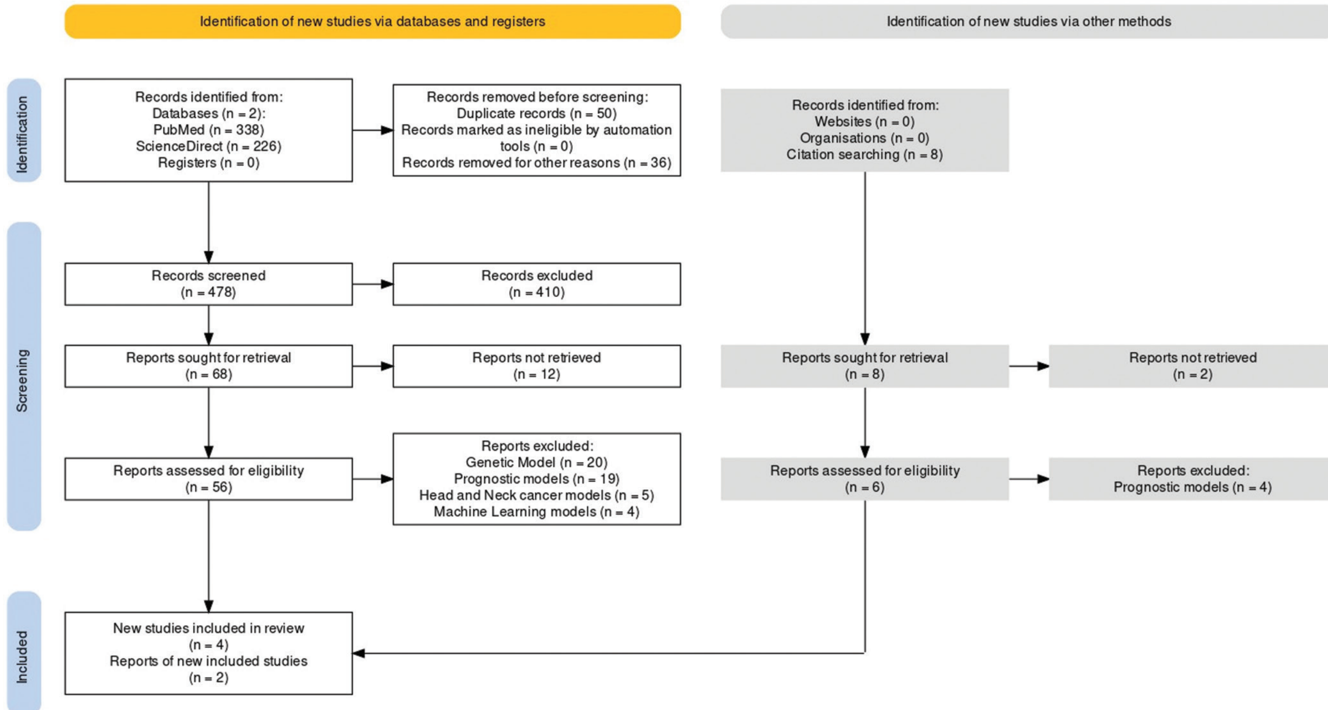

Figure 1: Flowchart showing the literature screening process

Table 1: Summary of key findings and performance of existing risk prediction models

Author	Sample	Features evaluated	Model validation	Key findings
Amarsinghe *et al.*[5]	A population-based case control study among 101 cases of OPMD and 728 controls in rural Sri Lanka.	Discrimination - AUC Accuracy - Sensitivity/ Specificity, PPV/NPV	External validation in a separate sample of 410 subjects	The risk score ranged from 0 to 26. The model had strong predictive value. (AUC=0.78). Overall sensitivity was 93.7% and specificity was 67.7%
Krishna Rao *et al.*[11]	A hospital-based unmatched case control study among 180 cases and 272 controls, in Karnataka, India.	Reliability - Hosmer Lemmeshow test Discrimination - ROC curves Accuracy - Sensitivity/Specificity	Bootstrap sampling with replacement	Chewing quid with tobacco was the strongest predictor of oral cancer. The risk scores ranged from 0 to 28. The model showed good discrimination (AUC=0.86). Sensitivity (74.6%) and specificity (84.6%) were similar in the bootstrap sample compared to the study sample.
Gupta *et al.*[17]	Hospital-based frequency matched case control study among 240 case control pairs in Pune India.	Discrimination - ROC curves and Youden's index. Accuracy - Sensitivity/ Specificity, PPV/NPV	Bootstrap sampling with replacement	Chewing tobacco in any form was the strongest predictor of oral cancer. The risk score ranged from 0-26. The model had strong predictive value. (AUC=0.9). Overall Sensitivity was 93.5% and specificity was 71.1%
Chen *et al.*[18]	A hospital-based case control study among 978 oral cancer patients and 2646 controls in China	Reliability - Restrictive Cubic splines Discrimination - Harrells Concordance index Calibration - Nomograms	No mention of validation	The risk scores ranged from 0–45 in men and 0–28 in women. The concordance index was 0.768 for men and 0.700 for women. The calibration curves matched well with the actual observation.
Hung *et al.*[19]	A retrospective cohort study was carried out among 6,275 subjects of which 2777 were included in Taiwan.	Discrimination - AUC Accuracy - Sensitivity/ Specificity, PPV/NPV	Not applicable	The incidence density ratio in Taiwan was 96 per 1,00,000 persons. The incidence of oral cancer was highest among those with a habit of betel nut chewing along with smoking. The AUC was 0.73 and sensitivity and specificity were 77.1% and 56.4%, respectively.
Adeoye *et al.*[20]	A community-based case control study among 44 cases of OPMD and 935 controls in Hong Kong.	Discrimination - AUC Accuracy - Sensitivity/ Specificity	External validation in a separate sample of 491 subjects	Irregular toothbrushing was the strongest risk factor for oral cancer in a population with low tobacco usage. The AUC was 0.82 and sensitivity and specificity were 71% and 78%, respectively.

Amarsinghe *et al.*'s[5] risk factor model is a straightforward, basic tool that was created in a Sri Lankan population through the use of a community-based case control study. This model showed an ideal specificity of 75.9% and good sensitivity of 85.3%. Similar results have also been found by the screening models created by Krishna Rao S *et al.*[11] and Gupta B *et al.*[17]

from hospital-based case control studies conducted in various parts of India. In all these models, the most significant predictor was chewing tobacco with quid. These risk factor models were validated using bootstrap sampling on a subset of the population, and they showed good predictive performance (AUC = 0.78, 0.86, and 0.9). Considering models must be trained and assessed on various datasets under various settings, the area under the curve values (AUC) by themselves do not permit meaningful comparisons of models.[29]

Due to a variety of lifestyle factors, studies conducted in the past have indicated that men are more likely than women to get oral cancer.[7] Chen *et al.*[18] created distinct prediction models for males and females based on comprehensive case control research carried out in China. For men, smoking and alcohol consumption were the most significant predictors of oral cancer; whereas, for women, passive smoking and cooking oil fume exposure were the most significant predictors. Additionally, they created reliable nomograms with strong prediction power. Most of the oral cancer risk assessment instruments generate a score for patients based on an algorithm.[28] It is doubtful that the patient can understand these scores. A nomogram or pictorial portrayal can serve as a useful tool for improving comprehension of risk classification. It can also motivate patients to adopt healthy behaviors, which can lead to a positive shift in the risk factor model.[30]

A higher false positivity rate is one of the main downsides of any risk assessment model. When the false positivity rates are high, patients and their families may become anxious and traumatized and undertake unnecessary testing. However, it is better to have a larger false positive rate than a higher false negative rate[25] for a condition like oral cancer, where early identification improves the survival outcomes enormously. The practical usability of these risk prediction models by end users, such as patients and healthcare professionals, presents another difficulty.[26] Research must be done to evaluate the effects of using these tools as well as how well patients absorb and comprehend risk information.

Memory bias and knowledge bias are intrinsic limitations of case control studies that were utilized to collect data regarding the risk factors to be included in these prediction models.[31] In certain research, techniques like the application of a life grid method have been included to reduce bias throughout the model-building process.[10,15] Using data from a retrospective population-based cohort study, Hung *et al.*[19] created a prediction model for oral cancer. The model can only be used by those who have the habit because it was created in a high-risk population in Taiwan who chewed betel nuts, smoked them, or both. With a moderate sensitivity and low specificity, it demonstrated a good predictive capacity (AUC = 0.73).

In Hong Kong, Adeoye *et al.*[20] created and validated an easy-to-use scoring system for risk assessment in a population where smoking and betel nut chewing are not common. The greatest risk factor for oral cancer with the best sensitivity and specificity (AUC = 0.82) turned out to be irregular brushing.

The health behaviors in a given area influence the risk factors for mouth cancer. To increase risk prediction models' accuracy, it is also necessary to recognize new factors and update them regularly.[12] By incorporating these risk models into cancer prevention programs, it is possible to considerably increase program efficacy and decrease diagnostic delay, both of which enhance survival rates.

For the early detection of oral cancer, a comprehensive clinical examination of the oral cavity by a dental health professional is required. Using risk prediction algorithms can have a significant impact in nations where oral health professionals are only consulted after advanced cancer symptoms have manifested.[29] However, it is still a fact that patients have trouble believing and accepting the outcomes of these tools. Research has indicated that patients may not express interest in additional testing and evaluation by a certified professional because they mistrust the validity of the results and doubt the reliability of these tools.[15] Encouraging patients at higher risk to undergo additional testing and early diagnosis of probable disease may be facilitated by teaching and training primary care physicians, who serve as the rural population's initial point of contact, on how to use these risk assessment tools.[11] Additionally, patient behaviors and attitudes underutilize PCPs' potential contribution to cancer prevention. It is important to spread the word about PCPs' ability to offer cancer prevention guidance. However, since time constraints are the primary barrier to routinely offering cancer prevention advice, systemic measures like the utilization of prediction models to support PCPs in leveraging their undeniable role in cancer prevention must be implemented.[32]

Conclusion

A promising technique to detect cancer in its early stages and help with better outcomes is the use of risk factor models to identify people who are more likely to be diagnosed with oral cancer.[33] The effectiveness of these tools can be increased by using the most appropriate one for the area, considering the healthcare system in place, the disease's incidence, the availability of medical resources, and the most common risk factors.[34] The integration of risk prediction models into current screening programs will enhance their effectiveness and contribute to the realization of the global goal of improving health and well-being.

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Conflicts of interest

There are no conflicts of interest.

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