Critical Review
Stomatology

Innovative reflection on oral cancer research priorities: the contribution of social network analysis

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Abstract: The objective of this study is to present a tool to help understand how variables associated with oral cancer prevention relate to each other in a social network. A search of the Scopus database was performed using terms related to oral cancer and prevention from 2000 to 2020. The keywords were used as nodes and were analyzed using NodeXL, which produced the network graphic analysis. From the 1004 publications available, 4038 different keywords were obtained and then grouped into 75 constructs based on conceptual similarity. The most influential nodes were risk factors, comorbidities, epidemiology, and treatment. However, topics such as technology, telemedicine, self-examination, and diagnostic delay remain far removed from central relations. Network analysis enabled us to observe the bias of biological and basic science in the field and identify a need for studies concerning primary prevention, behavioral interventions, and inequalities in oral cancer.

Keywords: Mouth Neoplasms; Social Network Analysis.

Introduction

Oral cancer, representing all malignancies that occur in the oral cavity, is the eighth-most incidental neoplasm worldwide.[1] The etiologies of oral cancer include tobacco intake, smoking, alcohol and areca nut intake, excessive sunlight exposure, and human papilloma virus (HPV).[2] Despite therapeutic improvements, the survival rate has not changed significantly over the past few decades, with a 5-year survival rate slightly above 50%.[3]

Oral cancer is particularly dangerous because it is relatively painless in its early stages.[4] Consequently, it is usually discovered in its late stages and is therefore associated with poor prognosis. Treatment can be very expensive; therefore, preventive measures are of great importance. Prevention requires a multidisciplinary approach involving coordinated efforts from all sectors of society.[2] Primary preventive measures should include an increase in public awareness of the risk factors and changes in individual's behavior; secondary preventive measures include regular oral head and neck examinations and treatment of potentially malignant conditions or *in situ* neoplasms.[5] Consequently, tertiary prevention aims to prevent redevelopment.[2]

Network analysis facilitates a visual demonstration of the positions and relationships between the variables, with two fundamental elements:

nodes and edges. In a graph, nodes are represented by circles, whereas edges are lines that connect these circles. Conceptually, nodes can represent many things, including people, organizations, websites, or keywords. The edges can represent connections in social networks, several relationships, hyperlinks, or relationships between variables, as in this study. Another significant contribution of this technique is the representation of the study of a topic through well-defined clusters. These clusters help clarify whether a particular subject has subtopics, divisions, or groups, allowing a detailed understanding of what is being researched. Statistical data allow quantitative analysis of the relevance of a topic (node) or its importance within a set (network) of related variables.[6,7,8]

Network analysis in science helps to identify influential terms based on several metrics. This is conceptually important because social influence has different definitions and measures of importance, called centralities[9]. These are degree centrality, closeness centrality, betweenness centrality, and eigenvector, which are described below. These basic centrality measures have been used extensively in the healthcare literature to quantify the network positions of individual actors in networks.[9,10,11]

The network analysis approach could represent an important contribution for scholars interested in oral cancer, as it identifies research gaps based on the strength of connections between keywords. The main goal of this study was to present a social network analysis of keywords used in studies in the field of oral cancer prevention.

Methodology

Eligibility criteria and Information source

To be included in this study, papers needed to present a minimum of one of the keywords identified by the authors and be published in English between January 2000 and April 2020.

Search

To identify potentially relevant documents, the Scopus database was examined, and the following terms were used: ("Oral cancer" OR "Oral squamous cell carcinoma" OR "mouth cancer" OR "oral malignancies" OR "oral neoplasm" OR "lip cancer" OR "head and neck cancer") AND (prevention OR "Preventive measures" OR preventive).

Study selection

The electronic search was performed independently by two authors (A.P. and C.P.F.). Information such as author, year, title, and keywords were organized in an Excel spreadsheet, and a third researcher (E.S.), experienced in network analysis, cleaned and excluded papers that did not include the author's keywords and all duplicates were removed. Author keywords were chosen because they were more available and abundant

Data collection process

To avoid an overload of information in the presentation of the network, the keywords were grouped manually into constructs based on nature and conceptual similarity. Initially, two oral medicine specialists (A.P and C.P.F) independently classified all keywords into constructs. Then, three experienced oral medicine specialists (C.C.T.P., J.M.A.C., and J.S.) reviewed all the keywords and suggested the main constructs by consensus. Inconsistencies in the classification were revised and solved by all researchers. Inter-observer agreement was not calculated. More details about the spreadsheet organization can be found in the supplemental material.

Geometry of the network

The data were analyzed using NodeXL with Microsoft Excel 2007/2010 version 1.0.1.361. The layout of the chosen graphic was a non-directional type named Fruchterman–Reingo, which was created automatically. It included network metrics such as centrality, centralization, density, distance, bonding, and bridging, to understand how the system was operating at each of the three points in time.

Results

Study selection

A total of 1495 studies were identified using the search strategy described above. Duplicates were

removed, and 1004 papers with 4038 author keywords were included. All of these studies were published between 2000 and 2020. The selection process is shown in Figure 1.

Summary of network geometry

The proposed network contained 75 vertices and 372 unique relations (Figure 2). The nodes with larger measures of centralities are, naturally, those eligible as search terms (oral cancer, prevention, head and neck cancer, oral malignancies); therefore, we ignored them in the presentation of the results to better explore other interactions. The study design also had higher centrality measurements because we grouped all the different study methods into a single construct. Consequently, this will also be ignored in this textual data presentation. The full details of the data are shown in Table.

Degree centrality

The degree of centrality indicates the activity of the nodes and their popularity in a network. A construct with a high degree of centrality in a social network has a high number of direct connections with other network actors.[8] Our study is a measure of the most popular topics of the articles. The ten constructs that had the highest measures of degree centrality in the network were risk factors (64), comorbidities (63), epidemiology (59), other cancer topography (59), treatment (57), chemoradiotherapy (57), post-treatment complications (57), screening (56), molecular biology/biomarkers, and potentially malignant conditions (53).

Closeness centrality

Closeness centrality represents the reachability of an actor in relation to other actors in a network. Closeness can be regarded as a measure of how fast information can be spread to all other nodes. The ten constructs that had the highest values of closeness centrality in the network were risk factors (0.012), comorbidities (0.011), other cancer topographies (0.011), epidemiology (0.011), treatment (0.0108), chemoradiotherapy (0.0108), post-treatment

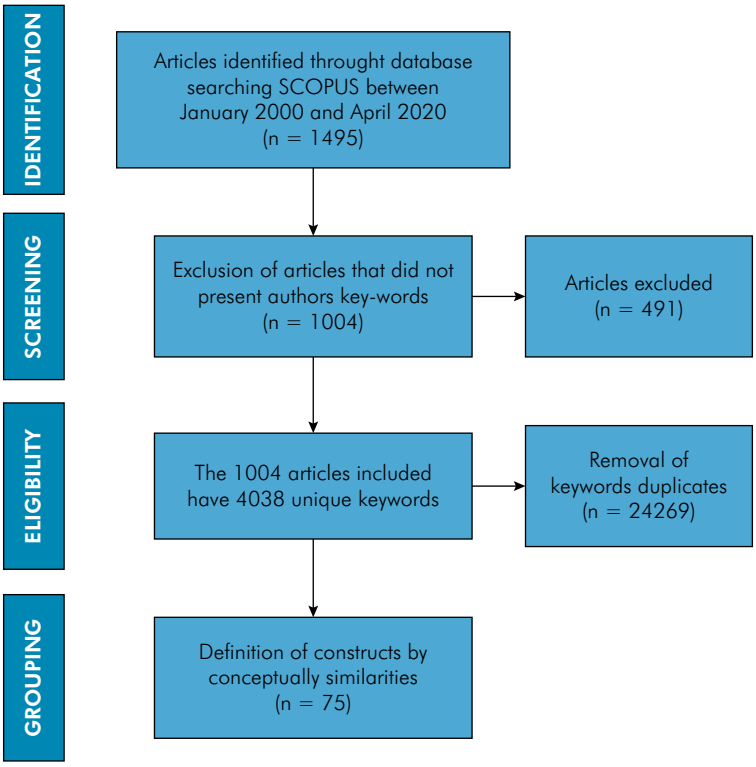

Figure 1. Flow chart of methodological steps.

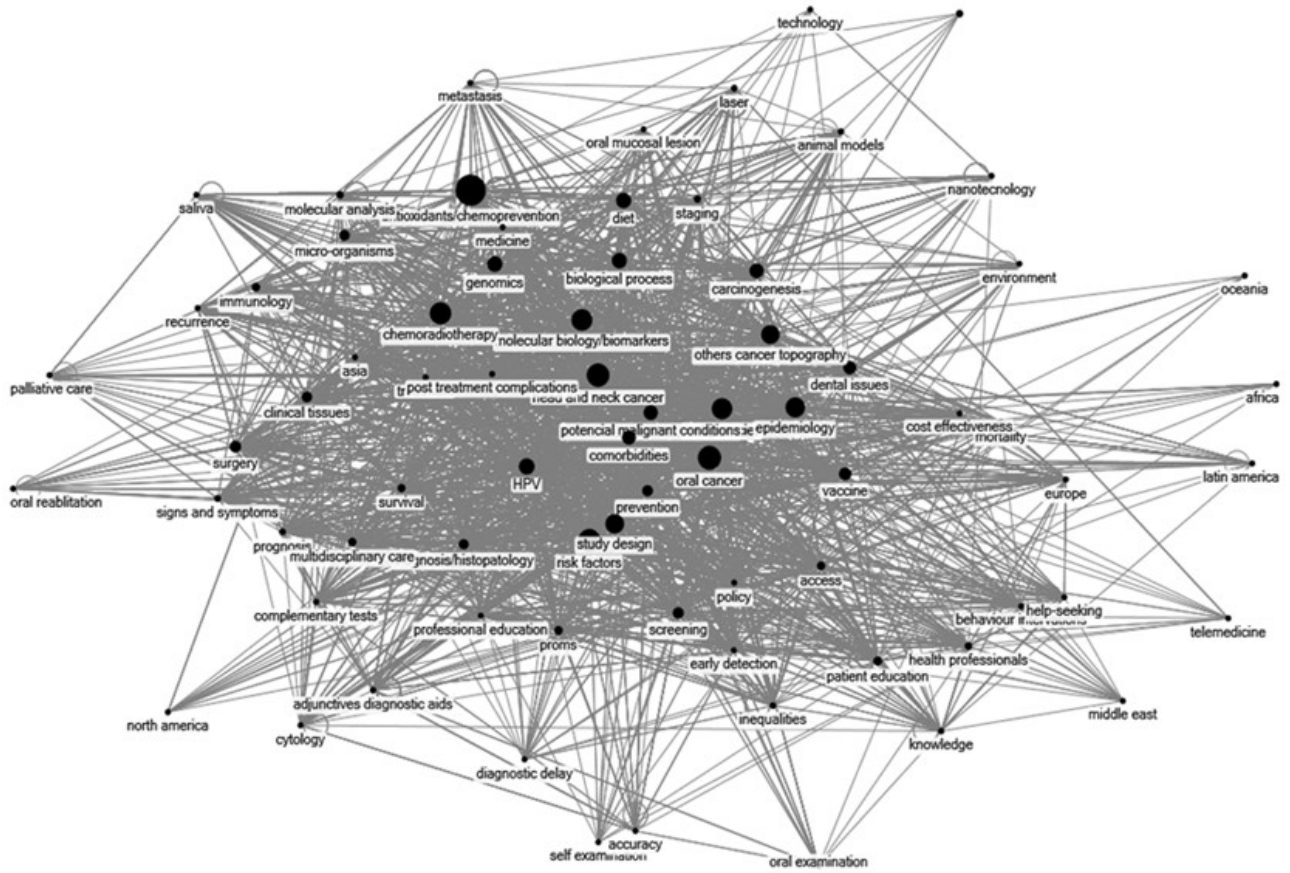

Figure 2. Network of variables on oral cancer.

complications (0.0108), screening (0.0106), molecular biology/biomarkers (0.0104), and potential malignant conditions (0.0103).

Betweenness centrality

The betweenness centrality represents the capacity of a node to control the flow of information in the network between any pair of nodes in the network. The underlying assumption of the betweenness centrality is that 'nodes in the middle' have more 'Intra organizational influence' on others in a network. In other words, it reflects the nodes that serve as bridges between the vertices of the network. The ten constructs that had the highest measures of betweenness centrality in the network were comorbidities (76.04), other cancer topography (63.96), risk factors (52.67), screening (48.33), post-treatment complications (40.29), epidemiology (38.38), chemoradiotherapy (35.35), early detection (29.36), carcinogenesis (27.59), and dental issues (26.95).

Eigenvector

The eigenvector is an ideal measurement for determining the prestige or influence of an actor within its network. It can also be interpreted as how well connected a given actor is to other well-connected actors. In this sense, prestige is a different measure of popularity; this difference comes from the fact that prestige considers the characteristics of the connections and if they are important themselves as well. The ten most influential nodes were risk factors (0.021), comorbidities (0.020), epidemiology (0.020), treatment (0.019), other cancer topography (0.019), chemoradiotherapy (0.019), post-treatment complications (0.019), molecular biology/biomarkers (0.019), potential malignant conditions (0.019), and screening (0.018). On the other hand, the constructs

Table. Details of measured network vertices.

Vertex	Degree	Betweenness Centrality	Closeness Centrality	Eigenvector Centrality
access	46	22.543	0.010	0.016
accuracy	19	2.506	0.008	0.00607
adjunctive diagnostic aids	32	8.620	0.008	0.011
africa	9	0.00000	0.0071	0.00383
animal models	27	2.139	0.008	0.010
antioxidants/chemoprevention	47	15.931	0.010	0.016
asia	40	5.981	0.009	0.015
behavior interventions	30	3.663	0.008	0.011
biological process	46	12.894	0.010	0.017
carcinogenesis	49	27.593	0.010	0.017
chemo radiotherapy	57	35.359	0.0108	0.019
clinical tissues	46	11.301	0.010	0.017
comorbidities	63	76.042	0.0115	0.0204
complementary tests	37	6.459	0.009	0.014
cost effectiveness	31	2.290	0.008	0.012
cytology	26	2.621	0.008	0.00948
dental issues	49	26.959	0.010	0.017
diagnosis/histopathology	51	17.519	0.010	0.018
diagnostic delay	21	3.791	0.008	0.00812
diet	42	9.581	0.009	0.015
early detection	47	29.364	0.010	0.015
environment	26	1.944	0.008	0.010
epidemiology	59	38.384	0.0110	0.0200
europe	30	3.795	0.008	0.011
genomics	49	21.047	0.010	0.017
head and neck cancer	66	77.184	0.012	0.0214
health professionals	35	17.382	0.009	0.011
help-seeking	27	3.618	0.008	0.00945
HPV	49	18.566	0.010	0.017
immunology	36	2.849	0.009	0.014
inequalities	32	9.861	0.008	0.011
knowledge	29	7.026	0.008	0.010
laser	22	3.454	0.008	0.00769
latin america	14	0.14806	0.0074	0.00499
malignancies	68	85.259	0.012	0.0217
medicine	46	18.211	0.010	0.016
metastasis	29	6.436	0.008	0.010
micro-organisms	41	11.000	0.009	0.015
middle east	14	0.38317	0.007	0.00532

Continue

Continuation				
molecular analysis	37	11.287	0.009	0.013
molecular biology/biomarkers	54	25.981	0.0104	0.019
mortality	35	12.715	0.009	0.013
multidisciplinary care	43	9.810	0.009	0.016
nanotechnology	21	2.879	0.008	0.00730
north america	12	0.06479	0.0074	0.00534
oceania	7	0.13777	0.0070	0.00258
oral cancer	73	114.213	0.013	0.0225
oral examination	11	0.675	0.0072	0.00389
oral mucosal lesion	28	3.462	0.008	0.010
oral rehabilitation	15	0.09877	0.0074	0.00571
others cancer topography	59	63.963	0.0110	0.019
palliative care	21	0.505	0.008	0.00803
patient education	38	11.338	0.009	0.013
policy	49	16.975	0.010	0.017
post treatment complications	57	40.298	0.0108	0.019
potential malignant conditions	53	23.778	0.0103	0.019
prevention	70	87.692	0.013	0.0221
professional education	48	20.431	0.010	0.017
prognosis	40	6.365	0.009	0.015
proms	46	17.243	0.010	0.016
recurrence	32	4.259	0.009	0.012
risk factors	64	52.676	0.0116	0.0211
saliva	24	0.937	0.008	0.00929
screening	56	48.335	0.0106	0.018
self-examination	13	0.26860	0.0074	0.00517
signs and symptoms	38	7.878	0.009	0.014
staging	37	14.983	0.009	0.014
study design	69	85.872	0.012	0.0218
surgery	44	11.357	0.009	0.016
survival	47	14.459	0.010	0.017
technology	9	0.19168	0.0072	0.00361
telemedicine	10	0.49886	0.0072	0.00381
treatment	57	26.627	0.0108	0.0198
vaccine	48	24.040	0.010	0.017

with less general centralities were Oceania, technology, telemedicine, Africa, oral examination, Latin America, self-examination, the Middle East, and North America.

The strongest relationships were between the nodes' antioxidants/chemoprevention and molecular biology/biomarkers, followed by biological processes and antioxidants/chemoprevention and antioxidants/chemoprevention and oral cancer.

Clusters

Figure 3 shows a network that is grouped into clusters. Cluster 1 (dark blue) has 15 vertices and 35

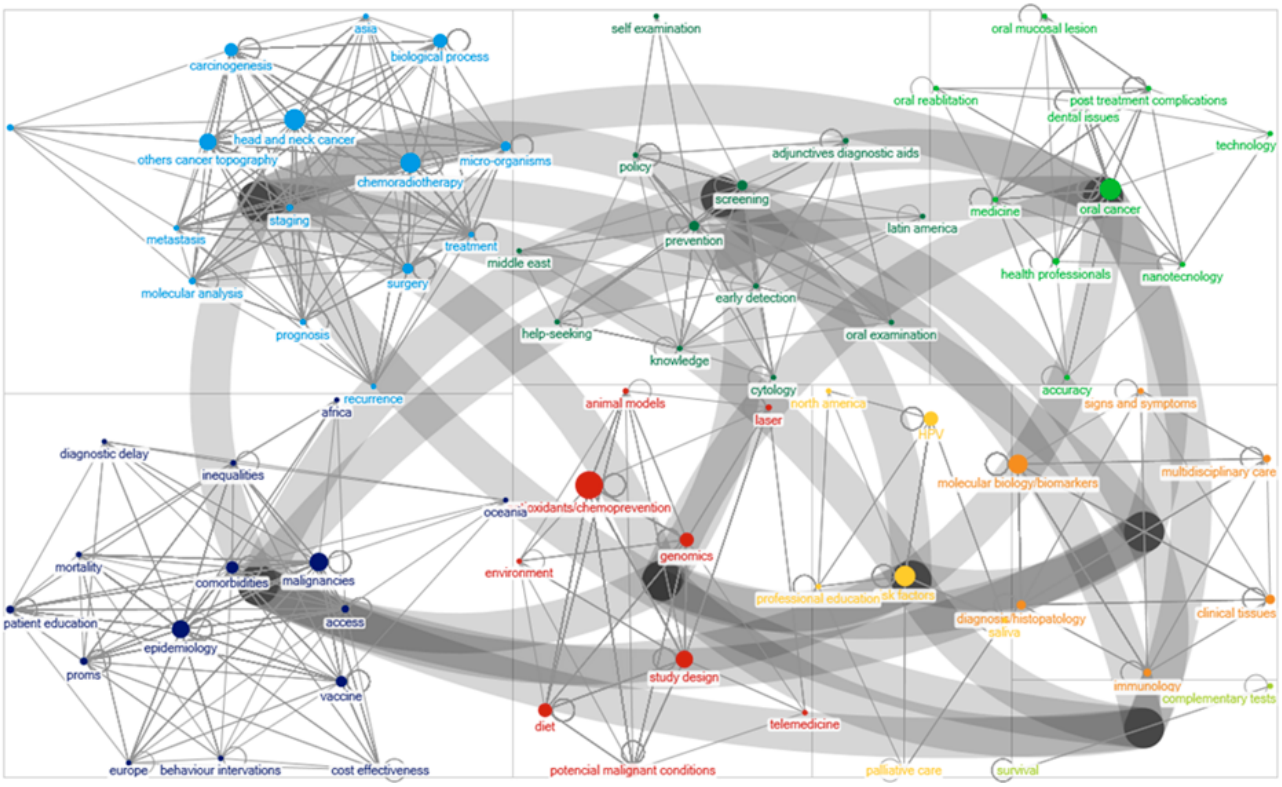

Figure 3. Clustered network graph

relationships between the nodes. Cluster 2 (blue) has 15 vertices and 23 relationships between nodes. Cluster 3 (dark green) has 12 vertices and adds 20 relationships between nodes. Cluster 4 (green) has 10 nodes and 12 unique edges. Cluster 5 (red) has nine vertices and ten unique edges. Cluster 6 (orange) and Cluster 7 (yellow) have six nodes and three unique edges. Finally, Cluster 8 (purple) has two nodes with one unique edge.

Discussion

The major goal of reducing oral cancer is to focus on preventive measures. Strategies for prevention have not been fully explored.[2] To the best of our knowledge, this is the first network analysis to evaluate the interactions among keywords presented in articles published in the field of oral cancer prevention. Prevention is very important in the context of oral cancer, which still concentrates diagnosis in late stages, causing great morbid-mortality.[12] The main result of this analysis reveals key influential terms as risk factors, comorbidities, epidemiology, and treatment as the most influential nodes. However, it was interesting to note topics related to oral cancer prevention that remain foreign from central relations such as technology, telemedicine, oral examination, self-examination, and diagnostic delay are of value.

Although social network analysis differs from bibliometric studies, which use citation index to understand and present the volume of publications and their characteristics, the results point to the same path. Social network analysis uses centrality measures to indicate popularity and influence. In a bibliometric study published by Pena-Cristóbal et al.,[13] which analyzed the top 100 most-cited articles in oral cancer, the predominant area of study was the etiopathogenesis of oral cancer (42%), followed by prognosis (16%) and treatment (11%), reinforcing the major connections within molecular research in the field of oral cancer. Along the same lines, Hassona et al.[14] analyzed the 100 most-cited articles on squamous cell carcinoma of the mouth, lips, and

oropharynx. Etiology and risk factors, especially HPV, are the most commonly discussed topics.[14]

Telemedicine and technology were constructs that appeared as small centrality values. However, they may indicate a recent uniqueness, growing interest, and development. Telemedicine has the potential to promote equitable health care and streamline patient management, which could result in early detection of OC.[15] It can improve the quality of primary healthcare by bridging the gap between primary and specialized healthcare. In view of the historical moment when the global population is experiencing the COVID-19 pandemic, new technologies and prevention paths need to be discovered.[16] Hopefully, advances in telemedicine and new technologies will be seen in future studies.

The clustered network allowed us to understand some subgroups of relationships. The vertices in each cluster are not isolated from the relationships with other vertices belonging to other clusters. The thicker lines connecting the clusters in the chart demonstrate the relationships between them. It was not the purpose of this study to identify the place of origin of each publication geographically. However, where this data was available (indicated as a keyword) differences in oral cancer research could be noticed between the continents. It is interesting to note the relations of continents with different themes. Asia appears in the soft blue cluster, with constructs related to carcinogenesis, disease evolution, treatment, and prognosis. Asia has the highest rates of oral cancer worldwide due to cultural risk factors.[17] The Middle East and Latin America are sub-grouped in the dark green cluster, with topics such as early detection and screening. These countries have a high prevalence of traditional risk factors related to tobacco use and strong social determinants, as in many emerging countries.[18] North America appears closer to HPV and risk factors in the yellow cluster. Oceania, Africa, and Europe in the dark blue cluster are together with variables related to the patient (education, proms, and behavior interventions). A previous study warned of the notable lack of multicenter studies, indicating that there is a need to increase international collaboration in the field of oral cancer research.[19]

Cluster 1 (dark blue) included popular nodes, such as epidemiology and comorbidities. However, most variables related to patients, as education, behavior interventions, self-examination, and inequalities are also included in it and are clearly lacking in the literature. The subgroup is displaced when compared with another general view of the clustered network (Figure 2). It is well established that behavior is a risk factor in oral carcinogenesis, as a previous meta-analysis demonstrated that social determinants are an independent oral cancer risk factor.[20] Therefore, it is important to advance patient awareness, as indicated by the high morbidity associated with oral cancer due to late diagnosis. Future studies should address this gap, as it could potentially be a low-cost and effective measure to improve prevention and early diagnosis.

Altimetric Explorer was used to analyze the top-100 articles on oral cancer that generated the highest online attention. It was found that treatment outcomes and quality of life were the most popular topics.[14] Oral cancer can lead to serious and important social and effective consequences because the treatment may result in facial distortion, oral dysfunction, swallowing, and speech problems.[21,22] Quality of life among oral cancer patients has become one of the most important parameters worth considering in diagnosis and post-treatment follow-up. Delayed diagnosis prevents successful treatment and favorable outcomes, resulting in the costliest and less effective treatment.[23] In addition to the fact that diagnostic delay is presented as a small node, it is also isolated in the network. Since it has a great impact on prevention and treatment success, studies should be conducted to improve the diagnostic process.

Clusters 2 (blue) and 4 (green) concentrated on topics related to treatment and post-treatment complications. It is interesting to note that Cluster 3 (dark green), which presents betweenness centrality topics as early detection and screening, is in the middle of these two and can be seen as a connection point. In fact, high-risk target screening has demonstrated an impact on reducing mortality rates.[24] Moreover, Cluster 5 (red) has central node oxidants and chemoprevention, including

potential malignant conditions, diet, and genomics. Prevention through chemoprevention and/or the use of systemic medications is an extensively studied strategy and continues to hold promise as a way to diminish the negative indicators associated with oral cancer.[25]

Cluster 7 (yellow) draws attention to HPV, highlighting the fact that despite having a high degree or prevalence, it does not stand out in the network in relation to centrality values. HPV is the most commonly addressed topic and the most cited term among articles focused on etiology and risk factors.[14] However, when analyzed in measures of centrality, one can notice that it does not occupy an articulated position in the network. Therefore, despite its great popularity, HPV has not built many interdisciplinary research bridges.

Cluster 6 (orange) points out that molecular biology/biomarkers are the most important nodes and appear close to signs and symptoms, diagnosis/histopathology, and immunology. The strong relationship between this node and chemoprevention is due to biomarkers being expected to determine the effectiveness and safety of chemotherapy preventives.[26] Finally, Cluster 8 (purple) resulted in only two nodes, survival and complementary tests, suggesting that tertiary prevention has not yet been articulated in the context of oral cancer prevention.

Conclusion

This study applied an innovative methodology to analyze published data in the field of oral cancer. However, there are some limitations to this study. The first is the omission of articles not detected by the search methods employed. The Scopus database is an important database and provides a good sample of present scientific production, but not all, and certainly, other important studies, might have been omitted. Second, the large number of keywords made the graphic interpretation more complex, which required additional categorization in constructs. Five specialists performed the review of the constructs; however, the results could not be easily replicated because of subjectivity in the interpretation of each term.

Nevertheless, within the limits of this methodology, it is possible to recognize publishing patterns in the field of oral cancer research and prevention. In contrast to bibliometric studies, network analysis enabled us to graphically visualize how different topics relate to recent research. It also facilitated recognition of the dominance and bias of biological and basic science in the field and identification of a need for studies concerning primary prevention, behavioral interventions, and inequalities in oral cancer. Future research should also investigate the gaps in network analysis and ways to encourage financial support and attention in these less-studied areas.

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