

# SQUAMOUS CELL CARCINOMA IN YOUNGER POPULATION: A SYSTEMIC REVIEW AND META ANALYSIS

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## **ABSTRACT:**

**Introduction:** Squamous cell carcinoma (SCC) specifically of the tongue usually is seen in the senile population with a long standing tobacco habit. But recently the trend has changed to incidence of TSCC in younger adults with no risk factors. Hence we aim to conduct a systemic review and meta-analyse to assess the prevalence and risk factors of tongue carcinoma in the younger group of patients.

**Materials and methods:** We conducted the search for the data from the online sources like the "EMBASE", "Pubmed", "Scopus" and other sources. Only human studies were collected. Terms searched were CBCT, microtomography, permanent teeth, and root canal morphology. The data extraction and meta-analysis were based on the PRISMA guidelines. Out of the 109 articles, only 23 were selected based on the inclusion and exclusion criteria. For the assessment of the risk factors and the variables the statistical analysis was done keeping  $p < 0.05$  as significant.

**Results:** we observed that most of the subjects were at ages 30-50 years. The majority of reports were <40 years of age. Almost equal gender distribution was seen. No association between the habits was seen in the younger adults.

***Conclusion: Prognosis of younger adults is poor than the older patients with the TSCC. Hence, evaluation of the etiology along with other risk factors exposure is expected. It can be proposed that identification of the potential risk factors aside from traditional factors is vital to control the incidence of TSCC in young patients.***

***Keywords: Squamous Cell Carcinoma, Young Adults, Cancer, Risk Factors.***

## **INTRODUCTION**

Oral squamous cell carcinoma (OSCC) embodies about 90%–95% of all intraoral malignancies.[1] Approximately 100,000 cases are stated every year in India. The reported incidence was also high in other countries such as Sri Lanka, Bangladesh and Pakistan.[2] A latest report exposed that about 45% of all oral cavity cancers were tongue SCC (TSCC).[3] TSCC is the most often occurring cancer in young age group patients.[4-7] This may increase in the coming years.[4] OSCC predominantly affects men of sixth and eighth decades of life. In India, oral cancer is the third most common cancer and accounts for 30% of all cancers.[2,5] The carcinomatous change typically occurs as a consequence of the incremental accumulation of mutations which on the long run lead to neoplastic initiation and progression.[8,9] However, there is a significant increase in the prevalence of OSCC in young adults during the recent decades.[7,9] The exposure of the oral epithelium to potential carcinogens at a very young age might reduce the latency period of carcinogenesis in this group.[3] The incidence of OSCC in the younger population has risen from 0.4% to 13%.[4,5,10-15] The data from some developed countries like the UK showed that 6% of all oral cancers occurred in young people under the age of 45 years in both men and women.[2] Hart et al. report stated that about 16% of OSCC occur in younger patients of of <45 years of age.[6] The alarming rise in early-onset cancer occurrence is estimated to be 16% to 28% of all oral malignancies seen at various institutions in different parts of India.[7] The better understanding of TSCC in young patients will enable us to offer better therapeutics to improve the prognosis of the patients. Hence in this review we aim to assess the prevalence and risk factors of tongue carcinoma in the younger group of patients.

## **MATERIALS AND METHODS**

We conducted the search for the data from the online sources like the “EMBASE”, “Pubmed”, “Scopus” and other sources. Only human studies were collected. Terms searched were CBCT, microtomography, permanent teeth, and root canal morphology. The data extraction and meta-analysis were based on the PRISMA guidelines.

The terms of search were “SCC,” “tongue” and “young”. Case reports, reviews and researches deviating from TSCC in young patients were excluded. The analyzed variables were author, year, country of data collection, cohort, age, gender and habits. 109 articles were initially retrieved. After search refinement, 59 articles were not related to study title, and abstract were excluded. In the remaining 50 articles, after extraction of the review articles and case reports, only 27 articles were chosen. Only 23 articles fit the criteria. For the assessment of the risk factors and the variables the statistical analysis was done keeping  $p < 0.05$  as significant.

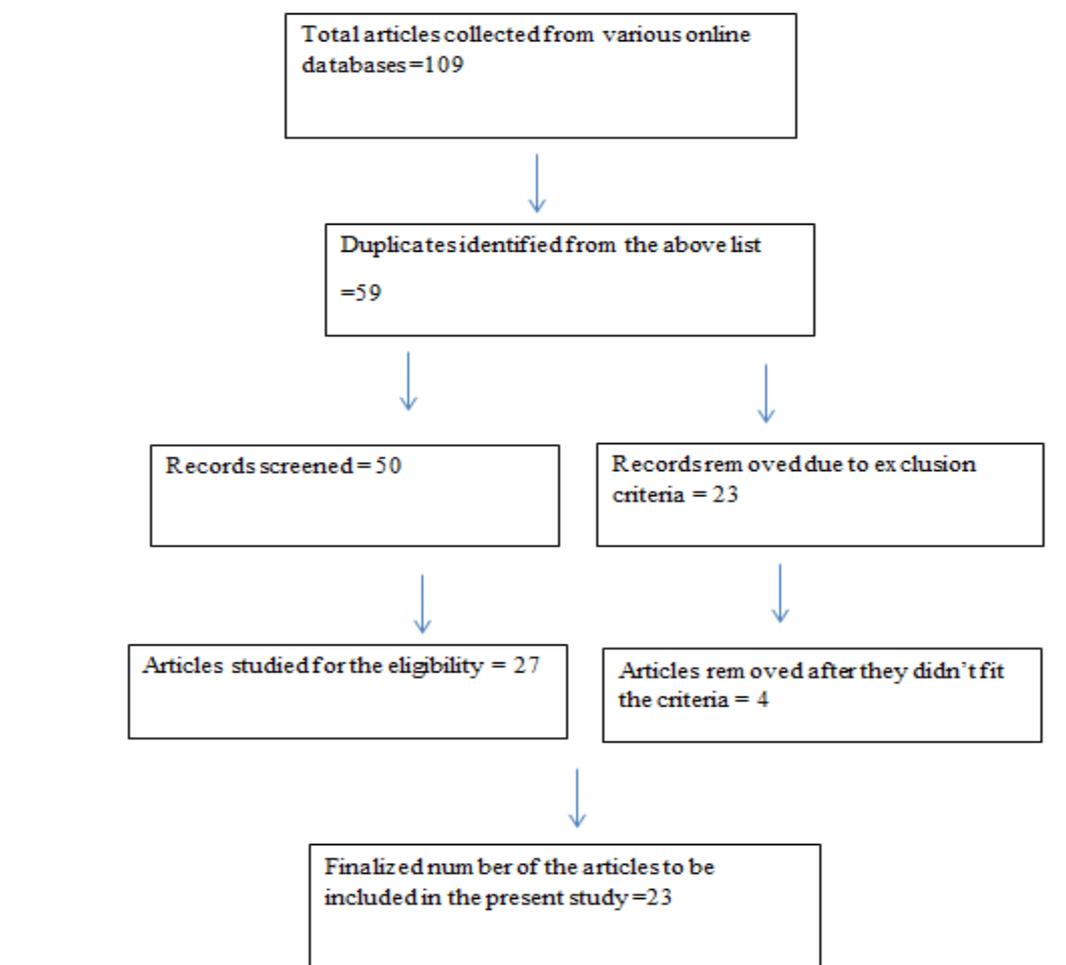
## RESULTS

Ten studies were from the USA in our study. The cohort size ranged from 3 to 819 in young individuals. No proper definition was established for the term “young.” The selected cohort of younger age group was varied: individuals considered young were those aged  $\leq 30$  years (25%) [Table 1].[7-13]

Thirteen articles had subjects with  $< 40$  years as the younger group (64%) [Table 2].[3,4,6,14-23] Three articles had subjects with  $< 45$  years (13%) as the young group [Table 3].[24-26] almost equal distribution of the genders was seen.

Only 15 studies showed less association ( $< 50\%$ ) between tobacco and TSCC[4,6-10,13,16-18,21-25] Comparison of TSCC within the different age group of younger patients exhibited statistically significant differences. The present study showed male predominance in the younger age group ( $P < 0.01$ ). The data also expressed the fact that more than 50% of the patients were nonsmokers and nondrinkers within the younger age group. Habitual tobacco use is statistically not significant within the younger group ( $P > 0.05$ ). There is statistical significance in alcohol use within the younger group ( $P < 0.01$ ) [Table 4]. Comparison of habitual usage of tobacco is statistically significant within the older age groups ( $P < 0.01$ ).

**Figure 1:** Flowchart showing the selection of the articles.



**Table 1: Evaluation of TSCC among younger age group  $\leq 30$  years.**

Authors	Country	Total cases	Young cases, <i>n</i> (%)	Male/female	Tobacco/alcohol, <i>n</i> (%)
1. Venables and Craft[8]	Brazil	819	13 (2)	4/9	2/0 (15)
2. Byers[9]	USA	418	11 (3)	7/4	0
3. Newman <i>et al.</i> [10]	USA	13	13 (100)	7/6	5/4 (38/31)
4. Sankaranarayanan <i>et al.</i> [7]	India	307	22 (7)	10/12	5/2 (23/9)
5. Oliver <i>et al.</i> [11]	UK	3	3 (100)	1/2	2/1 (67/67)
6. Mallet <i>et al.</i> [12]	France	52	52 (100)	34/18	33/15 (63/28)
7. Morris <i>et al.</i> [13]	USA	50	10 (20)	2/8	1/2 (10/20)

**Table 2: Evaluation of TSCC among younger age group  $\leq 40$  years**

Authors	Country	Total cases	Young cases, <i>n</i> (%)	Male/female	Tobacco/alcohol, <i>n</i> (%)
8. Jones <i>et al.</i> [14]	Canada	121	11 (9)	4/7	6/1 (55/9)
9. Sarkaria and Harari.[15]	USA	14	6 (43)	5/1	4/0 (67)
10. Atula <i>et al.</i> [16]	Finland	34	34 (100)	22/11	15/18 (44/53)
11. Friedlander <i>et al.</i> [17]	USA	72	36 (50)	20/16	15/22 (42/61)
12. Myers <i>et al.</i> [4]	USA	64	64 (100)	37/27	26/35 (41/55)
13. Vargas <i>et al.</i> [18]	USA	34	17 (50)	0/17	3/0 (18)
14. Hyam <i>et al.</i> [19]	Australia	129	15 (12)	9/6	8/6 (53/40)
15. Siriwardena.[6]	Srilanka	30	23 (77)-		7/0 (30)
16. Liao <i>et al.</i> [20]	Taiwan	296	76 (26)	71/5	70/44 (92/58)
17. Harris <i>et al.</i> [21]	USA	25	25 (100)	10/15	12/0 (48)
18. Fang <i>et al.</i> [22]	China	176	15 (8)	6/9	5/2 (33/13)
19. Qahtani <i>et al.</i> [23]	KSA	61	8 (13)	6/2	1/3 (13/38)
20. Jeon <i>et al.</i>	Korea	117	23 (20)	15/8	12/11 (52/48)

al.[3]					
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**Table 3: Evaluation of TSCC among younger age group  $\leq 45$  years**

Authors	Country	Total cases	Young cases, n (%)	Male/female	Tobacco/alcohol, n (%)
21. Danieli S <i>et al.</i> [24]	USA	87	30 (34)	22/8	12/0 (40)
22. Park <i>et al.</i> [25]	Korea	85	23 (27)	11/12	5/6 (22/26)
23. Goepfert <i>et al.</i> [26]	USA	54	18 (33)	0/18	9/3 (50/17)

**Table 4: Comparison of tongue carcinoma within the younger age group**

VARIABLES	PERCENTAGE	$\chi^2$	P
<b>AGE (years)</b>		368.91**	$P < 0.01$ **
$\leq 30$	124 (23)		
$\leq 40$	353 (64)		
$\leq 45$			
<b>SEX</b>		25.66**	$P < 0.01$ **
Male	303		
Female	221		
Unknown	24		
<b>TOBACCO</b>		3.74	NS
Users	258		
Nonusers	290		
<b>ALCOHOL</b>		143.08**	$P < 0.01$ **
Users	175		
Nonusers	373		

## DISCUSSION

The tongue is the common affected area in younger groups.[4-7,38-41] Funk *et al.* stated that of all head and neck SCC, 76% were seen in tongue that occurred in patients  $< 35$  years old.[2,5,6] In India, TSCC incidence happens at 40 and 45 years of age.[4,3]

Our review presented that the prevalence of TSCC is statistically significant in both the different sets of the younger group and older groups ( $P < 0.01$ ). Some authors have tried to assess the differences and factors for etiology of TSCC, by comparing them with those in older patients.[3,6,7,19,20,22-26] The predominance of the male sex is found in thirteen of the published studies with  $P < 0.01$ . [3,4,6,9,10,12,15-17,19,20,23,24] The present report displayed the statistical significance in male gender predilection within the younger group ( $P$

< 0.01).contrary to OSCC in TSCC women predilection was seen in this review.[7,8,11,13,14,21,22,25] Bektas-Kayhan et al. reported ~80 % of patients were <40 years.

Passive smoking may be the cause for increasing cancer incidence in female patients. These variances highlight the value of documenting the history of environmental smoke exposure. Site commonly seen on tongue was lateral border.

Tobacco and alcohol consumption were the main causative factors for OSCC among older adults.[30] In our review also majority of patients, i.e., ~70% were tobacco users and ~36% of patients were alcohol users. Only four reported studies had conveyed that the traditional risk factors could be the causative factor for TSCC in the young group too.[12,15,20,52]

Our study shows a lesser association of alcohol use, i.e., 32% within the younger groups, and it is statistically significant within the younger groups ( $P < 0.01$ ). Few other reported studies had found that there is a positive association of chewing tobacco use with early-onset TSCC.[20,53]

Oral submucous fibrosis(OSF) is associated with betel quid and areca nut chewing, mostly prevalent in the population of South East Asia. Nevertheless, there are other reports which claim that the etiological factors for TSCC in young are different from those responsible for OSCC in the older group.[3,7,9,14,23] Myers et al.'s and Newman et al.'s study stated that nearly half of their patients were nonsmokers and non drinkers.[4,10]

Preponderance of the reports conveyed that TSCC in young patients was not related with the use of tobacco or alcohol.[4,6-10,13,16-18,21-25,61] Several of the latest reports revealed that more than 80% of the patients with lingual carcinoma aged below 35 years had no evidence of any common risk factors.[7,23] Morris et al.'s study presented about 70% of patients did not report to have any habit history.[13] In our study Habitual tobacco use is statistically not significant within the younger group ( $P > 0.05$ ). Since there is less association with traditional risk factors, TSCC in the younger group might be considered as different entity from the older population.

There is also increasing incidence reported in female patients who did not practice any habit in the young group compared with the old age group.[6,13,18,21,22] Morris et al. pointed that previous history of the Fanconi's anemia should also be taken as a known risk factor for TSCC in young adults.[13]

Hirota et al.'s study predicted the high rate, i.e., 84.6% of positive family history for cancer in these younger group patients (compared to 29.6% in older group patients) at a significant level.[5] It is also meaningful to note the recent history of therapeutic procedures endured by the patients. Some of the factors such as viruses,[72] dental status,[72,76,77] occupation and environmental exposure,[78] dietary factors,[31] iron deficiency[79] and immunodeficiency[80] may be cofactors in the etiology. Hence, it is still not possible to reveal the etiology of oral cancer in younger adults, and it remains uncertain. One of the main factors which is influencing the different study outcome may be the selected young age cutoff range varies from 30 to 45 years. Due to these reasons, investigators have started examining for the discrete mutations linked with the disease in young patients to find the little alterations at the genetic level between these groups.

## CONCLUSION

Prognosis of younger and older group carcinomas is bound to differ since etiology is likely dissimilar for these cases. Therefore, complete documentation of the habits along with other risk factors exposure is mandatory. Further investigations with multicentric approaches are required to identify etiology, biological behavior and the molecular mechanisms by which young patients, despite the absence of risk factors, go on to develop tongue cancers have to be emphasized.

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## REFERENCES

1. Lee CY, Hirata KY. Squamous cell carcinoma of the tongue in a 21-year old female: A case report with review of the literature. *Int J Dent Oral Health* 2016;3:3.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009;45:309-16.
3. Jeon JH, Kim MG, Park JY, Lee JH, Kim MJ, Myoung H, *et al.* Analysis of the outcome of young age tongue squamous cell carcinoma. *Maxillofac Plast Reconstr Surg* 2017;39:41.
4. Myers JN, Elkins T, Roberts D, Byers RM. Squamous cell carcinoma of the tongue in young adults: Increasing incidence and factors that predict treatment outcomes. *Otolaryngol Head Neck Surg* 2000;122:44-51.
5. Hirota SK, Braga FP, Penha SS, Sugaya NN, Migliari DA. Risk factors for oral squamous cell carcinoma in young and older Brazilian patients: A comparative analysis. *Med Oral Patol Oral Cir Bucal* 2008;13:E227-31.
6. Siriwardena BS, Tilakaratne A, Amaratunga EA, Tilakaratne WM. Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka. *Oral Oncol* 2006;42:831-6.
7. Sankaranarayanan R, Duffy SW, Day NE, Nair MK, Padmakumary G. A case-control investigation of cancer of the oral tongue and the floor of the mouth in Southern India. *Int J Cancer* 1989;44:617-21.
8. Venables CW, Craft IL. Carcinoma of the tongue in early adult life. *Br J Cancer* 1967;21:645-50.
9. Byers RM. Squamous cell carcinoma of the oral tongue in patients less than thirty years of age. *Am J Surg* 1975;130:475-8.
10. Newman AN, Rice DH, Ossoff RH, Sisson GA. Carcinoma of the tongue in persons younger than 30 years of age. *Arch Otolaryngol* 1983;109:302-4.
11. Oliver RJ, Dearing J, Hindle I. Oral cancer in young adults: Report of three cases and review of the literature. *Br Dent J* 2000;188:362-5.
12. Mallet Y, Avalos N, Le Ridant AM, Gangloff P, Moriniere S, Rame JP, *et al.* Head and neck cancer in young people: A series of 52 SCCs of the oral tongue in patients aged 35 years or less. *Acta Otolaryngol* 2009;129:1503-8.

13. Morris LG, Patel SG, Shah JP, Ganly I. Squamous cell carcinoma of the oral tongue in the pediatric age group: A matched-pair analysis of survival. *Arch Otolaryngol Head Neck Surg* 2010;136:697-701.
14. Jones JB, Lampe HB, Cheung HW. Carcinoma of the tongue in young patients. *J Otolaryngol* 1989;18:105-8.
15. Sarkaria JN, Harari PM. Oral tongue cancer in young adults less than 40 years of age: Rationale for aggressive therapy. *Head Neck* 1994;16:107-11.
16. Atula S, Grénman R, Laippala P, Syrjänen S. Cancer of the tongue in patients younger than 40 years. A distinct entity? *Arch Otolaryngol Head Neck Surg* 1996;122:1313-9.
17. Friedlander PL, Schantz SP, Shaha AR, Yu G, Shah JP. Squamous cell carcinoma of the tongue in young patients: A matched-pair analysis. *Head Neck* 1998;20:363-8.
18. Vargas H, Pitman KT, Johnson JT, Galati LT. More aggressive behavior of squamous cell carcinoma of the anterior tongue in young women. *Laryngoscope* 2000;110:1623-6.
19. Hyam DM, Conway RC, Sathiyaseelan Y, Gebiski V, Morgan GJ, Walker DM, *et al.* Tongue cancer: Do patients younger than 40 do worse? *Aust Dent J* 2003;48:50-4.
20. Liao CT, Wang HM, Hsieh LL, Chang JT, Ng SH, Hsueh C, *et al.* Higher distant failure in young age tongue cancer patients. *Oral Oncol* 2006;42:718-25.
21. Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. *Head Neck* 2011;33:1622-7.
22. Fang QG, Shi S, Liu FY, Sun CF. Tongue squamous cell carcinoma as a possible distinct entity in patients under 40 years old. *Oncol Lett* 2014;7:2099-102.
23. Qahtani KA, Brousseau V, Islam T. Prognosis of patients less than 40 years age with squamous cell cancer of oral tongue. *Int J Head Neck Surg* 2015;6:53-6.
24. Siegelmann-Danieli N, Hanlon A, Ridge JA, Padmore R, Fein DA, Langer CJ. Oral tongue cancer in patients less than 45 years old: Institutional experience and comparison with older patients. *J Clin Oncol* 1998;16:745-53.
25. Park JO, Sun DI, Cho KJ, Joo YH, Yoo HJ, Kim MS. Clinical outcome of squamous cell carcinoma of the tongue in young patients: A stage-matched comparative analysis. *Clin Exp Otorhinolaryngol* 2010;3:161-5.
26. Goepfert RP, Kezirian EJ, Wang SJ. Oral tongue squamous cell carcinoma in young women: A matched comparison-do outcome justifies treatment intensity? *ISRN Otolaryngol* 2014;2014:6.
27. Sharma D, Singh G. Squamous cell carcinoma of the oral cavity and oropharynx in young adults. *Indian J Cancer* 2016;53:399-401.
28. van Monsjou HS, Wreesmann VB, van den Brekel MW, Balm AJ. Head and neck squamous cell carcinoma in young patients. *Oral Oncol* 2013;49:1097-102.
29. Annertz K, Anderson H, Björklund A, Möller T, Kantola S, Mork J, *et al.* Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. *Int J Cancer* 2002;101:95-9.
30. Chen JK, Eisenberg E, Krutchkoff DJ, Katz RV. Changing trends in oral cancer in the United States, 1935 to 1985: A connecticut study. *J Oral Maxillofac Surg* 1991;49:1152-8.