

# Prevalence of malignant melanoma in anatomical sites of the oral cavity: A meta-analysis

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## Abstract

Oral malignant melanoma (OMM) is a very rare disease entity accounting <1% of all other melanomas. Till date, no comprehensive meta-analysis has been conducted regarding the prevalence of malignant melanoma in the oral cavity. Therefore, the present meta-analysis was conducted to update on the prevalence of malignant melanoma in anatomical sites of the oral cavity. Literature search was performed to congregate reports of last 10 years using databases, such as PubMed and ScienceDirect. The search strings used were "palate," "buccal," "gingiva," "gum," "maxillary," "mandibular," "lip," "tongue," "melanoma," "oral melanoma," "malignant melanoma," "prognosis," "risk factors," "noncutaneous" and "diagnosis" of OMM by combining terms using the Boolean operators. MedCalc 16.4.3 software was used for the analysis. "Random effects model" was used in the analysis due to significant heterogeneity in the studies. Proportion method was used to analyze the prevalence. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to report the analysis. Out of 130 studies screened, 19 were included in the meta-analysis and a total of 1323 patients were included. The median age of the patients was found to be  $61.87 \pm 7.78$  years (confidence interval 53.8–67 years). All the screened studies showed significant heterogeneity in gender as well as tumor sites ( $P < 0.0001$ ). Palate (34.29%) was the most commonly affected site in OMM patients. Overall, the results of the meta-analysis suggest that palate is the most prevalent site in OMM. Furthermore, OMM is high in patients between the fifth and sixth decade of life with a male predominance.

**Keywords:** Gingiva, meta-analysis, oral malignant melanoma, oral mucosa, palate, proportion, tumor

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## INTRODUCTION

Melanoma is a highly aggressive tumor of melanin-producing cells called melanocytes derived from the neural crest cells in the basal layer of the epithelium.<sup>[1]</sup> It predominantly occurs in cutaneous surfaces and rarely in the ocular ball and mucosal

surfaces.<sup>[2]</sup> Oral malignant melanoma (OMM) is a highly rare malignancy accounting for only 0.5% of all oral malignancies and <1% of all other melanomas.<sup>[1,3]</sup>

OMM is usually asymptomatic in the early stages. Pain, bleeding and ulceration occur at advanced stages of

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### Age

The weighed median age of the patients in the screened studies was  $61.87 \pm 7.78$  years (CI 53.8–67 years). Out of 19 studies assessed, the median age of OMM patients in six studies was above the calculated age and the remaining 13 studies reported below the calculated age.

### Anatomical sites

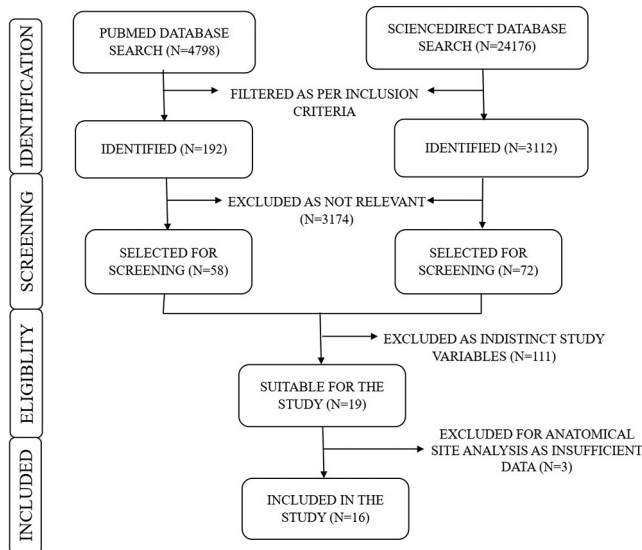
Of the 19 screened studies, three studies were excluded from the analysis due to unspecified tumor site. Therefore, only 16 studies comprising of 1277 patients were included in the meta-analysis regarding the tumor site. All the screened studies reported significant heterogeneity ( $P < 0.0001$ ) in the primary tumor sites (palate, gingiva, buccal mucosa, tongue, mandible gum, maxillary gum and lips). Palate (34.29% with CI 24.54%–44.75%) was the most commonly

affected site in OMM patients [Figure 2]. The other affected sites included the gingiva (8.88% with CI 1.73%–20.76%), buccal mucosa (4.38% with CI 1.91%–7.79%), tongue melanoma (2.30% with 0.92%–4.28%), maxillary gum melanoma (7.06% with CI 2.17%–14.46%), mandibular gum melanoma (3.63% with CI 1.00%–7.81%) and lips [1.50% with CI 0.44%–3.17%; Figures 3-5].

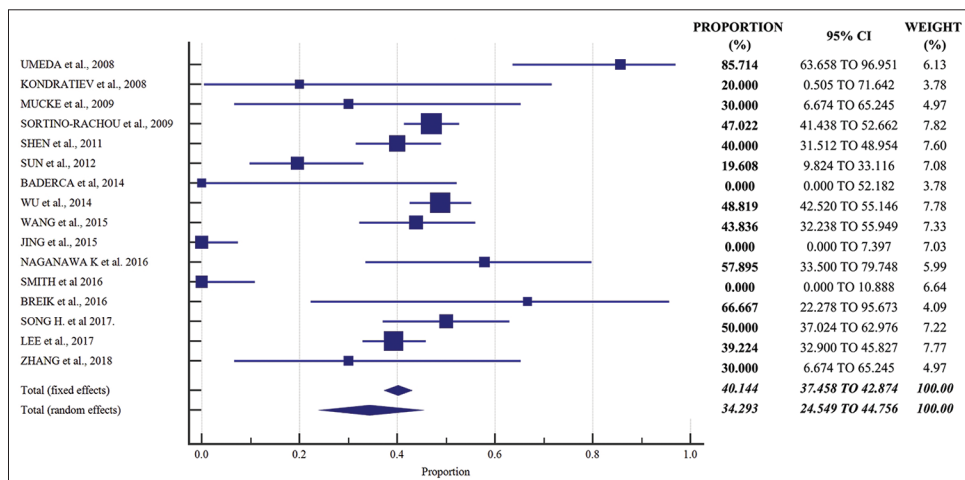
### DISCUSSION

OMM is a very rare disease entity. Age, gender, race, tumor site, stage of disease and treatment are different factors that influence the survival of OMM patients.<sup>[14]</sup> OMM has been stable from past 25 years, hence, the present study intended to update the recent prevalence. Moreover, this is the first study of its kind assimilating and analysing all the prominent anatomical sites that are prone to OMM. The update of the recent prevalence also lay down recommendations for future research. Therefore, through detailed meta-analysis on the latest literature, we assimilated and provided the prevalence of malignant melanoma in different anatomical sites of the oral cavity. In addition to tumor site, we also focused on the prevalence of OMM in both age and gender.

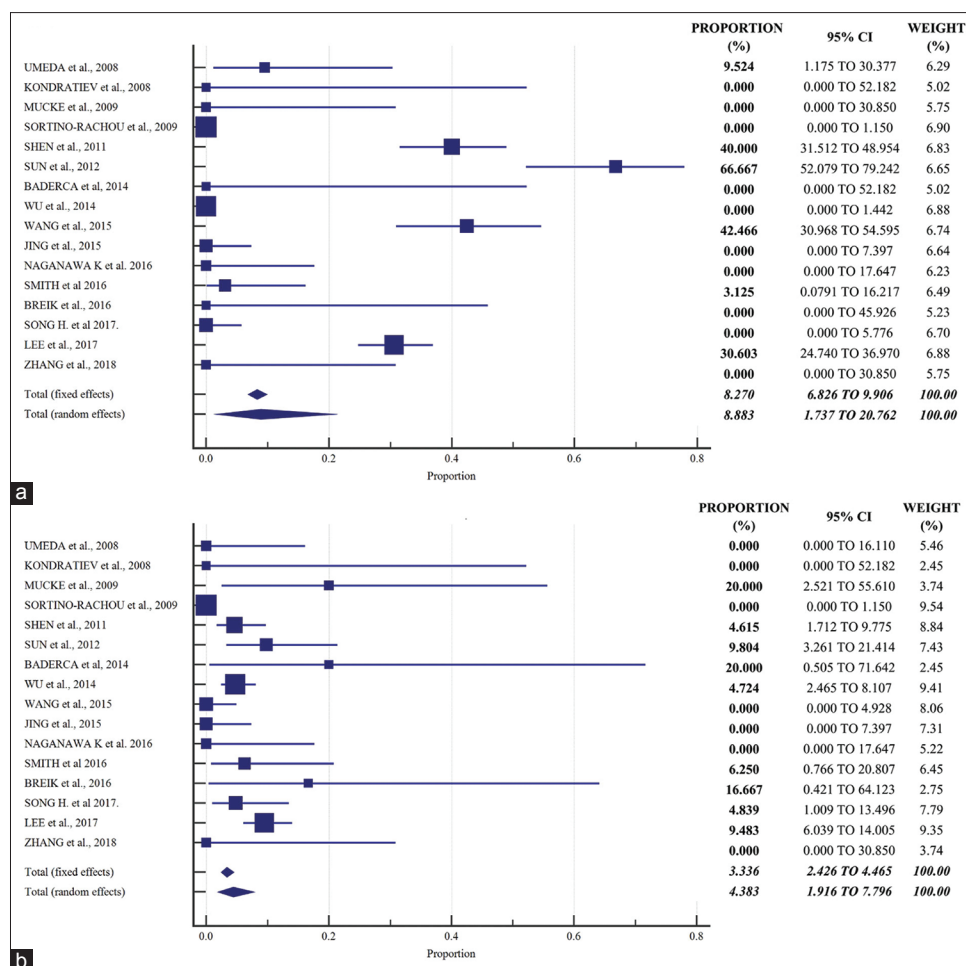
Literature has reported a higher prevalence of OMM among men. Similarly, our meta-analysis also revealed the male to female ratio of 1:0.78. Male prevalence (33.33%) was lowest in a study conducted by Umeda *et al.*<sup>[15]</sup> with a sample size of 21; whereas, Baderca *et al.*<sup>[16]</sup> reported highest prevalence (80%) with a sample size of five. Sortino-Rachou *et al.*<sup>[17]</sup> reported highest male (54.54%) and female (45.45%) prevalence with a sample size of 319. In contrast, Smith *et al.* (62.50%)<sup>[13]</sup> and Umeda *et al.* (66.66%)<sup>[15]</sup> reported a high prevalence of OMM in women. Moreover, in a study by Kim *et al.*,<sup>[18]</sup> sex predilection was not observed



**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the total number of included studies



**Figure 2:** Forest plot for the prevalence of palate melanoma

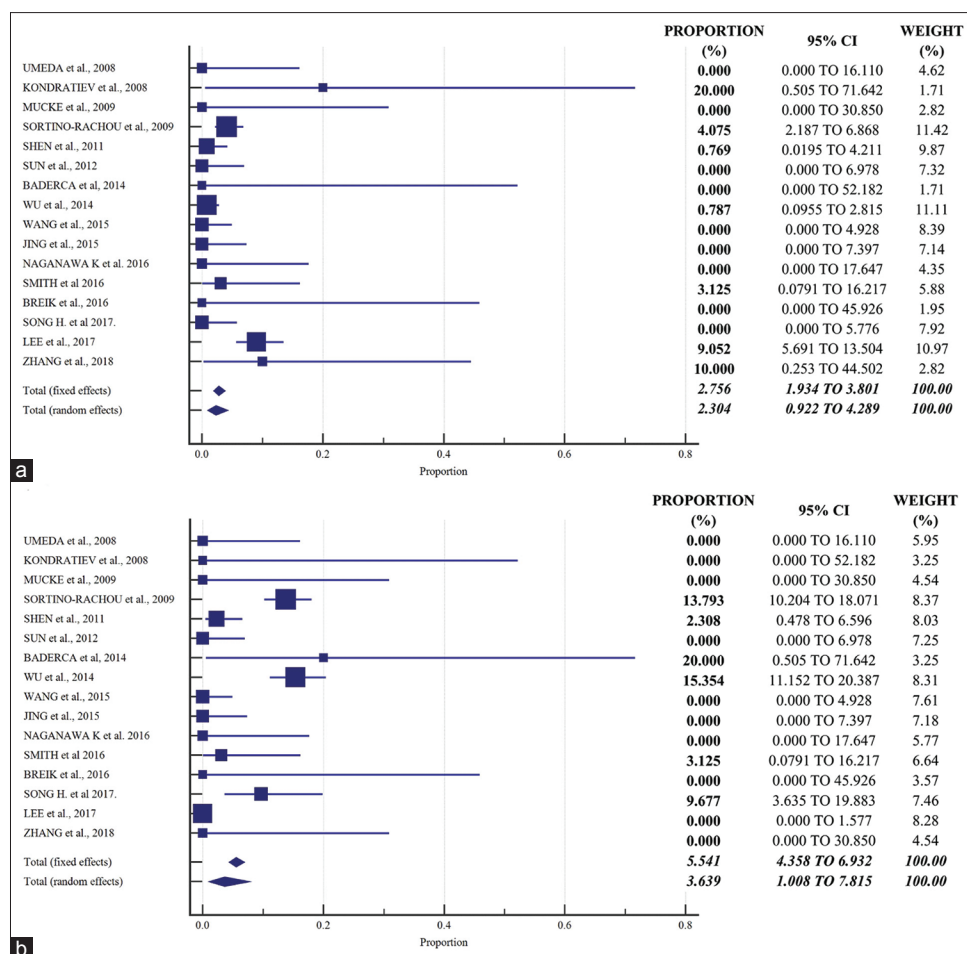


**Figure 3:** Forest plot for the prevalence of (a) gingival and (b) buccal melanoma

in OMM patients. The probable reason for the higher prevalence of OMM in males might be due to alcohol and tobacco consumption and smoking. However, there is a lack of literature to support this observation. Therefore, the exact cause for gender disparity is still to be explored in future studies. Furthermore, studies should also focus on correlation between habits (smoking and alcohol consumption) and OMM.

Age is considered as the prognostic indicator for OMM. Similarly, our meta-analysis also reported an age range of 50–70 years. Highest (73 years) and lowest (51.5 years) median ages were observed in two different studies conducted by Baderca *et al.*<sup>[16]</sup> (with a sample size of five) and Wang *et al.*,<sup>[14]</sup> respectively. However, the median age of the patients in all the studies was in-between 50 and 75 years. Late clinical manifestations, slow progression of the disease and patients with the history of radiation or chemotherapy for other carcinomas are the probable reasons for late diagnosis and high incidence of OMM in advancing age.<sup>[3,19]</sup> However, few studies showed the prevalence of OMM both in children as well as in young adults.<sup>[7,13,20,21]</sup>

The anatomical sites affected with OMM were observed to be palate, gingiva, buccal mucosa, tongue, mandible and maxillary gum and lips in our meta-analysis. Most of the studies screened in our meta-analysis reported palate as the commonly affected tumor site in OMM patients. The highest prevalence of palate melanoma was observed in a study by Umeda *et al.*,<sup>[15]</sup> wherein 21 patients were included. It was reported that anterior regions of the mouth were extensively pigmented than the posterior regions; therefore, buccal/labial regions are intensely pigmented than the palatal/lingual surfaces.<sup>[22]</sup> Nevertheless, literature has reported that palate was the most common site involved in OMM with an overall prevalence of 32%–40%.<sup>[1]</sup> Similarly, our meta-analysis reported palate melanoma in 34.29% patients. In contrast, few studies reported gingiva as the most commonly affected tumor site in OMM patients.<sup>[6,23]</sup> In our analysis, the highest prevalence of gingival melanoma was observed in a study by Sun *et al.*,<sup>[23]</sup> who included 51 patients. However, the overall prevalence of patients with gingival melanoma (8.88%) was less than that reported in the literature, i.e., 16%.<sup>[1]</sup>



**Figure 4:** Forest plot for the prevalence of (a) tongue and (b) mandibular gum melanoma

Other than palate and gingiva, mandible, maxilla, tongue and buccal mucosa are the most prominent sites for metastatic melanoma;<sup>[24]</sup> however, the prevalence of patients presenting with malignant melanoma in these sites is low in our analysis. In our meta-analysis, the overall prevalence of patients with buccal mucosal melanoma (4.38%) was less than that reported in the literature, i.e., 7%.<sup>[1]</sup> The exact prevalence of patients with maxillary gum melanoma, mandibular melanoma and tongue melanoma was not specified in the literature. In our meta-analysis, overall prevalence of tongue melanoma, maxillary gum melanoma and mandibular gum melanoma was 2.30%, 7.06% and 3.63%, respectively.

Literature has reported that lip was the least possible site for the incidence of OMM.<sup>[21]</sup> Similarly, in our meta-analysis, the overall prevalence of patients with lip melanoma was very less (1.50%) than reported in the literature, i.e., 7%.<sup>[1]</sup> The least incidence of melanoma in the lip region might be due to the absence of melanocytes.<sup>[25]</sup> Whereas, a study conducted by Jing *et al.*<sup>[21]</sup> was exclusively on the melanoma in subregions of

the lip. Over the period of 20 years, i.e., 1992–2013, only 48 cases of lip melanoma were recorded, which indicates the rarity of lip melanoma.

Anatomical site is another prognostic indicator, which correlates significantly with the overall survival rate of OMM patients. A study conducted by Wang *et al.*<sup>[14]</sup> reported that the overall median survival rate among OMM patients with different tumor sites were 51, 40 and 43 months for gingiva, hard palate and other sites, respectively. The higher survival rate in gingiva-affected OMM patients might be due to its easy prognosis.

The current meta-analysis has few potential limitations that need to be considered in the future analyses. First, free full-text articles restricted to only English language were screened for the analysis. Second, a subgroup analysis of anatomical sites was not performed as it was not mentioned in all the studies. Third, analysis was not done regarding symptoms, etiological factors, treatment and therapy standards as the data were not available/clear in the screened studies. Fourth, most of the screened studies

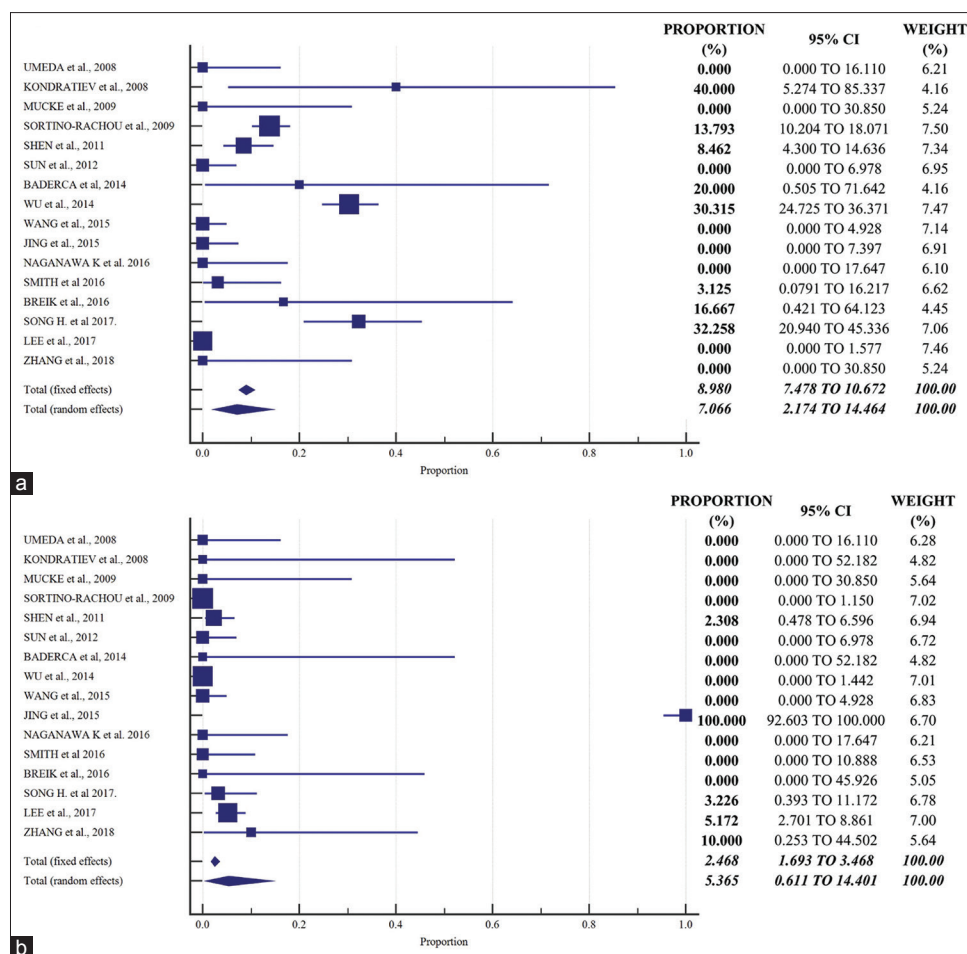


Figure 5: Forest plot for the prevalence of (a) maxillary gum and (b) lip melanoma

were from China and few were conducted in Japan and the United States of America; hence, this might produce selection bias. Despite these limitations, the current meta-analysis is the first study of its kind that determined the prevalence of malignant melanoma with respect to age, gender and tumor sites.

Till date, etiological/risk factors involved in the development of OMM has not been identified. Genetic studies revealed that either carcinogenic factors or other irritants have not shown any influence on the pathogenesis of OMM. Therefore, in the future, studies need to be conducted to identify risk factors that cause OMM. However, few studies have reported that BRAF mutation/expression was involved in the pathogenesis of OMM.<sup>[26,27]</sup> Therefore, further research is desired in gene mutations for molecular classification of OMM. This, in turn, aids in the better prognosis of the disease in the early stages.<sup>[16]</sup> Furthermore, research needs to determine the biological factors that influence the treatment of OMM to improve overall survival of OMM patients.<sup>[2]</sup>

## CONCLUSION

Our meta-analysis has reassessed and reported that palate is the most prevalent site in OMM patients in advancing age with male predominance. Our analysis has not focused on gene alterations, targeted therapies and survival rate. Therefore, this analysis may open the door for further research to determine other prognostic indicators, gene mutations and biomarkers and evaluate the risk factors involved in the development of OMM.

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## Conflicts of interest

There are no conflicts of interest.

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