Association of non-tobacco products (NTP) with oral cancer, oesophageal cancer, pharyngeal cancer, and oral potentially malignant disorders (OPMD) in adults - A Systematic review and Meta-analysis.

Contents of the supplementary material

Contents

1. Definitions used in the review

Various cancers included in our review: The ICD codes of various cancers included are as follows: C00-C06 (Oral cavity), C10-C14 (Pharynx) and C15 (Esophagus)

lip and oral cavity cancers: It is a disease in which malignant (cancer) cells form in the lips or mouth.

Potentially malignant disorders (PMD): Oral potentially malignant disorders (OPMDs) are conditions that precede the onset of invasive cancers of the oral cavity which includes Leukoplakia, erythroplakia, Proliferative Verrucous Leukoplakia, Erythroplakia, Erythroleukoplakia, Oral Lichen Planus, Oral Lichenoid Lesions, Oral Sub Mucous Fibrosis, palatal lesions.

The operational definition of betel quid for the study was - a 'betel quid' (synonymous with 'pan' or 'paan') generally contains betel leaf, areca nut and slaked lime, and may contain tobacco. [10] Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard, or sweeteners, are added according to local preferences.

2. Search strategy

2a. Study selection criteria

- Inclusion criteria:
  - Language: Articles in English language.
  - Year of publication: Studies published up to December 2023.
  - Data type: Primary research or secondary data analysis of the available data.
  - Study design: Observational as well as experimental studies
  - Study setting:
  - Study population: Studies focused on oral cavity and lip cancer, esophageal, pharyngeal cancer and OPMDs.
  - Study exposure: Studies that report on usage of betel quid without tobacco as risk factor for oral cancer.
  - Study comparator: Studies that report on non-usage of betel quid without tobacco as risk factor for oral cancer.
  - Outcomes: Odds ratio, Relative risk, and Relative risk ratio
  - In case of duplicate data or articles based on same study population, article providing the largest sample and most complete appropriate data will be included.

- Exclusion criteria:
  - Studies: Study design/Other: Conference abstracts, editorials, letters, opinion papers, unpublished studies, same studies published in different journals with the same or a different title.

2b. Keywords for search.

Table S 1. 1Keyword used for PubMed search.

BLOCKS		Results
1(A)	**Cancers of oral cavity, esophagus, and pharynx** 1. Mouth neoplasms [MeSH Terms] OR "oral cavity cancer" [tw] OR "oral cavity carcinoma" [tw] 2. Esophageal neoplasm [MeSH Terms] OR "esophagus cancer" [tw] 3. Pharyngeal neoplasm [MeSH Terms] OR "pharynx cancer" [tw] 4. squamous cell carcinoma of head and neck [MeSH Terms] OR "oral squamous cell carcinoma" [tw] 5. lip neoplasms [MeSH Terms] OR "carcinoma lip" [tw] 6. tongue neoplasms [MeSH Terms] OR "carcinoma tongue" [tw] 7. gingival neoplasms [MeSH Terms] OR "carcinoma gingival" [tw] 8. palatal neoplasms [MeSH Terms] OR "carcinoma palate" [tw] 9. neoplasm, oropharyngeal [MeSH Terms] OR "oropharyngeal cancer" [tw] 10. pharyngeal neoplasms/etiology [MeSH Terms] 11. pharyngeal neoplasms/epidemiology [MeSH] 12. Mouth neoplasm/etiology [MeSH] 13. Esophageal neoplasms/etiology [MeSH Terms] 14. Esophageal neoplasm/epidemiology [Mesh Terms]	**176,106**

1(B)	**Oral precancerous lesions** 1. Leukoplakia [MeSH Terms] 2. Condition, precancerous [MeSH Terms] 3. "Erythroplakia" [tw] 4. Erythroleukoplakia [tw] 5. "Speckled leukoplakia" [tw] 6. "Oral sub-mucous fibrosis"	**63,622**
2	**Exposure to non-tobacco products** 1. Areca [MeSH Terms] OR "Betel quid" [tw] "Betel quid NOT tobacco" [tw] OR "areca nut NOT tobacco" [tw] OR "Pan masala NOT tobacco" [tw] OR "betel quid chewing" [tw] OR "areca nut chewing" [tw] OR "pan masala chewing" [Tw] OR "Betel quid chewing habit" [tw] 2. Nontobacco products [tw] 3. tobacco, smokeless [MeSH Terms] 4. Paan NOT tobacco [tw] 5. Habits [MeSH Terms] 6. Mastication [MeSH Terms]	**30,078**

2c. Search results

Table S1. 2PubMed search results

Blocks		Results
1	(((Leukoplakia, oral[MeSH Terms]) OR (condition, precancerous[MeSH Terms])) OR (oral submucous fibrosis[MeSH Terms])) AND (((((((areca[MeSH Terms]) OR (betel nut[MeSH Terms])) OR (" betel quid"[Text Word])) OR (" pan masala chewing"[Text Word])) OR (" non tobacco products"[Text Word])) OR ((Paan[Text Word]) NOT (Tobacco[Text Word]))) OR ((Pan masala[Text Word]) NOT (Tobacco[Text Word]))) Filters: from 2013/1/1 - 2022/7/31 ((((((((((((((((((((mouth neoplasms[MeSH Terms]) OR (esophageal neoplasm[MeSH Terms])) OR (pharyngeal neoplasms[MeSH Terms])) OR (squamous cell carcinoma of head and neck[MeSH Terms])) OR (lip neoplasms[MeSH Terms])) OR (tongue neoplasms[MeSH Terms])) OR (gingival neoplasms[MeSH Terms])) OR (palatal neoplasms[MeSH Terms])) OR (neoplasm, oropharyngeal[MeSH Terms])) OR (pharyngeal neoplasms/etiology[MeSH Terms])) OR (pharyngeal neoplasms/epidemiology[MeSH Terms])) OR (Mouth neoplasm/etiology[MeSH Terms])) OR (Esophageal neoplasm/epidemiology[MeSH Terms])) OR ("oral cavity cancer"[Text Word])) OR ("esophagus cancer"[Text Word])) OR ("pharynx cancer"[Text Word])) OR ("oral squamous cell carcinoma"[Text Word])) OR ("oropharyngeal cancer"[Text Word])) OR ("carcinoma lip"[Text Word])) OR ("carcinoma tongue"[Text Word])) OR ("carcinoma gingival"[Text Word])) AND ((((((((((areca[MeSH Terms]) OR (betel nut[MeSH Terms])) OR ("betel quid"[Text Word])) OR (" pan masala chewing"[Text Word])) OR ("non tobacco products"[Text Word])) OR (("Betel quid "[Text Word]) NOT (tobacco[Text Word]))) OR (("areca nut"[Text Word]) NOT (tobacco[Text Word]))) OR (" areca nut chewing"[Text Word])) OR ("pan masala chewing"[Text Word])) OR (habits[MeSH Terms])) OR (mastication[MeSH Terms])) OR ((Paan[Text Word]) NOT (tobacco[Text Word]))) Filters: till – Dec 31/12/2023	2179
	Total: 2179 Results	

2d. Keywords used for Embase search.

Table S1. 3Keywords used for Embase search with results.

Blocks	
1	‘‘Mouth cancer'/exp OR 'lip carcinoma'/exp OR 'tongue carcinoma'/exp OR 'gingiva tumor'/exp OR 'pharynx tumor'/exp OR ' esophagus tumor'/exp OR ' palatal tumor'/exp OR 'oropharynx tumor'/exp
2	'Smokeless tobacco'/exp OR 'areca'/exp OR ‘betel’/exp OR 'betel quid'/exp OR 'nontobacco products'/exp OR 'paan’ /exp OR ‘pan masala’/exp OR ‘mastication’/exp OR ‘habits’/exp OR ‘areca nut chewing’/exp OR ‘betel quid chewing’/exp.
	1 AND 2 1497 results

2e. Keywords used for Google Scholar search.

Table S1. 4Keywords used for Google Scholar search.

allintitle: (((Oral cancer) OR (premalignant)) AND ((Betel quit without tobacco)
Total: 138 Results

3. Characteristics of studies included in the review

Table S2.1 Characteristics of Included studies (Case-control studies)

S. No	Study ID	Study Design	Start year	End year	Country	Urban/ Rural	Population		Exposure
							Cases	Control	
1.	Chandra 1962	Case-control	N/A	N/A	N/A	N/A	N/A	N/A	Betel quid
2.	Shanta V 1962	Case-control	N/A	N/A	India	N/A	Histologically confirmed. Upper alimentary cancer (M+ F) 1) Oral cancer 2) Esophageal cancer 3) Pharyngeal cancer	Non-tumorous population matched for age, sex, and social class only.	Betel and nut
3.	Hirayama 1966	Case-control	1963	1964	India and Ceylon	N/A	Oral-cancer patients	Patients (matched by sex and age) with other diseases were used as controls.	Betel and nut
4.	Jussawalla 1971	Case-control	1968	1971	India	Urban	Histopathological proven patients of: 1) Oral cancer 2) Pharyngeal cancer 3) Esophageal cancer	Age, sex, and religion, matched controls.	Betel quid
5.	Jafarey 1976	Case-control	1967 May	1972 Dec	Pakistan	N/A	Biopsy proven cases of carcinoma of 1) Oral cavity and oro-pharynx	Age, sex, and place of birth matched controls.	Pan (betel leaf)

S. No	Study ID	Study Design	Start year	End year	Country	Urban/ Rural	Population		Exposure
6.	Nandakumar 1990	Case-control	1982	1985	India	N/A	Microscopically confirmed cases of oral cancer	Non- cancer patients.	Pan without tobacco
7.	Maher 1994	Case-control	1989	1990	Pakistan	Urban	Clinically detected cases of OPMD (Oral premalignant disorders)	All subjects attending for dental treatment at JPMC were available for potential entry to the study.	1)Pan 2)Areca
8.	Ko Yc 1995	Case-control	1992	1993	Taiwan	N/A	Histopathological proven patients of oral cancer	Non-carcinoma patients treated during the same period.	Betel quid
9.	Lu 1996	Case-control	1990	1992	Taiwan	Urban	Histopathologic ally diagnosed oral cancer patients	Non- cancer patients matched for sex, age, living in the same Li and educational background	Betel quid
10.	Shah & Sharma 1998	Case-control	N/A	N/A	India	N/A	Clinically proven OSF (OPMD) patients.	Persons belonging to similar socio-economic status, matched for age, and sex.	1) Areca Nuts/quid 2) Pan Masala
11.	Wasnik 1998	Case-control	N/A	N/A	India	Urban	Confirmed by histopathology oro-pharyngeal cancer patients	Age and sex matched with two hospital controls (One non-cancer and other having cancer of other sites)	1)Pan 2) Betel Nut
12.	Merchant 2000	Case-control	1996	1998	Pakistan	Urban	Biopsy-proven cases of oral squamous-cell carcinoma.	Pair-matched hospital controls	Pan

S. No	Study ID	Study Design	Start year	End year	Country	Urban/ Rural	Population		Exposure
13.	Dikshit 2000	Case-control	1989	1992	India	N/A	Patients of 1) Oral cancer and 2) Oro-pharyngeal cancer	Non- age matched controls	Chewers without tobacco
14.	Shiu 2000	Case-control	1998 Feb	1998 June	Taiwan	N/A	OPMD patients	Age and sex matched controls	Betel quid
15.	Kietthubthew 2001	Case-control	1998	1999	Thailand	N/A	Oral cavity cancer patients	Location matched controls	Betel quid
16.	Balaram 2002	Case-control	1996	1999	India	N/A	Oral cavity cancer patients	Frequency-matched by centre, quinquennium of age and gender	Paan without tobacco
17.	Chen 2002	Case-control	1994	1997	Taiwan	N/A	OSCC	Equal negative controls	Betel quid
18.	Lee 2003	Case-control	1994	1995	Taiwan	N/A	Histologically confirmed OPMDs.	Randomly selected controls	Betel quid
19.	Znaor 2003	Case-control	1993	1999	India	Urban	Cases of: 1) Oral 2) Pharyngeal cancer 3) Esophageal cancer male patients.	Male patients with non-tobacco-related cancers.	Chewers without tobacco
20.	Jacob 2004	Case-control	N/A	N/A	India	N/A	Histo-logically confirmed Leukoplakias (OPMDs) and clinically diagnosed other oral precancers	Subjects free of oral diseases	1) Betel quid 2) Areca nut
21.	Shiu and Chen 2004	Cohort initial then case-control	1998 Feb	1998 June	Taiwan	N/A	Patients of: 1)Oral cancer 2) OPMDs	Non-disease controls	Betel quid

S. No	Study ID	Study Design	Start year	End year	Country	Urban/ Rural	Population		Exposure
22.	Yang 2005	Case-control	N/A	N/A	Taiwan	N/A	Pathologically confirmed OPMDs	Age matched lesions free controls.	Areca quid
23.	Lee 2005	Case-control	November 2000	Dec-03	Taiwan	N/A	Pharyngeal cancer patients	Non-frequency-matched controls.	Areca/Betel quid
24.	Wu 2006	Case-control	N/A	N/A	Taiwan	Urban	Pathologically proven esophageal SCC patients	Age and sex matched controls	Betel quid
25.	Thomas 2007	Case-control	Jan-85	Jul-87	N/A	N/A	OSCC cases	Controls with no evidence of OSCC	Betel quid
26.	Thomas 2008	Nested case-control study	1992	N/A	Papua New Guinea (PNG)	N/A	OPMD cases	Controls with no evidence of OPMDs	Betel quid
27.	Chiang 2008	Case-control	N/A	N/A	Taiwan	N/A	OSCC patients	Frequency-matched with OSCCs by age.	Betel quid
28.	Muwonge 2008	Case-control	1996	2004	India	N/A	Histologically confirmed oral cancer.	Randomly selected controls	Pan without tobacco
29.	Amarasinghe 2010	Nested case-control	2006	2007	Sri Lanka	N/A	Those with OPMD: Leukoplakia, erythroplakia, OSF, LP as ‘cases.	‘‘controls” being those free of OPMD or other oral abnormalities	Betel quid
30.	Yuan 2011	Case-control	N/A	N/A	Taiwan	N/A	Clinically diagnosed oral cancer patients	Hospital controls	Betel quid
31.	Akhtar 2012	Case-control	1998	2002	Pakistan	Urban	Patients of esophageal squamous-cell carcinoma.	Age and sex matched controls.	Areca nut
32.	Madani 2012	Case-control	2005	2006	India	Urban	Oral cavity cancer patients	Hospital controls	1) Supari 2) Betel quid

S. No	Study ID	Study Design	Start year	End year	Country	Urban/ Rural	Population		Exposure
33.	Loyha 2012	Case-control	Jul-10	Apr-11	Thailand	N/A	Oral cancer patient	Non-cancerous controls	Betel quid
34.	Mahapatra 2015	Case-control	2013	2013	India	N/A	Oral cancer patient	Controls with history of no oral cancer.	Betel quid
35.	Merchant 2015	Case-control	1996	1998	Pakistan	N/A	Oral cancer patient	Controls were recruited contemporaneously with the cases.	Paan without tobacco
36.	Hu 2020	Case-control	2014	2015	China	Both rural and urban	Patients with OSCC	Age and sex matched controls	Betel quid
37.	Shih 2022	Case-control	N/A	N/A	Taiwan	N/A	Oral cancer patients	Age and sex matched controls	Betel quid
38.	Wang 2022	Case-control	2016	2018	Taiwan	Urban	Histopathologic ally confirmed Oral cancer patients	Age and sex matched controls	Betel quid
39.	Edirisinghe 2022	Case-control	2022	N/A	Sri Lanka	N/A	Histopathologic ally confirmed Oral cancer patients	Gender matched controls	Betel quid
40.	Yeh 2023	Case-control	2012	2021	Taiwan	N/A	Oral cancer patients	Cancer free controls	Betel quid

Table S2.2 Characteristics of Included studies (Cross-sectional studies)

S. No	Study ID	Study design	Start year	End year	Country	Urban/ Rural	Population	Exposure
1.	Juntanong 2016	Cross-sectional	N/A	N/A	Thailand	N/A	2,300 screening subjects were recruited over the period 1st February 2014, to 30th April 2014.	Betel nut
2.	Hernandez 2017	Cross-sectional	Jul-13	Oct-14	U. S	N/A	A convenience sample of 122 study subjects were recruited from patients between July 2013 and October 2014.	Betel nut
3.	Pahwa 2018	Cross-sectional	2015	2017	India	N/A	A total of 2033 individuals were recruited into the study	Areca nut
4.	Chuang 2019	Cross-sectional	2008	2013	Taiwan	N/A	Recruited 9275 subjects who aged≥20 years, received upper endoscopies, agreed to participate	Areca nut
5.	Rimal 2019	Cross-sectional	2012	2014	Nepal	N/A	A total of 3,200 people, consisting of 200 from each district with age range of 16-70 years.	Areca nut
6.	Chung 2005	Cross-sectional study	Sep 1998	April 1999	N/A	N/A	1075 subjects 15 years of age or older from 591 households were included.	Areca quid
7.	Yasin 2022	Cross-sectional study	2019	2021	Pakistan	Urban	100 known cases of an oral squamous cell carcinoma were included	Betel quid

Table S2.3 Characteristics of Included studies (Cohort studies)

S. No	Study ID	Study design	Start year	End year	Country	Urban/ Rural	Population	Exposure
1.	Lin JW 2011	Cohort	Mar-05	Dec-08	Taiwan	N/A	A total of 10,657 patients were enrolled in this study from March 2005 to December 2008	Betel quid
2.	Klongnoi 2022	Cohort	2019	2020	Thailand	N/A	A target population of 371,911 subjects was estimated from the registry of the Ministry of Public Health.	Betel quid

4.Main Analysis

Table S3.1 Association of any Non-tobacco product with various cancers and OPMDs (Random Effects Model)

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total number of NTP users	Event	Total number of non NTP users	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
	Oral cancer													
	OR for Oral cancer	3312	6413	9725	22831	4.5	2.9,7.0	100%	1.1461	<0.01	95%	24	6.64	<0.01
1	Chiang 2008	321	368	41	418	62.8	40.3,98.0	3.6%						
2	Shiu and chen 2004	53	61	21	200	56.5	23.7,134.8	3.3%						
3	Wang 2022	193	222	40	312	43.3	27.1, 75.5	3.6%						
4	Chen 2002	19	24	3	27	30.4	6.4,143.6	2.6%						
5	Lin J W 2011	126	690	104	9797	20.8	15.8,27.4	3.7%						
6	Yuan 2011	89	122	12	83	16.0	7.7,33.1	3.4%						
7	Lu 1996	33	71	7	129	15.1	6.2,37.0	3.3%						

8	Yeh 2023	775	970	285	1273	13.8	11.2, 16.9	3.7%						
9	Edirisinghe 2022	31	78	4	74	11.5	34.8, 3.8	3.1%						
10	Balaram 2002	29	40	156	639	8.2	4.0,16.7	3.4%						
11	Ko Yc 1995	76	123	31	184	8.0	4.7,13.6	3.6%						
12	Hu 2020	138	180	166	428	5.2	3.5,7.7	5.2%						
13	Loyha 2012	56	79	48	129	4.1	2.2,7.5	3.5%						
14	Merchant 2000	20	41	36	182	4.1	2.0,8.2	3.5%						
15	Shih 2022	773	1281	185	635	3.7	3.0,4.5	3.7%						
16	Muwonge 2008	13	57	80	995	3.4	1.7,6.5	3.5%						
17	Mahapatra 2015	20	41	36	181	3.2	1.7,6.2	3.5%						
18	Jussawalla 1971	44	196	129	1469	3.0	2.1,4.4	3.7%						
19	Madani 2012	88	131	262	569	2.4	1,6,3.6	3.7%						
20	Shanta V 1962	71	216	14	82	2.4	1.3,4.5	3.5%						
21	Znaor 2003	34	215	424	3503	2.1	1.6,2.8	3.7%						
22	Dikshit 2000	4	16	28	168	1.7	0.5,5.5	3.0%						

23	Jafarey 1976	40	256	88	216	1.5	1.0,2.2	3.7%						
24	Thomas 2007	141	609	2	11	1.4	0.3,6.3	2.6%						
25	Nandakumar 1990	24	69	111	389	1.3	0.8,2.3	3.6%						
26	Hirayama 1966	13	53	27	129	1.2	0.6,2.6	3.4%						
27	Chandra 1962	45	118	135	389	1.2	0.8,1.8	3.6%						
28	Yasin 2022	18	34	82	166	1.2	0.6,2.4	3.4%						
29	Kietthubthew 2001	25	52	28	54	0.9	0.4,1.8	3.4%						
	Pharyngeal cancer													
	OR for pharyngeal cancer	329	2043	887	4479	1.9	0.8,4.9	100%						
1	Lee 2005	115	216	33	154	19.3	11.5,32.3	15.5%	1.3561	<0.01	95%	6	1.39	0.16
2	Jussawalla 1971	123	1340	340	275	3.2	2.4,4.2	16.0%						
3	Wasnik 1998	7	25	21	174	2.8	1.1,7.6	13.8%						
4	Hirayama 1966	2	42	3	105	1.7	0.3,10.6	10.2%						
5	Znaor 2003	34	215	424	3503	1.4	0.9,2.0	15.8%						
6	Shanta V 1962	44	189	38	106	0.5	0.3,0.9	15.5%						

7	Dikshit 2000	4	16	28	162	0.3	0.1,1.1	13.1%						
	Esophageal cancer													
	OR for esophageal cancer	247	1056	715	10413	3.0	1.2,7.5	100%	1.2444	<0.01	95%	5	2.33	0.02
1	Chuang 2019	22	290	22	4677	17.4	9.5,31.8	16.4%						
2	Wu 2006	93	132	72	288	7.2	4.5,11.3	16.8%						
3	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	17.2%						
4	Akhtar 2012	15	39	76	416	2.8	1.4,5.6	16.0%						
5	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	17.2%						
6	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	16.5%						
	OPMD													
	OR for OPMD	789	3715.5	379	32670	15.3	8.8,26.7	100%	0.7594	<0.01	84%	14	9.62	<0.01
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,279 29,0	3.4%						
2	Maher 1994	8	8.5	2	84	561.0	24.8,126 71.3	3.0%						
3	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	8.5%						
4	Chung 2005	37	47	99	998	33.6	16.2,69.6	8.6%						

5	Yang 2005	43	82	0.5	14.5	31.6	1.8,553.2	3.4%						
6	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	9.2%						
7	Shiu 2000	Not given in the study				25.9	3.3,204.2	4.9%						
8	Lee 2003	180	364	39	731	17.4	11.8,25.4	9.3%						
9	Thomas 2008	189	1233	1	90	16.1	2.2,116.3	5.1%						
10	Hernandez 2017	9	64	1	58	9.3	1.1,76.1	7.4%						
11	Amarsinghe 2010	13	147	4	281	6.7	2.1,21.0	7.4%						
12	Pahwa 2018	34	286	42	1747	5.5	3.4,8.8	9.2%						
13	Juntanong 2016	37	302	50	1998	5.4	3.5,8.5	9.3%						
14	Merchant 2015	20	41	36	181	3.8	1.9,7.8	8.6%						
15	Shiu 2000	Not given in the study				3.8	0.6,23.4	5.5%						

Table S3.2 Association of betel leaf with areca nut and various cancers and OPMDs (Random Effects Model)

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	Df	Z	P(Z)
Oral cancer (n=24)														
	OR for Oral cancer	3145	5750	1987	18531	5.9	3.7,9.5	100%	1.2653	<0.01	96%	23	7.37	<0.01
1	Chiang 2008	321	368	41	418	62.8	40.3,98.0	4.4%						
2	Shiu and chen 2004	53	61	21	200	56.5	23.7,134.8	4.0%						
3	Wang 2022	193	222	40	312	45.3	27.1-75.5	4.3%						
4	Chen 2002	19	24	3	27	30.4	6.4,143.6	3.1%						
5	Lin J W	126	690	104	9797	20.8	15.8,27.4	4.5%						
6	Yuan 2011	89	122	12	83	16.0	7.7,33.1	4.1%						
7	Lu 1996	33	71	7	129	15.1	6.2,37.0	4.0%						
8	Yeh 2023	775	970	285	1273	13.8	11.2,16.9	4.5%						
9	Edirisinghe 2022	31	78	4	74	11.5	3.8,34.8	3.7%						
10	Balaram 2002	29	40	156	639	8.2	4.0,16.7	4.2%						

11	Hu 2020	138	180	166	428	5.2	3.5,7.7	4.4%						
12	Loyha 2012	56	79	48	129	4.1	2.2,7.5	4.3%						
13	Merchant 2000	20	41	36	182	4.1	2.0,8.2	4.2%						
14	Shih 2022	773	1281	185	635	3.7	3.0,4.5	4.5%						
15	Muwonge 2008	13	57	80	995	3.4	1.7,6.5	4.2%						
16	Mahapatra 2015	20	41	36	181	3.2	1.7,6.2	4.2%						
17	Jussawalla 1971	44	196	129	1469	3.0	2.1,4.4	4.4%						
18	Madani 2012	88	131	262	569	2.4	1.6,3.6	4.4%						
19	Shanta V 1962	71	216	14	82	2.4	1.3,4.5	4.2%						
20	Thomas 2007	141	609	2	11	1.4	0.3,6.3	3.1%						
21	Nandakumar 1990	24	69	111	389	1.3	0.8,2.3	4.3%						
22	Chandra 1962	45	118	135	389	1.2	0.8,1.8	4.4%						
23	Yasin 2022	18	34	82	166	1.2	0.6,2.4	4.1%						
24	Kietthubthew 2001	25	52	28	54	0.9	0.4,1.8	4.1%						
	Pharyngeal cancer (N= 4)													

	OR for pharyngeal cancer	289	1770	432	709	3.1	0.8,12.2	100%	1.8368	<0.01	97%	3	1.64	0.10
1	Lee 2005	115	216	33	154	19.3	11.5,32.3	25.5%						
2	Jussawalla 1971	123	1340	340	275	3.2	2.4,4.2	26.4%						
3	Wasnik 1998	7	25	21	174	2.8	1.1,7.6	22.6%						
4	Shanta V 1962	44	189	38	106	0.5	0.3,0.9	25.5%						
	Esophageal cancer (N= 3)													
	OR for esophageal cancer	177	513	246	1870	2.2	0.5,9.5	100%	1.6575	<0.01	97%	2	1.01	0.10
1	Wu 2006	93	132	72	288	7.2	4.5,11.3	33.4%						
2	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	33.9%						
3	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	32.7%						
	OPMD (N= 11)													
	OR for OPMD	696	2918.5	282	28586	22.7	12.1,42.7	100%	0.6387	<0.01	77%	11	9.71	<0.01
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,27929,0	5.3%						
2	Maher 1994	8	8.5	2	84	561.0	24.8,12671.3	4.7%						
3	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	11.9%						

4	Chung 2005	37	47	99	998	33.6	16.2,69.6	12.0%						
5	Yang 2005	43	82	0.5	14.5	31.9	1.8,553.2	5.2%						
6	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	12.8%						
7	Shiu 2000	Numbers not given in the study				25.9	3.3, 204.2	7.3%						
8	Lee 2003	180	364	39	731	17.4	11.8,25.4	12.9%						
9	Thomas 2008	189	1233	1	90	16.1	2.2,116.3	7.6%						
10	Merchant 2015	20	41	36	181	3.8	1.9,7.8	12.1%						
11	Shiu 2000	Numbers not given in the study				3.8	0.6,23.3	8.1%						

Table S3.3 Association of areca nut with various cancers and OPMDs (Random Effects Model)

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
Oral cancer (N=1)														
1	Hirayama 1966	13	53	27	129	1.2	0.6,2.6	100.0%						
Pharyngeal cancer (N=1)														
1	Hirayama 1966	13	53	27	129	1.7	0.3,10.6	100.0%						
Esophageal cancer (N=2)														
	OR for esophageal ca	37	329	98	5093	7.0	1.2,42.1	100%	1.5584	<0.01	93%	1	2.13	0.03
1	Chuang 2019	22	290	22	4677	17.4	9.5,31.8	51.1%						
2	Akhtar 2012	15	39	76	416	2.8	1.4,5.6	48.9%						
OPMD (N=3)														
	OR for OPMD	80	652	93	3803	5.5	4.0,7.6	100%	0	0.88	0%	2	10.49	<0.01
1	Hernandez	9	64	1	58	9.3	1.1,76.1	15.3%						
2	Pahwa 2018	34	286	42	1747	5.5	3.4,8.8	42.1%						
3	Juntanong 2016	37	302	50	1998	5.4	3.5,8.5	42.6%						

Table S3.4 Association of Betel-leaf with various cancers and OPMDs (Random Effects Model)

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
Oral cancer (N=2)														
	OR for oral cancer	116	379	119	400	3.4	0.6,17.9	100%	1.3941	<0.01	96%	1	1.43	0.15
1	Ko Yc 1995	76	123	31	184	8.0	4.7,13.6	49.4%						
2	Jafarey 1976	40	256	88	216	1.5	1.0,2.2	50.6%						
OPMD (N=2)														
1	Amarsinghe 2010	13	147	4	281	6.7	2.1,21.0	100%						

Table S3.5 Association of Non-tobacco product not specified with various cancers (Random Effects Model)

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total number of NTP users	Event	Total number of non NTP users	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
Oral cancer (N=2)														
	OR for oral cancer	38	231	452	3671	2.1	1.6,2.7	100%	0	0.71	0%	1	5.51	<0.01
1	Znaor 2003	34	215	424	3503	2.1	1.6,2.8	79.7%						
2	Dikshit 2000	4	16	28	168	1.7	0.5,5.5	20.3%						
Pharyngeal ca (N=2)														
	OR for pharyngeal cancer	38	231	452	3665	0.8	0.2, 2.9	100%	0.7901	0.02	80%	1	-0.40	0.69
1	Znaor 2003	34	215	424	3503	1.4	0.9,2.0	76.1%						
2	Dikshit 2000	4	16	28	162	0.3	0.1,1.1	23.9%						
Esophageal cancer (N=1)														
1	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	100.0%						

5. Subgroup Analysis

Table S4.1: Association of oral cancer by NTP, publication year, comparator, type of user and country

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total number of NTP users	Event	Total number of non NTP users	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
On the basis of Publication Year (N=15)														
Before 2005														
	OR for oral cancer	530	1551	1238	7760	3.5	2.2,5.5	100%	0.7291	<0.01	90%	14	5.16	<0.01
1	Shiu and chen 2004	53	61	21	200	56.5	23.7, 134.8	6.4%						
2	Chen 2002	19	24	3	27	30.4	6.4, 143.6	5.0%						
3	Lu 1996	33	71	7	129	15.1	6.2, 37.0	6.4%						
4	Balaram 2002	29	40	156	639	8.2	4.0, 16.7	6.7%						
5	Ko Yc 1995	76	123	31	184	8.0	4.7, 13.6	7.0%						
6	Merchant 2000	20	41	36	182	4.1	2.0, 8.2	6.7%						
7	Jussawalla 1971	44	196	129	1469	3.0	2.1, 4.4	7.2%						
8	Shanta V 1962	71	216	14	82	2.4	1.3, 4.5	6.8%						
9	Znaor 2003	34	215	424	3503	2.1	1.6, 2.8	7.3%						
10	Dikshit 2000	4	16	28	168	1.7	0.5, 5.5	5.7%						
11	Jafarey 1976	40	256	88	216	1.5	1.0, 2.2	7.2%						

12	Nandakumar 1990	24	69	111	389	1.3	0.8, 2.3	7.0%						
13	Hirayama 1966	13	53	27	129	1.2	0.6, 2.6	6.6%						
14	Chandra 1962	45	118	135	389	1.2	0.8, 1.8	7.2%						
15	Kietthubthew 2001	25	52	28	54	0.9	0.4, 1.8	6.6%						
After 2005 (N=14)														
	OR (After 2005)	2782	4862	1347	15071	7.1	3.1,12.8	100%	1.0951	<0.01	96%	13	6.70	<0.01
1	Chiang 2008	321	368	41	418	62.8	40.3, 98.0	7.5%						
2	Wang 2022	193	222	40	312	45.3	27.1,75.5	7.4%						
3	Lin J W 2011	126	690	104	9797	20.8	15.8, 27.4	7.7%						
4	Yuan 2011	89	122	12	83	16.0	7.7, 33.1	7.0%						
5	Yeh 2023	775	970	285	1273	13.8	11.2,16.9	7.7%						
6	Edirisinghe 2022	31	78	4	74	11.5	3.8,34.8	6.2%						
7	Hu 2020	138	180	166	428	5.2	3.5, 7.7	7.5%						
8	Loyha 2012	56	79	48	129	4.1	2.2, 7.5	7.2%						
9	Shih 2022	773	1281	185	635	3.7	3.0, 4.5	7.7%						
10	Muwonge 2008	13	57	80	995	3.4	1.7, 6.5	7.1%						
11	Mahapatra 2015	20	41	36	181	3.2	1.7, 6.2	7.1%						
12	Madani 2012	88	131	262	569	2.4	1.6, 3.6	7.5%						

13	Thomas 2007	141	609	2	11	1.4	0.3, 6.3	5.2%						
14	Yasin 2022	18	34	82	166	1.2	0.6,2.4	7.0%						
On the basis of comparator (No habits) (N=5)														
	OR for oral cancer	124	525	129	427	2.0	1.1,3.6	100%	0.3147	<0.01	73%	4	2.32	<0.01
1	Edirisinghe 2022	31	78	4	74	11.5	3.8,34.8	17.8%						
2	Shanta V 1962	71	216	14	82	2.4	1.3,4.5	20.6%						
3	Jafarey 1976	40	256	88	216	1.5	1.0,2.2	21.6%						
4	Hirayama 1966	13	53	27	129	1.2	0.6,2.6	20.0%						
5	Yasin 2022	18	34	82	166	1.2	0.6,2.4	20.1%						
Non NTP with other risk factors														
	OR for oral cancer	2171	4584	2045	20579	5.9	3.7,9.4	100%	1.2184	<0.01	96%	21	6.77	<0.01
1	Chiang 2008	321	368	41	418	62.8	40.3,98.0	4.4%						
2	Shiu and chen 2004	53	61	21	200	56.5	23.7,134.8	4.0%						
3	Wang 2022	193	222	40	312	45.3	27.1,75.5	4.3%						
4	Chen 2002	19	24	3	27	30.4	6.4,143.6	3.1%						
5	Lin J W	126	690	104	9797	20.8	15.8,27.4	4.5%						
6	Yuan 2011	89	122	12	83	16.0	7.7,33.1	4.1%						
7	Lu 1996	33	71	7	129	15.1	6.2,37.0	3.9%						
8	Yeh 2023	775	970	285	1273	13.8	11.2,16.9	4.5%						

7	Balaram 2002	29	40	156	639	8.2	4.0,16.7	4.1%						
8	Ko Yc 1995	76	123	31	184	8.0	4.7,13.6	4.3%						
9	Hu 2020	138	180	166	428	5.2	3.5,7.7	4.4%						
10	Loyha 2012	56	79	48	129	4.1	2.2,7.5	4.3%						
11	Merchant 2000	20	41	36	182	4.1	2.0,8.2	4.2%						
12	Shih 2022	773	1281	185	635	3.7	3.0,4.5	4.5%						
13	Muwonge 2008	13	57	80	995	3.4	1.7,6.5	4.2%						
14	Mahapatra 2015	20	41	36	181	3.2	1.7,6.2	4.2%						
15	Jussawalla 1971	44	196	129	1469	3.0	2.1,4.4	4.4%						
16	Madani 2012	88	131	262	569	2.4	1,6,3.6	4.4%						
17	Znaor 2003	34	215	424	3503	2.1	1.6,2.8	4.5%						
18	Dikshit 2000	4	16	28	168	1.7	0.5,5.5	3.5%						
19	Thomas 2007	141	609	2	11	1.4	0.3,6.3	3.1%						
20	Nandakumar 1990	24	69	111	389	1.3	0.8,2.3	4.3%						
21	Chandra 1962	45	118	135	389	1.2	0.8,1.8	4.4%						
22	Kietthubthew 2001	25	52	28	54	0.9	0.4,1.8	4.1%						
(Type of user) Exclusive user (N=6)														

	OR for oral cancer	159	805	807	5874	1.8	1.4,2.4	100%	0.0622	0.06	53%	5	4.12	<0.01
1	Jussawalla 1971	44	196	129	1469	3.0	2.1, 4.4	17.6%						
2	Znaor 2003	34	215	424	3503	2.1	1.6, 2.8	17.9%						
3	Dikshit 2000	4	16	28	168	1.7	0.5, 5.5	13.6%						
4	Jafarey 1976	40	256	88	216	1.5	1.0, 2.2	17.6%						
5	Nandakumar 1990	24	69	111	389	1.3	0.8, 2.3	17.1%						
6	Hirayama 1966	13	53	27	129	1.2	0.6, 2.6	16.1%						
Non-exclusive user (N=18)														
	OR for oral cancer	2091	4186	1232	14743	6.7	4.0,11.3	100%	1.1406	<0.01	95%	17	7.14	<0.01
1	Chiang 2008	321	368	41	418	62.8	40.3, 98.0	6.0%						
2	Shiu and chen 2004	53	61	21	200	56.5	23.7, 134.8	5.3%						
3	Chen 2002	19	24	3	27	30.4	6.4, 143.6	4.0%						
4	Lin J W	126	690	104	9797	20.8	15.8, 27.4	6.1%						
5	Yuan 2011	89	122	12	83	16.0	7.7, 33.1	5.6%						
6	Lu 1996	33	71	7	129	15.1	6.2, 37.0	5.3%						
7	Balaram 2002	29	40	156	639	8.2	4.0, 16.7	5.6%						
8	Ko Yc 1995	76	123	31	184	8.0	4.7, 13.6	5.9%						

9	Hu 2020	138	180	166	428	5.2	3.5, 7.7	6.0%						
10	Loyha 2012	56	79	48	129	4.1	2.2, 7.5	5.8%						
11	Merchant 2000	20	41	36	182	4.1	2.0, 8.2	5.6%						
12	Shih 2022	773	1281	185	635	3.7	3.0, 4.5	6.2%						
13	Muwonge 2008	13	57	80	995	3.4	1.7, 6.5	5.7%						
14	Mahapatra 2015	20	41	36	181	3.2	1.7, 6.2	5.7%						
15	Madani 2012	88	131	262	569	2.4	1,6, 3.6	6.0%						
16	Shanta V 1962	71	216	14	82	2.4	1.3, 4.5	5.7%						
17	Thomas 2007	141	609	2	11	1.4	0.3, 6.3	4.0%						
18	Kietthubthew 2001	25	52	28	54	0.9	0.4, 1.8	5.5%						
By country (Indian Sub-continent) (N=13)														
	OR for oral cancer	445	1449	1526	8911	2.3	1.8,3.0	100%	0.1483	<0.01	70%	12	6.15	<0.01
1	Balaram 2002	29	40	156	639	8.2	4.0,16.7	7.5%						
2	Merchant 2000	20	41	36	182	4.1	2.0,8.2	7.5%						
3	Muwonge 2008	13	57	80	995	3.4	1.7,6.5	7.6%						
4	Mahapatra 2015	20	41	36	181	3.2	1.7,6.2	7.6%						
5	Jussawalla 1971	44	196	129	1469	3.0	2.1,4.4	8.1%						
6	Madani 2012	88	131	262	569	2.4	1,6,3.6	8.0%						

7	Shanta V 1962	71	216	14	82	2.4	1.3,4.5	7.7%						
8	Znaor 2003	34	215	424	3503	2.1	1.6,2.8	8.2%						
9	Dikshit 2000	4	16	28	168	1.7	0.5,5.5	6.4%						
10	Jafarey 1976	40	256	88	216	1.5	1.0,2.2	8.0%						
11	Nandakumar 1990	24	69	111	389	1.3	0.8,2.3	7.8%						
12	Hirayama 1966	13	53	27	129	1.2	0.6,2.6	7.4%						
13	Chandra 1962	45	118	135	389	1.2	0.8,1.8	8.0%						
Taiwan (N=10)														
	OR for oral cancer	2458	3932	729	13058	19.3	7.6, 44.1	100%	0.9882	<0.01	84%	9	2.05	0.04
1	Chiang 2008	321	368	41	418	62.8	40.3,98.0	10.5%						
2	Shiu and chen 2004	53	61	21	200	56.5	23.7,134.8	9.5%						
3	Wang 2022	193	222	40	312	45.3	27.1,75.5	10.4%						
4	Chen 2002	19	24	3	27	30.4	6.4,143.6	7.3%						
5	Lin J W	126	690	104	9797	20.8	15.8,27.4	10.8%						
6	Yuan 2011	89	122	12	83	16.0	7.7,33.1	9.9%						
7	Lu 1996	33	71	7	129	15.1	6.2,37.0	9.4%						
8	Yeh 2023	775	970	285	1273	13.8	11.2,16.9	10.9%						
9	Ko Yc 1995	76	123	31	184	8.0	4.7,13.6	10.4%						
10	Shih 2022	773	1281	185	635	3.7	3.0,4.5	10.9%%						
Others (N=4)														

	OR for oral cancer	360	920	244	622	2.5	1.0,5.9	100%	0.6024	<0.01	84%	3	2.05	0.04
1	Hu 2020	138	180	166	428	5.2	3.5,7.7	28.2%						
2	Loyha 2012	56	79	48	129	4.1	2.2,7.5	27.0%						
3	Thomas 2007	141	609	2	11	1.4	0.3,6.3	19.0%						
4	Kietthubthew 2001	25	52	28	54	0.9	0.4,1.8	25.8%						

Table S 4.2: Association of pharyngeal cancer with NTP by publication year, comparator, type of user and country.

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
	On the basis of Publication Year													
	Before 2005 (N=6)													
	OR for pharyngeal cancer	214	1827	854	4325	1.3	0.6,2.7	100%	0.6724	<0.01	90%	5	0.64	0.52
1	Jussawalla 1971	123	1340	340	275	3.2	2.4, 4.2	19.1%						
2	Wasnik 1998	7	25	21	174	2.8	1.1, 7.6	16.3%						
3	Hirayama 1966	2	42	3	105	1.7	0.3, 0.9	11.8%						
4	Znaor 2003	34	215	424	3503	1.4	0.9, 2.0	18.9%						
5	Shanta V 1962	44	189	38	106	0.5	0.3, 0.9	18.4%						
6	Dikshit 2000	4	16	28	162	0.3	0.1, 1.1	15.4%						
	After 2005													
1	Lee 2005	115	216	33	154	19.3	11.5,32.3							

On the basis of comparator (No habits) (N=2)														
	OR for pharyngeal cancer	46	231	41	211	0.7	0.3,1.6	100%	0.1818	0.24	28%	1	-0.86	0.39
1 2	Hirayama 1966	2	42	3	105	1.7	0.3, 0.9	39.1%						
	Shanta V 1962	44	189	38	106	0.5	0.3, 0.9	60.9%						
Non NTP with other risk factors (N=5)														
	OR for pharyngeal cancer	283	1812	846	4268	1.4	0.6,3.2	100%	1.1928	<0.01	95%	4	1.84	0.07
1	Lee 2005	115	216	33	154	19.3	11.5,32.3	20.9%						
2	Jussawalla 1971	123	1340	340	275	3.2	2.4, 4.2	21.7%						
3	Wasnik 1998	7	25	21	174	2.8	1.1, 7.6	18.5%						
4	Znaor 2003	34	215	424	3503	1.4	0.9, 2.0	21.4%						
5	Dikshit 2000	4	16	28	162	0.3	0.1, 1.1	17.5%						
(Type of user) Exclusive user (N=4)														
	OR for pharyngeal cancer	163	1613	795	4045	1.4	0.6,3.2	100%	0.4974	<0.01	87%	3	0.81	0.42
1	Jussawalla 1971	123	1340	340	275	3.2	2.4, 4.2	29.3%						
2	Hirayama 1966	2	42	3	105	1.7	0.3, 0.9	18.1%						
3	Znaor 2003	34	215	424	3503	1.4	0.9, 2.0	28.9%						

4	Dikshit 2000	4	16	28	162	0.3	0.1, 1.1	23.7%						
Non-exclusive user (N=3)														
	OR for pharyngeal cancer	166	430	92	434	3.1	0.6,2.7							
1	Lee 2005	115	216	33	154	19.3	11.5,32.3	34.7%	0.45722	<0.01		2	0.90	0.37
2	Wasnik 1998	7	25	21	174	2.8	1.1, 7.6	30.7%						
3	Shanta V 1962	44	189	38	106	0.5	0.3, 0.9							
By country (Indian Sub-continent) (N=6)														
	OR for pharyngeal cancer	241	1854	830	4301	1.3	0.6,2.7							
1	Jussawalla 1971	123	1340	340	275	3.2	2.4, 4.2	19.1%	0.6724	<0.01	90%	5	0.64	0.52
2	Wasnik 1998	7	25	21	174	2.8	1.1, 7.6	16.3%						
3	Hirayama 1966	2	42	3	105	1.7	0.3, 0.9	11.8%						
4	Znaor 2003	34	215	424	3503	1.4	0.9, 2.0	18.9%						
5	Shanta V 1962	71	216	14	82	2.4	1.3,4.5	18.4%						
6	Dikshit 2000	4	16	28	162	0.3	0.1, 1.1	15.4%						
Taiwan														
1	Lee 2005	115	216	33	154	19.3	11.5,32.3	100.0%	0.6724	<0.01	90%		0.64	0.52

Table S4.3: Association of esophageal cancer and NTP by publication year, comparator, type of user and country.

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total number of NTP users	Event	Total number of non NTP users	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
On the basis of Publication Year														
Before 2005 (N=3)														
	OR for esophageal cancer	117	595	545	5032	1.3	0.4,40.	100%						
1	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	33.8%	0.9266	<0.01	95%	2	0.45	0.65
2	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	33.7%						

3	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	32.5%						
After 2005 (N=3)														
	OR for esophageal cancer	130	461	170	5381	7.1	2.8, 18.0	100%	0.5783	<0.01	87%	2	4.16	<0.01
1	Chuang 2019	22	290	22	4677	17.4	9.5, 31.8	33.2%						
2	Wu 2006	93	132	72	288	7.2	4.5, 11.3	34.3%						
3	Akhtar 2012	15	39	76	416	2.8	1.4, 5.6	32.5%						
On the basis of comparator (No habits)														
1	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	100.0%						
Non NTP with other risk factors (N=5)														
	OR for esophageal cancer	217	881	679	10309	4.4	2.0,9.6	100%	0.7181	<0.01	93%	4	3.76	<0.01
1	Chuang 2019	22	290	22	4677	17.4	9.5, 31.8	19.6%						
2	Wu 2006	93	132	72	288	7.2	4.5, 11.3	20.2%						
3	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	20.6%						
4	Akhtar 2012	15	39	76	416	2.8	1.4, 5.6	19.2%						
5	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	20.5%						
(Type of user) Exclusive user (N=3)														

	OR for esophageal cancer	102	459	585	5344	2.4	1.4, 4.3	100%	0.1992	<0.01	79%	2	3.01	<0.01
1	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	34.1%						
2	Akhtar 2012	15	39	76	416	2.8	1.4, 5.6	31.9%						
3	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	34.0%						
Non-exclusive user (N=3)														
	OR for esophageal cancer	145	597	130	5069	3.6	0.4, 30.9	100%	3.4887	<0.001	98%	2	1.19	0.24
1	Chuang 2019	22	290	22	4677	17.4	9.5, 31.8	32.9%						
2	Wu 2006	93	132	72	288	7.2	4.5, 11.3	33.9%						
3	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	33.2%						
By country (Indian Sub-continent) (N=4)														
	OR for esophageal cancer	132	634	621	5448	1.3	0.6,2.7	100%	0.7655	<0.01	93%	3	0.96	0.33
1	Jussawalla 1971	54	206	138	1478	3.4	2.4,4.9	19.1%						
2	Akhtar 2012	15	39	76	416	2.8	1.4, 5.6	16.3%						
3	Znaor 2003	33	214	371	3450	1.5	1.0,2.2	11.8%						
4	Shanta V 1962	30	175	36	104	0.4	0.2,0.7	18.9%						
Taiwan (N=2)														

	OR for esophageal cancer	115	422	94	4965	10.9	4.6, 26.0	100%	0.3186	0.02	81%	1	5.39	<0.01
1	Chuang 2019	22	290	22	4677	17.4	9.5, 31.8	49.2%						
2	Wu 2006	93	132	72	288	7.2	4.5, 11.3	50.8%						

Table S 4.4: Association of OPMD and NTP by publication year, country, type of user, comparator, and user type

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
On the basis of Publication Year Before 2005 (N=7)														
	OR for OPMD	407	1515.5	145.5	27302.5	29.2	14.7,57.9	100%	0.4199	<0.01	71%	6	9.67	<0.01
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,27929,0	6.5%						
2	Maher 1994	8	8.5	2	84	561.0	24.8,12671.3	5.6%						
3	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	20.3%						
4	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	22.9%						
5	Shiu 2000	Numbers not given in the study				25.9	3.3, 204.0	9.9%						
6	Lee 2003	180	364	39	731	17.4	11.8, 25.4	23.3%						
7	Shiu 2000	Numbers not given in the study				3.8	0.6, 23.3	11.4%						
After 2005 (N=8)														
	OR for OPMD	382	2202	233.5	5367.5	8.4	4.6,15.1	100.0%	0.4123	<0.01	72%	8	9.67	<0.01
1	Chung 2005	37	47	99	998	33.6	16.2, 69.6	15.8%						

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
2	Yang 2005	43	82	0.5	14.5	31.6	1.8, 553.2	4.9%						
3	Thomas 2008	189	1233	1	90	16.1	2.2, 116.3	8.0%						
4	Hernandez 2017	9	64	1	58	9.3	1.1, 76.1	7.5%						
5	Amarsinghe 2010	13	147	4	281	6.7	2.1, 21.0	12.9%						
6	Pahwa 2018	34	286	42	1747	5.5	3.4, 8.8	17.4%						
7	Juntanong 2016	37	302	50	1998	5.4	3.5, 8.5	17.5%						
8	Merchant 2015	20	41	36	181	3.8	1.9, 7.8	15.9%						
On the basis of user type (Current, ever, or former) Current user (N=2)														
	OR for OPMD	37	47	99	998	32.6	16.4,64.9	100%	0	0.81	0%	1	9.94	<0.01
1	Chung 2005	37	47	99	998	33.6	16.2, 69.6	73.1%						
2	Shiu 2000	Numbers not given in the study				25.9	3.3,204.0	26.9%						
Ever (N=5)														
	OR for OPMD	282	2032	98	4174	5.7	4.2,7.8	100%	0	0.84	0%	4	11.28	<0.01

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
1	Thomas 2008	189	1233	1	90	16.1	2.2, 116.3	10.2%						
2	Hernandez 2017	9	64	1	58	9.3	1.1, 76.1	9.4%						
3	Amarsinghe 2010	13	147	4	281	6.7	2.1, 21.0	19.3%						
4	Pahwa 2018	34	286	42	1747	5.5	3.4, 8.8	30.4%						
5	Juntanong 2016	37	302	50	1998	5.4	3.5, 8.5	30.8%						
Former														
1	Shiu 2000	Numbers not given in the study				3.8	0.6, 23.3	100%				1		
On the basis of comparator (No habits) (N=5)														
	OR for OPMD	208	1173.5	141	27340	55.5	21.2,145.5	100%	0.5592	0.03	64%	4	8.18	<0.01
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,27929,0	10.5%						
2	Maher 1994	8	8.5	2	84	561.0	24.8,12671.3	9.1%						
3	Chung 2005	37	47	99	998	33.6	16.2, 69.6	33.3%						
4	Yang 2005	43	82	0.5	14.5	31.6	1.8, 553.2	10.4%						

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
5	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	36.8%						
Non NTP with other risk factors (N=10)														
	OR for OPMD	581	2544	238	5330	9.1	5.3,15.7	100%	0.4656	<0.01	77%	9	7.98	<0.01
1	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	12.0%						
2	Shiu 2000	Numbers not given in the study				25.9	3.3,204.2	5.9%						
3	Lee 2003	180	364	39	731	17.4	11.8,25.4	13.8%						
4	Thomas 2008	189	1233	1	90	16.1	2.2, 116.3	6.2%						
5	Hernandez 2017	9	64	1	58	9.3	1.1, 76.1	5.8%						
6	Amarsinghe 2010	13	147	4	281	6.7	2.1, 21.0	10.0%						
7	Pahwa 2018	34	286	42	1747	5.5	3.4, 8.8	13.5%						
8	Juntanong 2016	37	302	50	1998	5.4	3.5, 8.5	13.6%						
9	Merchant 2015	20	41	36	181	3.8	1.9, 7.8	12.4%						

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
10	Shiu 2000	Numbers not given in the study				3.8	0.6, 23.4	6.8%						
Exclusive user (N=4)														
	OR for OPMD	171	1126.5	42	26342	129.7	16.0,1050.8	100%	3.1100	0.01	73%	3	4.56	<0.01
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,27929,0	15.9%						
2	Maher 1994	8	8.5	2	84	561.0	24.8,12671.3	13.7%						
3	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	54.7%						
4	Yang 2005	43	82	0.5	14.5	31.6	1.8, 553.2	15.7%						
Non-exclusive user (N=9)														
	OR for OPMD	618	2591	337	6328	10.8	6.0,19.3	100%	0.5754	<0.01	84%	8	7.98	<0.01
1	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	12.1%						

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
2	Chung 2005	37	47	99	998	33.6	16.2, 69.6	12.3%						
3	Lee 2003	180	364	39	731	17.4	11.8, 25.4	13.8%						
4	Thomas 2008	189	1233	1	90	16.1	2.2, 116.3	6.3%						
5	Hernandez 2017	9	64	1	58	9.3	1.1, 76.1	5.9%						
6	Amarsinghe 2010	13	147	4	281	6.7	2.1, 21.0	10.1%						
7	Pahwa 2018	34	286	42	1747	5.5	3.4, 8.8	13.5%						
8	Juntanong 2016	37	302	50	1998	5.4	3.5, 8.5	13.6%						
9	Merchant 2015	20	41	36	181	3.8	1.9, 7.8	12.4%						
By country (Indian Sub-continent) (N=6)														
	OR for OPMD	195	1518.5	123.5	28536.5	18.8	6.1,58.0	100%						
1	Shah & Sharma 1998	82	98	0.5	165.5	1655.0	98.1,27929,0	6.9%	1.14642	<0.01	90%	5	5.11	<0.01
2	Maher 1994	8	8.5	2	84	561.0	24.8,12671.3	5.9%						
3	Jacob 2004	38	938	39	26078	28.2	17.9,44.3	23.9%						

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
4	Amarsinghe 2010	13	147	4	281	6.7	2.1, 21.0	17.7%						
5	Pahwa 2018	34	286	42	1747	5.5	3.4, 8.8	23.8%						
6	Merchant 2015	20	41	36	181	3.8	1.9, 7.8	21.8%						
Taiwan (N=6)														
	OR for OPMD	359	600	203.5	1987.5	22.3	13.9,35.9	100%	0.1078	0.18	34%	5	12.81	<0.01
1	Shiu and Chen 2004	99	107	65	244	34.1	15.7,73.9	22.0%						
2	Chung 2005	37	47	99	998	33.6	16.2, 69.6	22.5%						
3	Yang 2005	43	82	0.5	14.5	31.6	1.8, 553.2	7.0%						
4	Shiu 2000	Numbers not given in the study				25.9	3.3, 204.2	10.8%						
5	Lee 2003	180	364	39	731	17.4	11.8, 25.4	25.3%						
6	Shiu 2000	Numbers not given in the study				3.8	0.6, 23.4	12.4%						
Others (N=3)														

S. No	Name of study with year	Non-Tobacco Product users		Non-users										
		Event	Total	Event	Total	Odds Ratio	95% CI	Weight	Chi square	P-value of chi square	I square	df	Z	P(Z)
	OR for OPMD	235	1599	52	2146	5.8	3.8, 8.9	100%	0	0.52	0%	2	8.16	<0.01
1	Thomas 2008	189	1233	1	90	16.1	2.2	24.2%						
2	Hernandez 2017	9	64	1	58	9.3	1.1, 76.1	22.6%						
3	Juntanong 2016	37	302	50	1998	5.4	3.5, 8.5	53.1%						

6.Figures (Main Analysis): Forest Plot

Figure S6.1 Association of betel leaf with areca nut and various cancers & OPMD

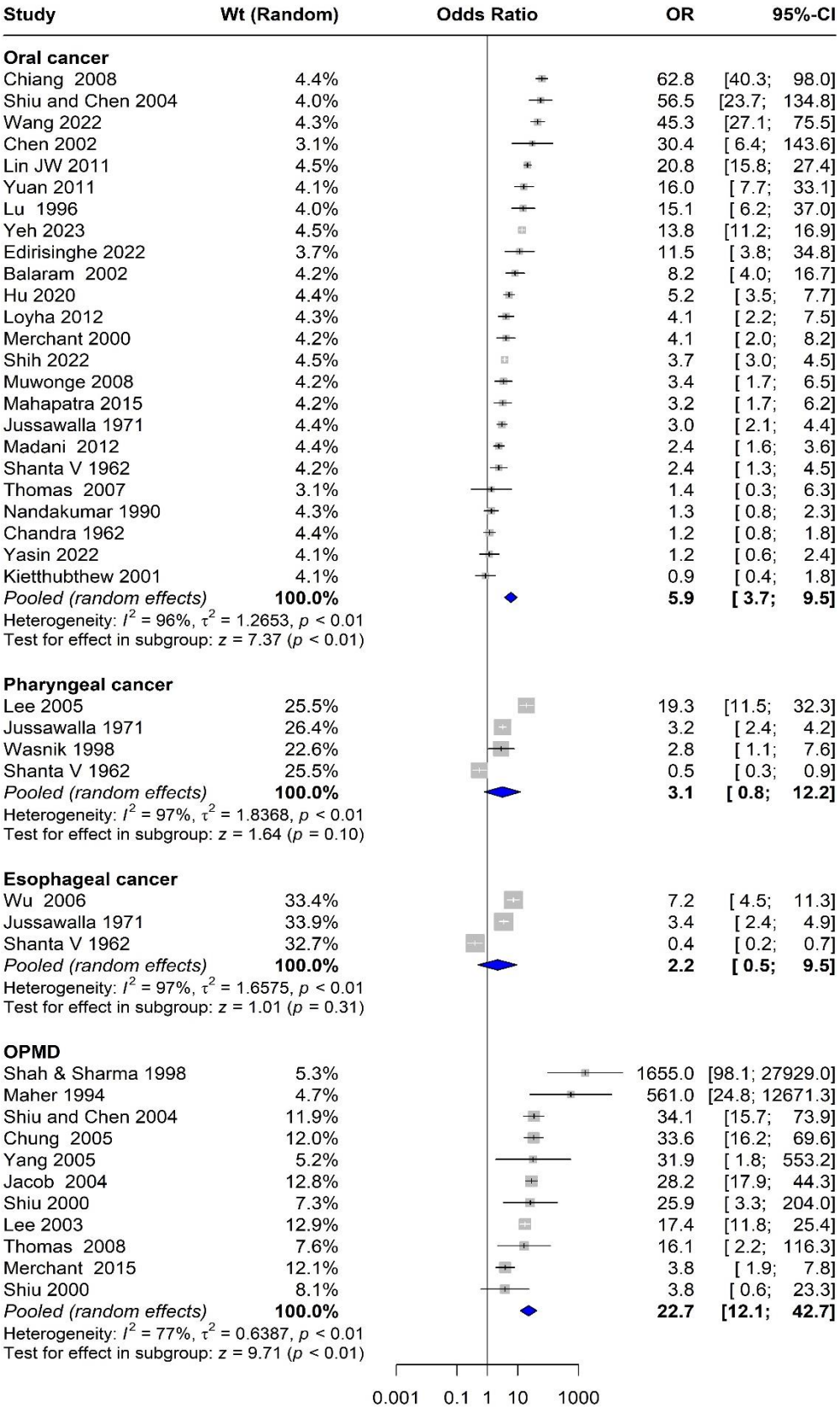


Figure S6.2 Association of areca nut with various cancers & OPMD

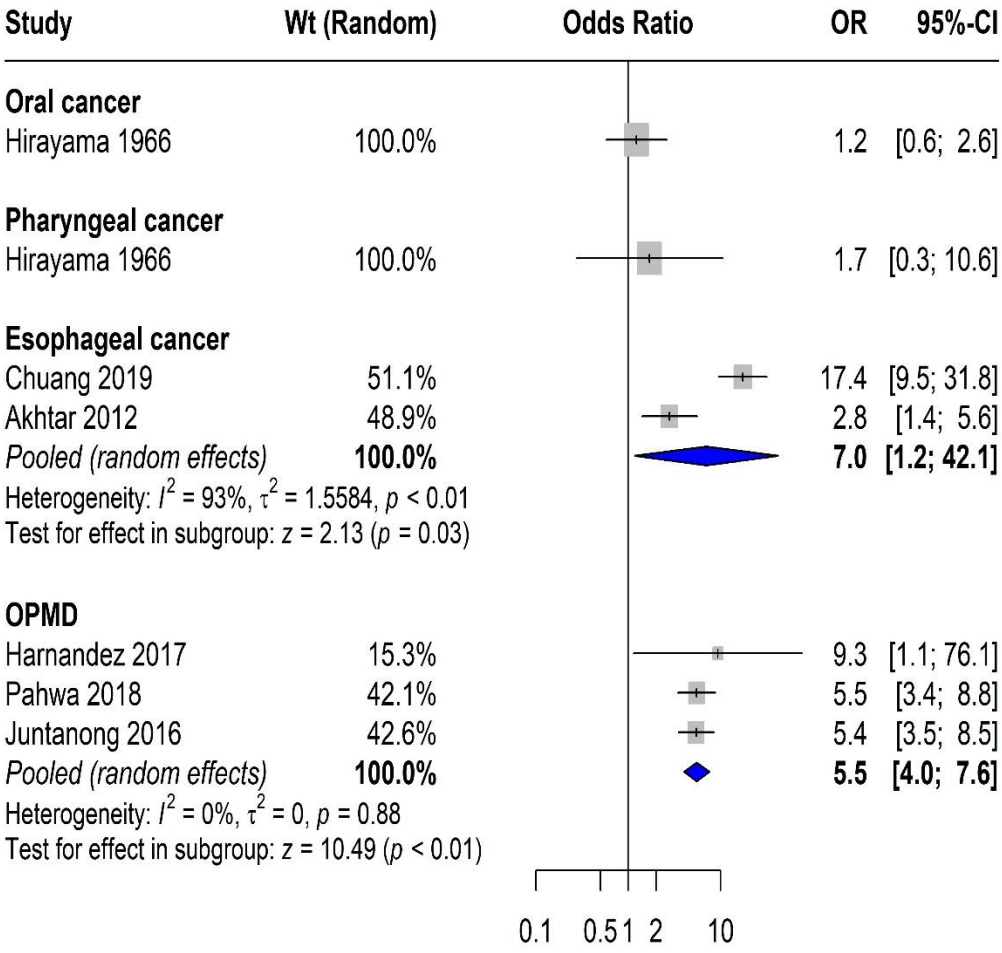


Figure S6.3 Association of betel leaf with various cancers & OPMD

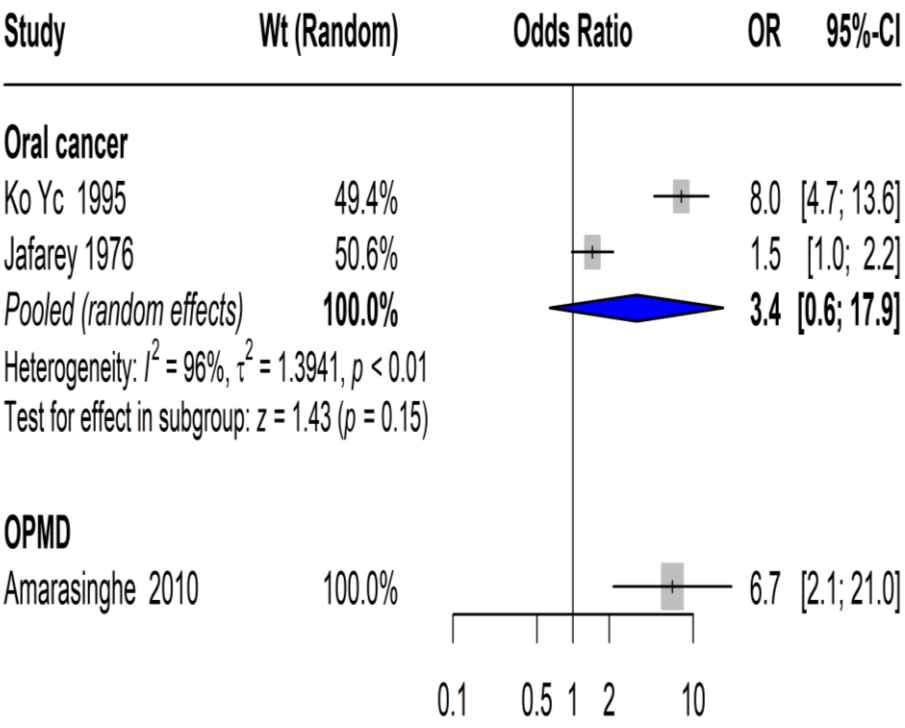
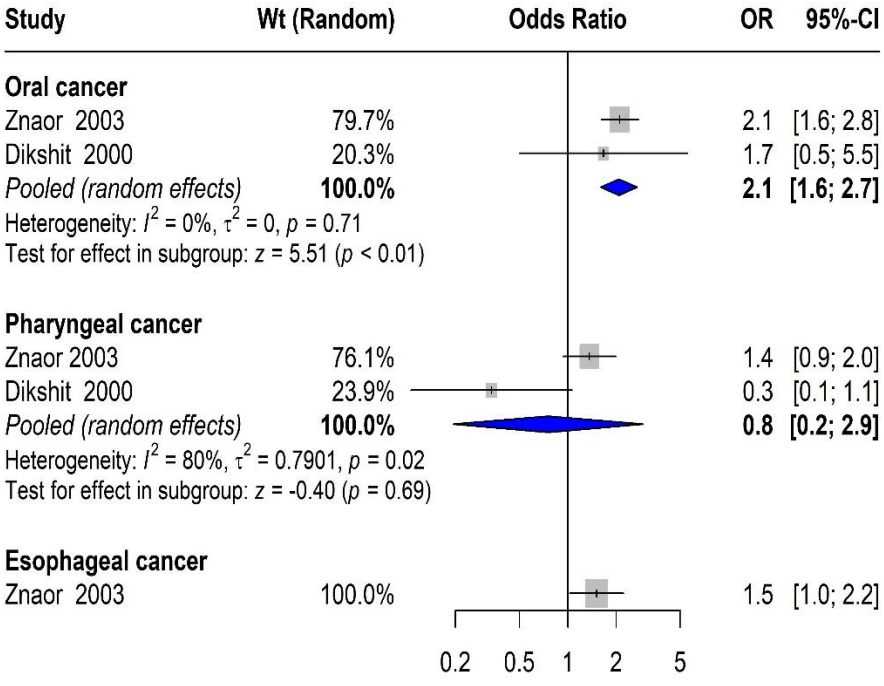


Figure S6.4 Association of NTP not specified with various cancers & OPMD.



7 Figures: Sub-group Analysis (Forest Plot)

Figure S 7. 1 Association of Oral cancer with NTP by comparator

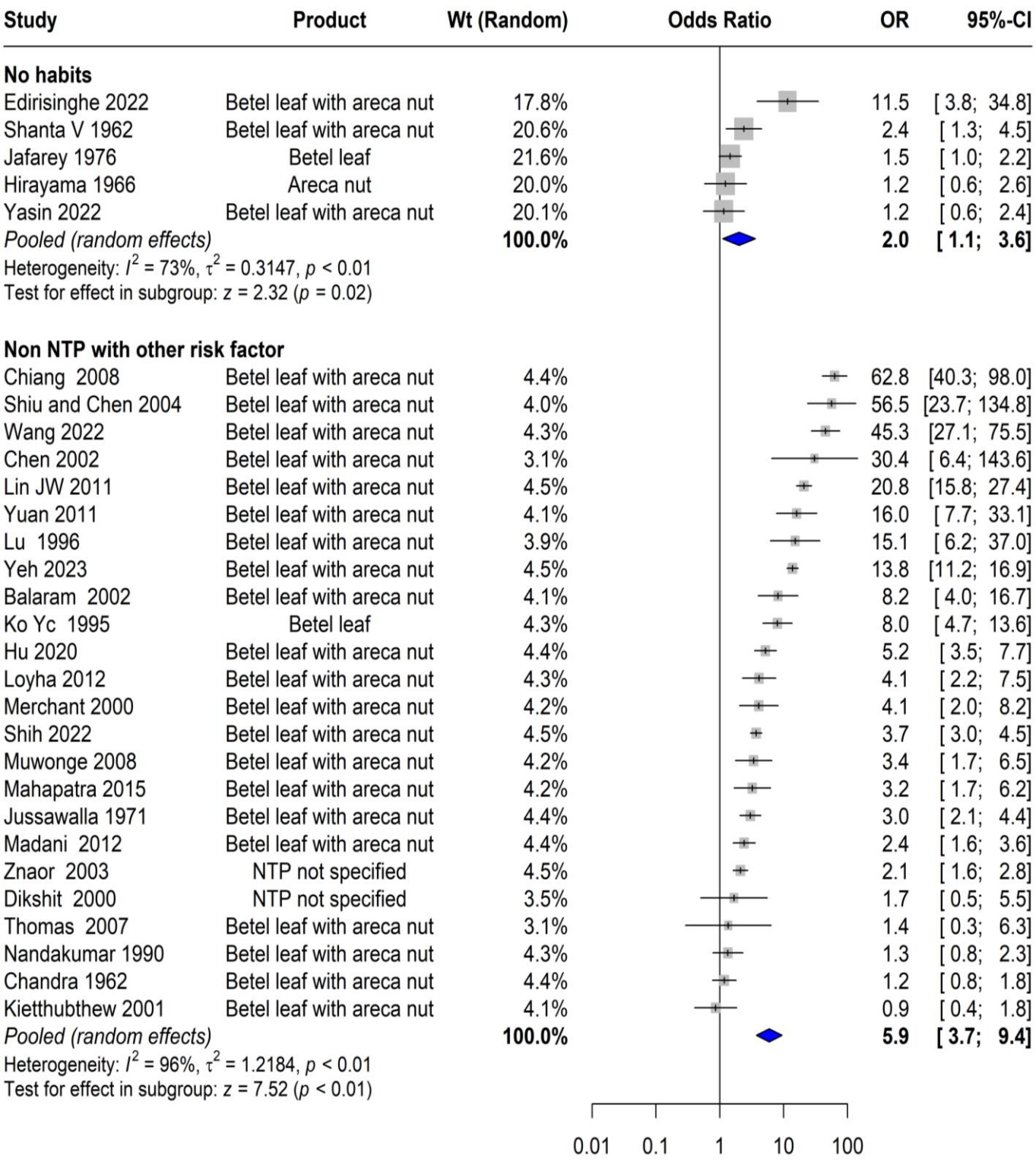


Figure S 7. 2 Association of Oral cancer by country

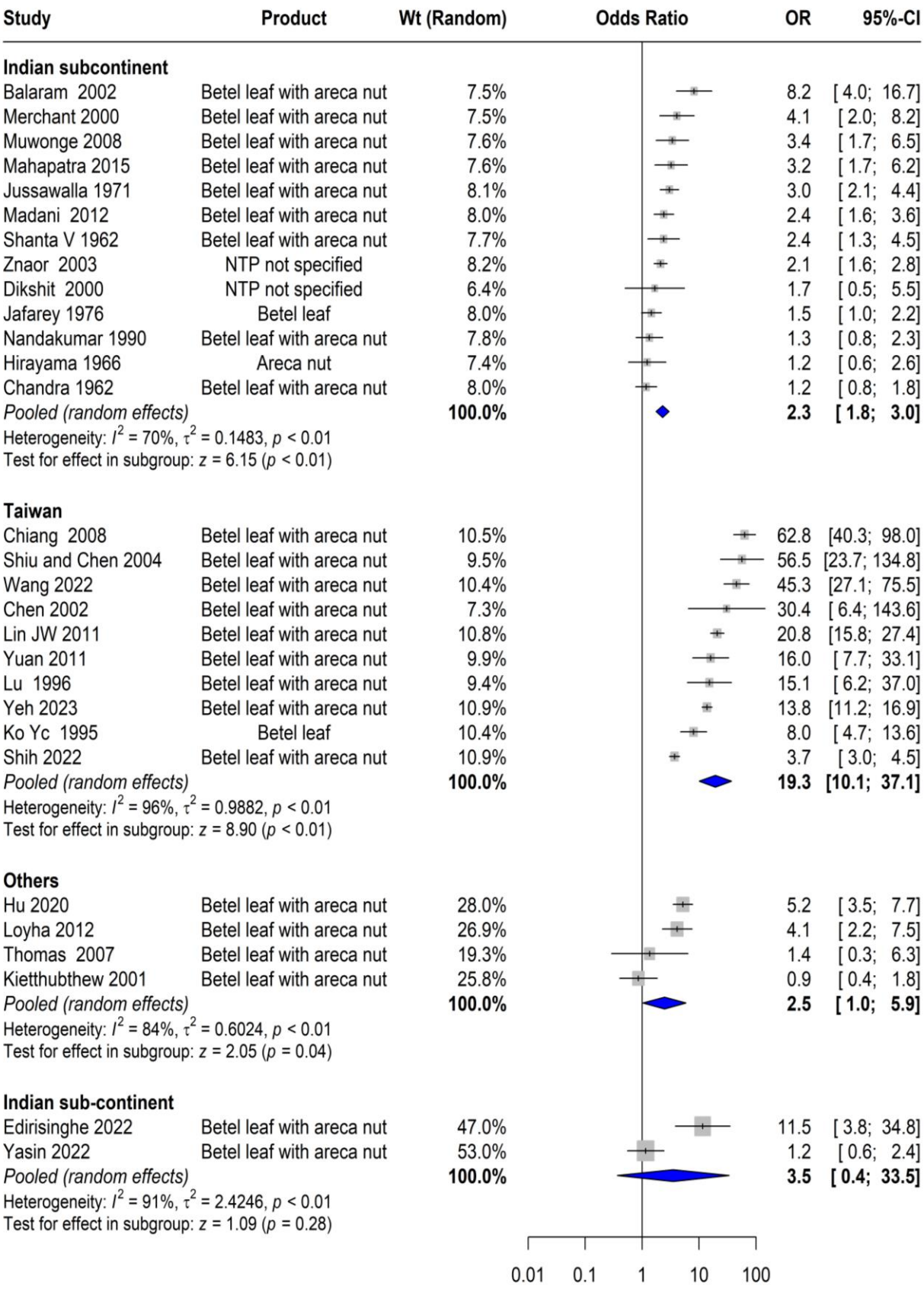


Figure S 7.3 Association of Oral cancer by Exclusive user

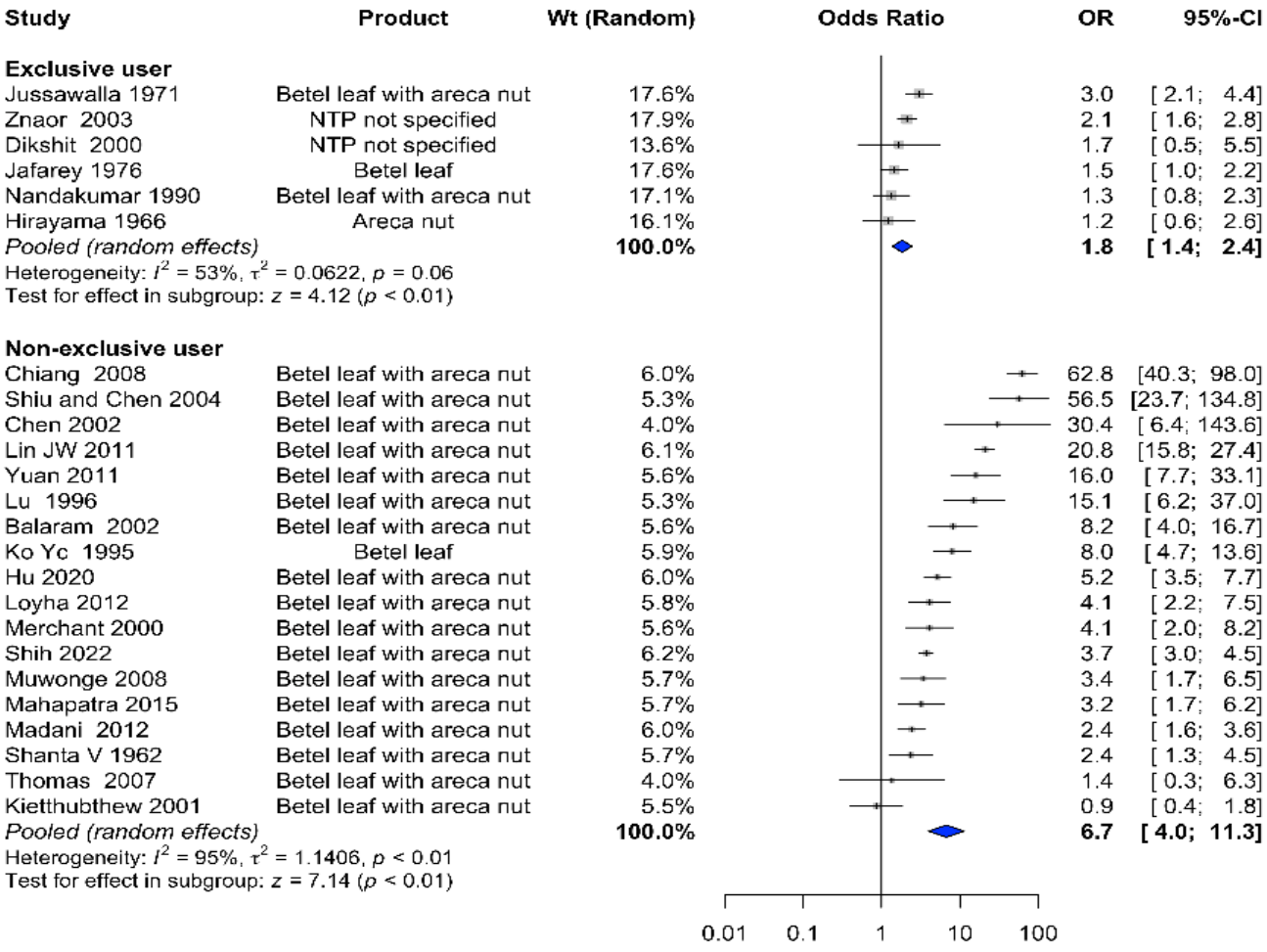


Figure S 7. 4 Association of Oral cancer by Publication Year

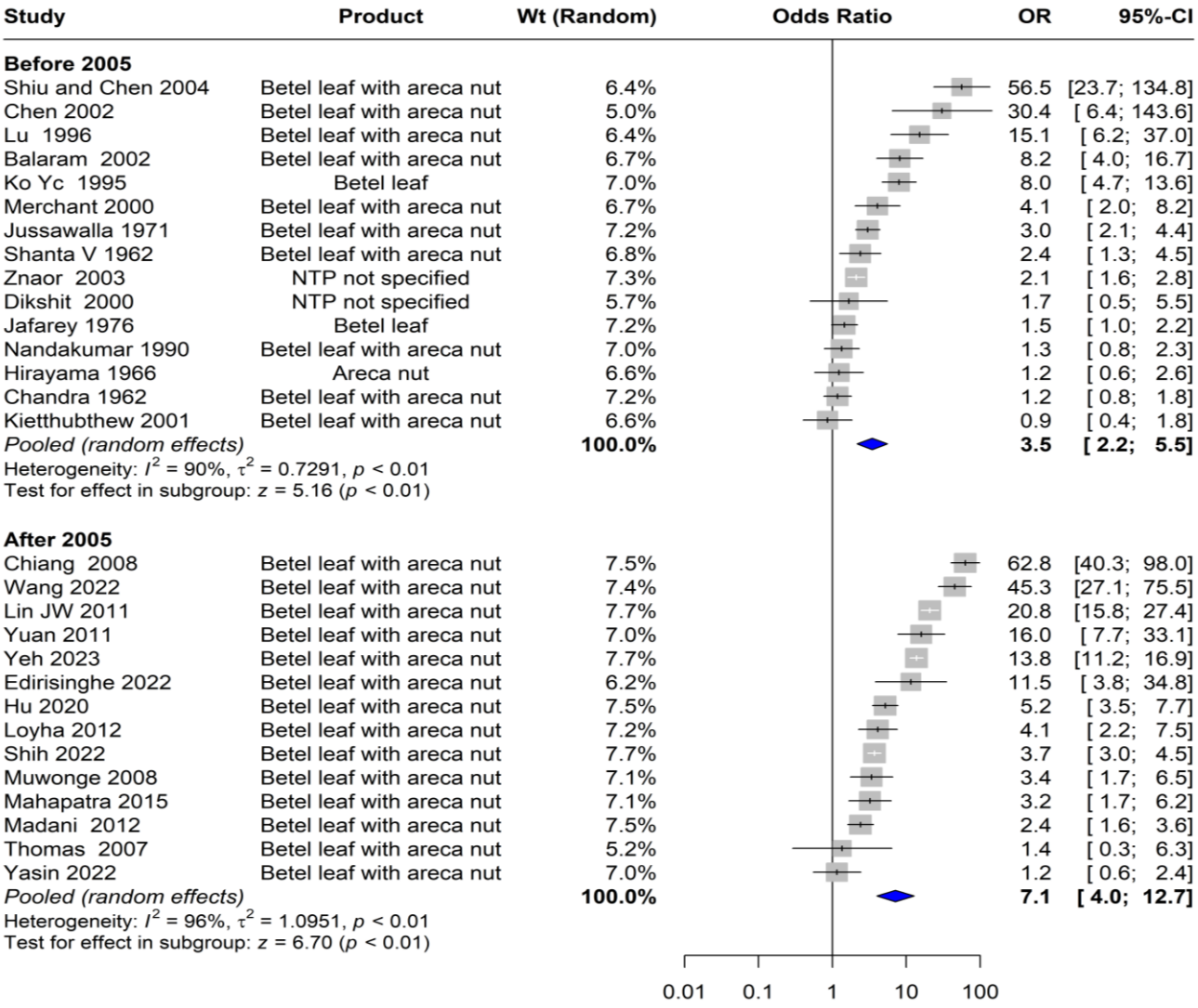


Figure S 7.5 Association of Pharyngeal cancer by Country

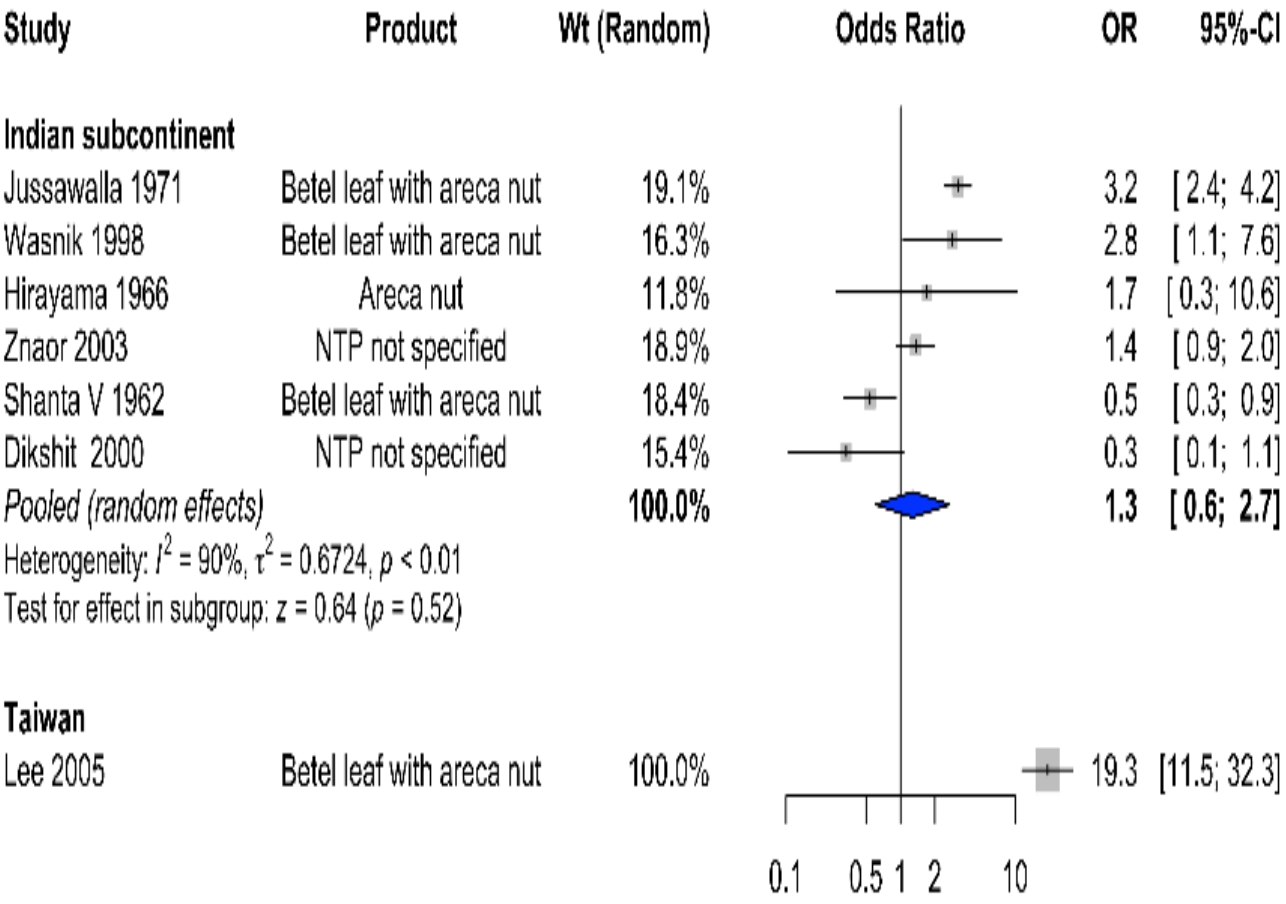


Figure S 7. 6 Association of Pharyngeal cancer by Comparator

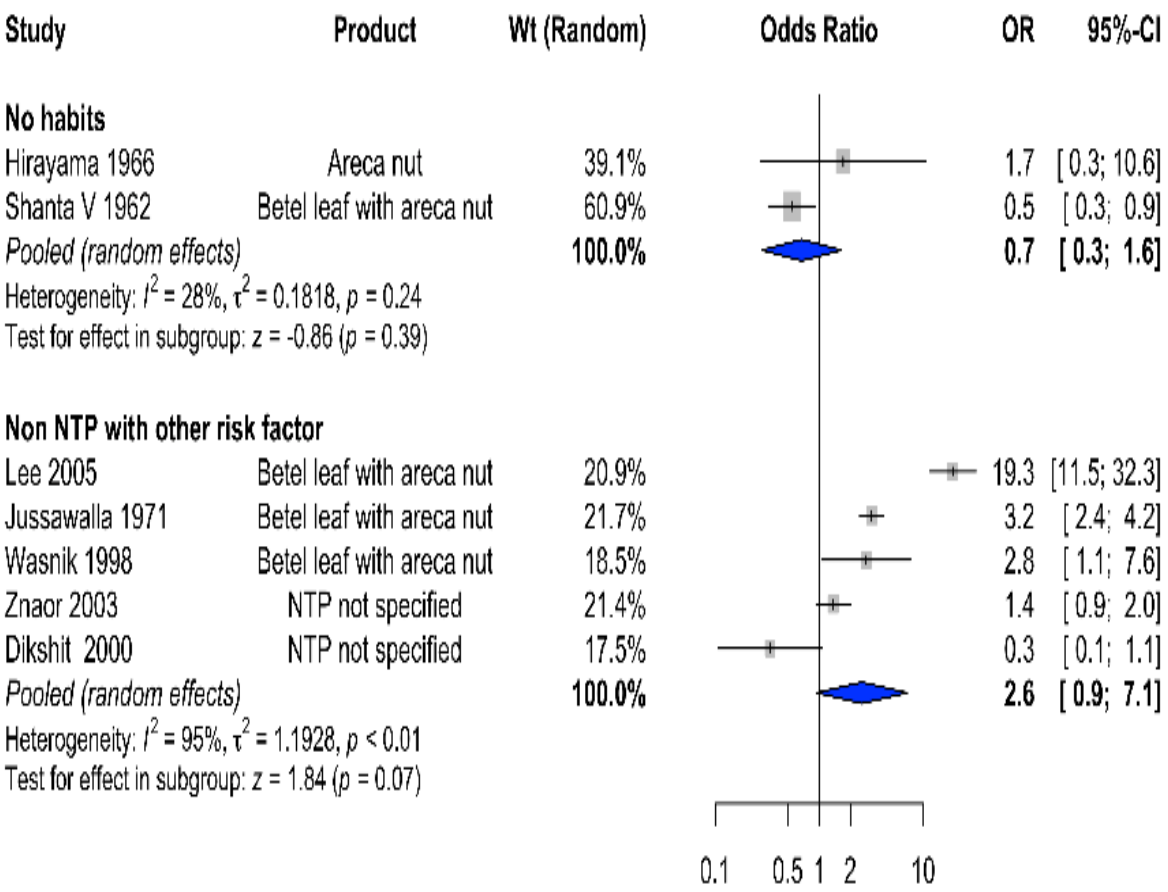


Figure S 7.7 Association of Pharyngeal cancer by Exclusive user

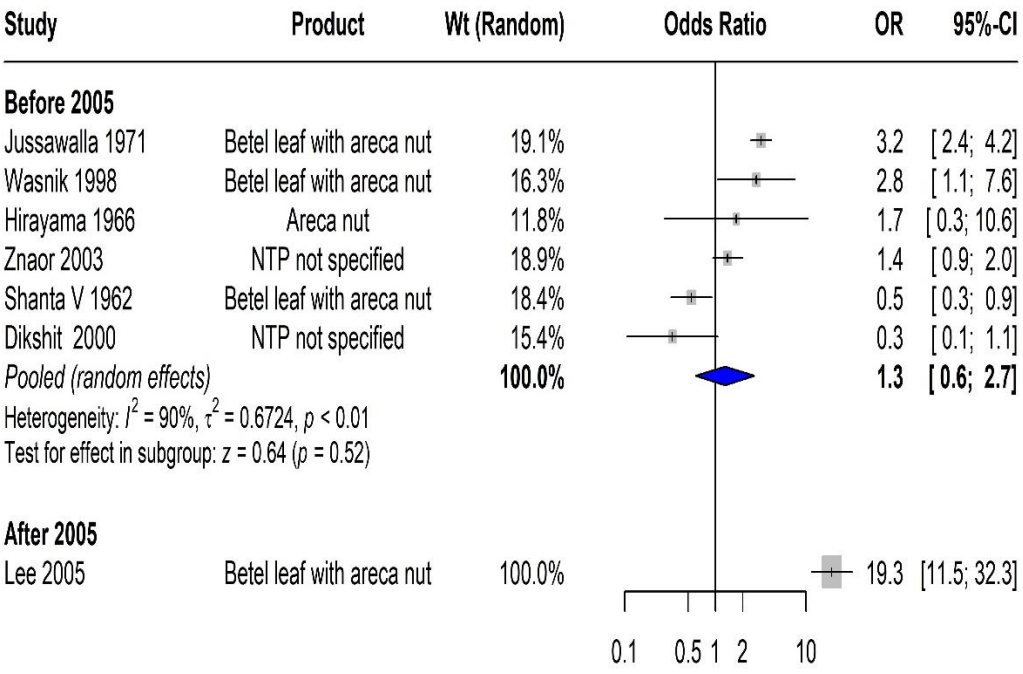


Figure S 7. 8 Association of Pharyngeal cancer by Publication Year

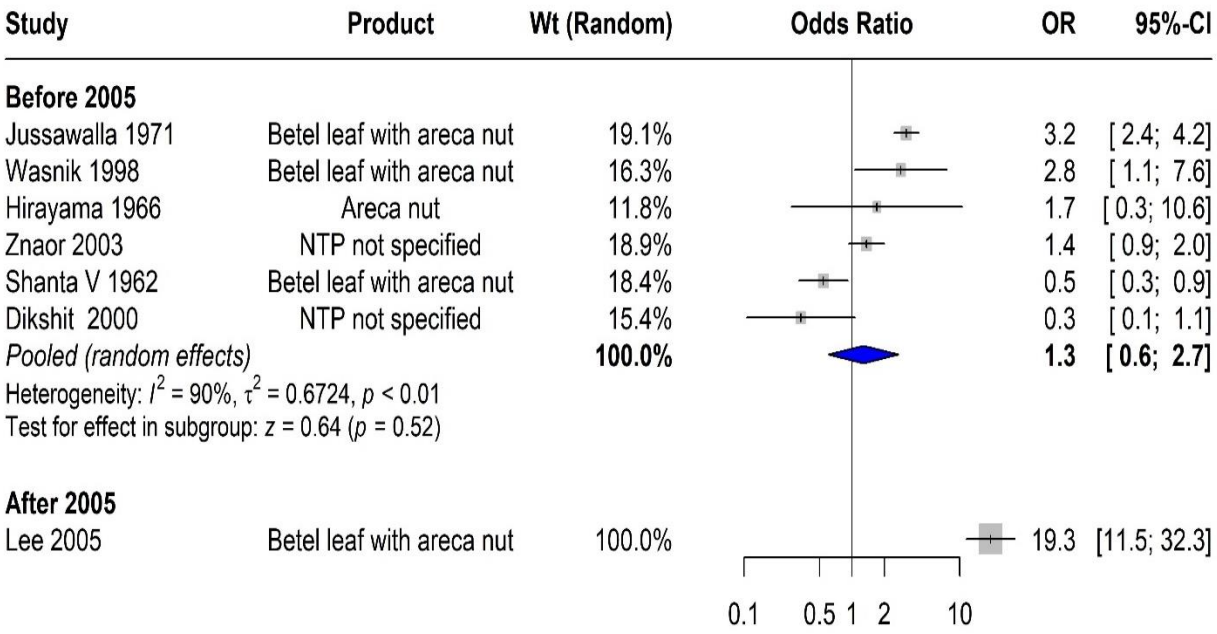


Figure S7.9 Association of esophageal cancer with NTP by comparator.

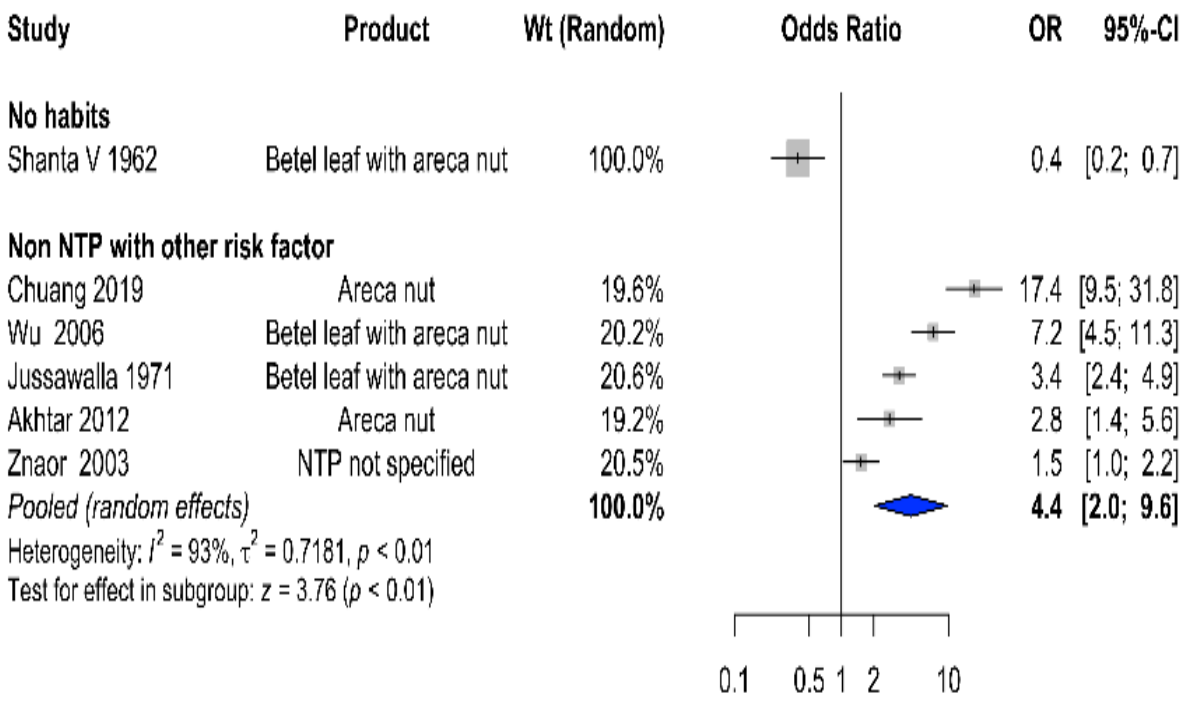


Figure S7.10 Association of Esophageal cancer by Country

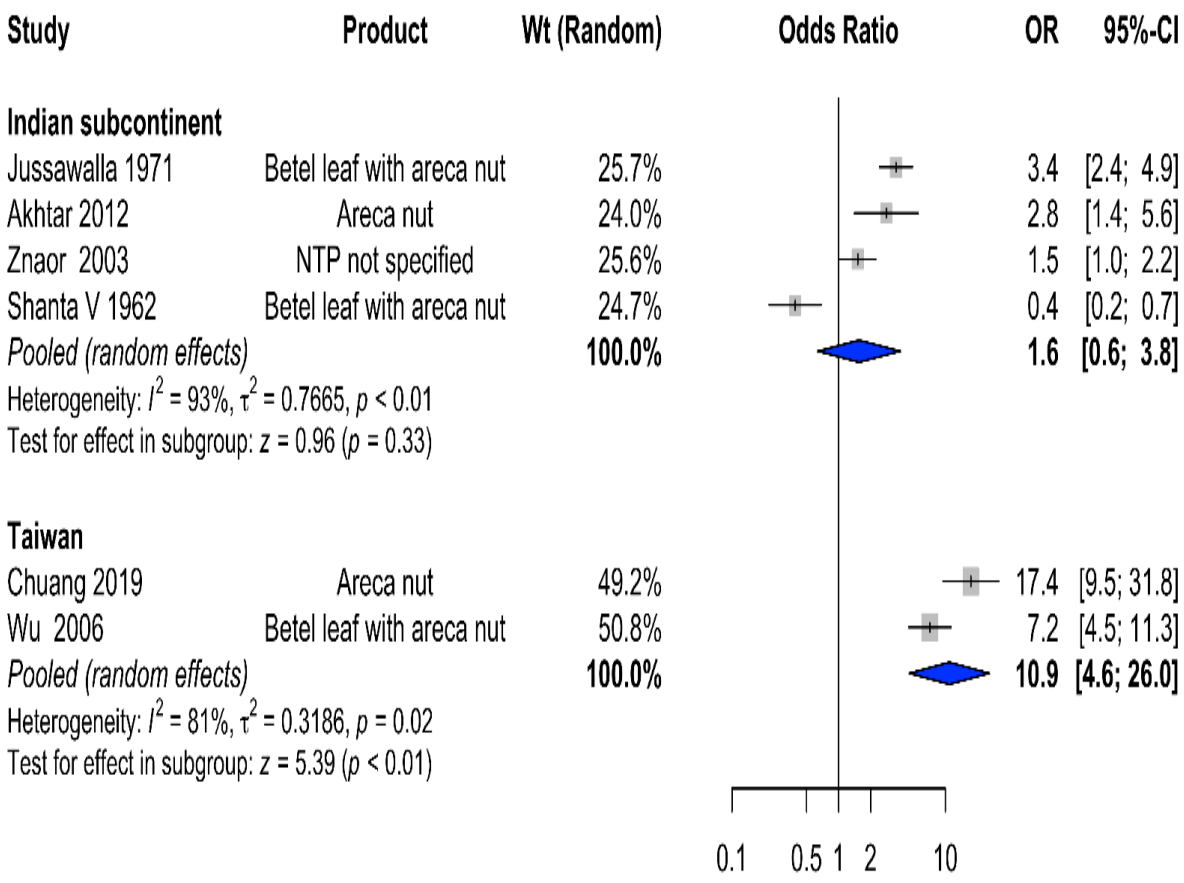


Figure S 7.11 Association of esophageal cancer by Exclusive user

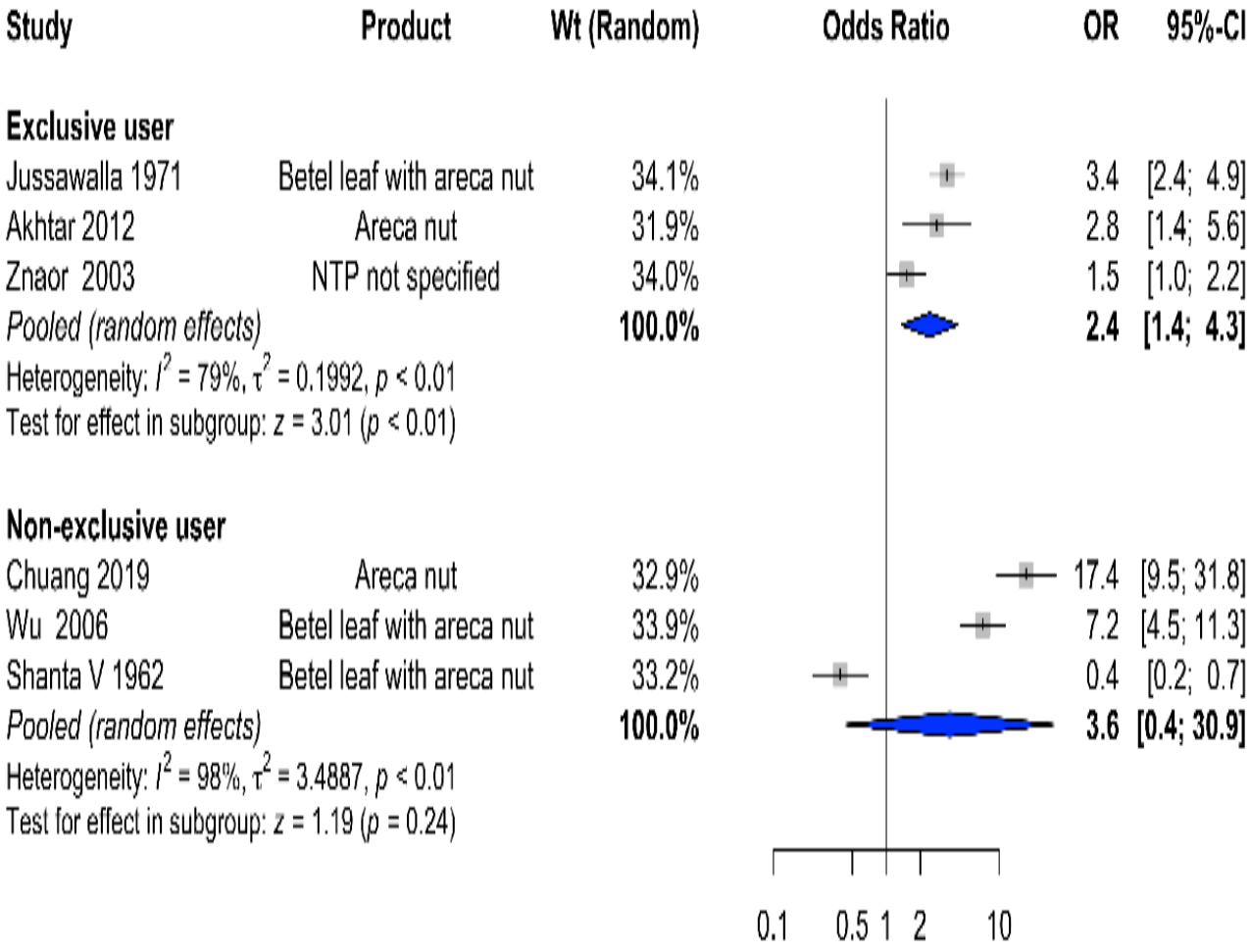


Figure S 7.12 Association of Esophageal cancer by Publication Year

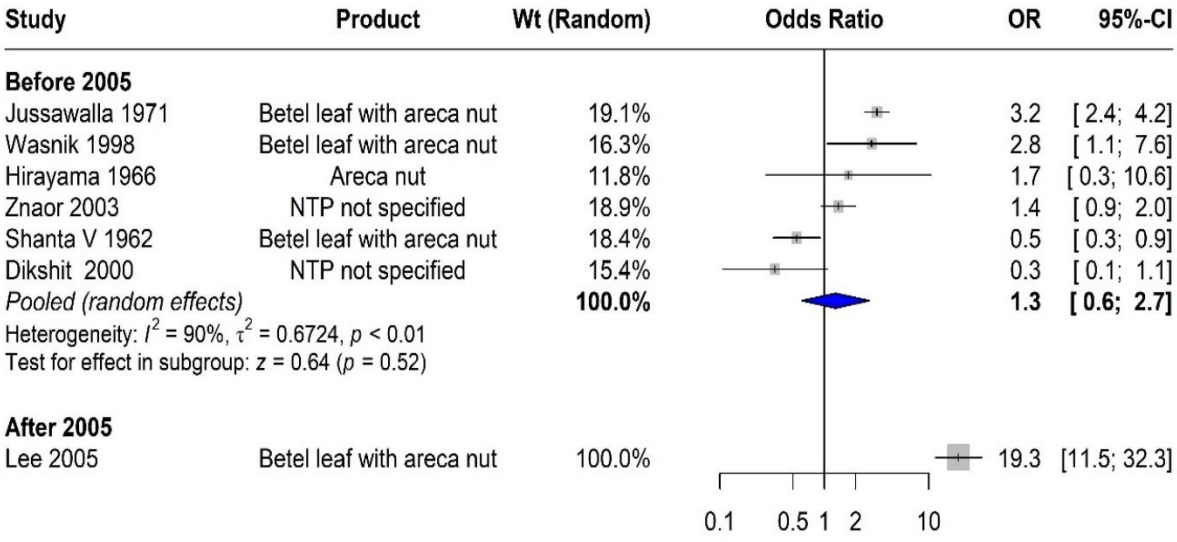


Figure S 7.13 Association of OPMD by comparator

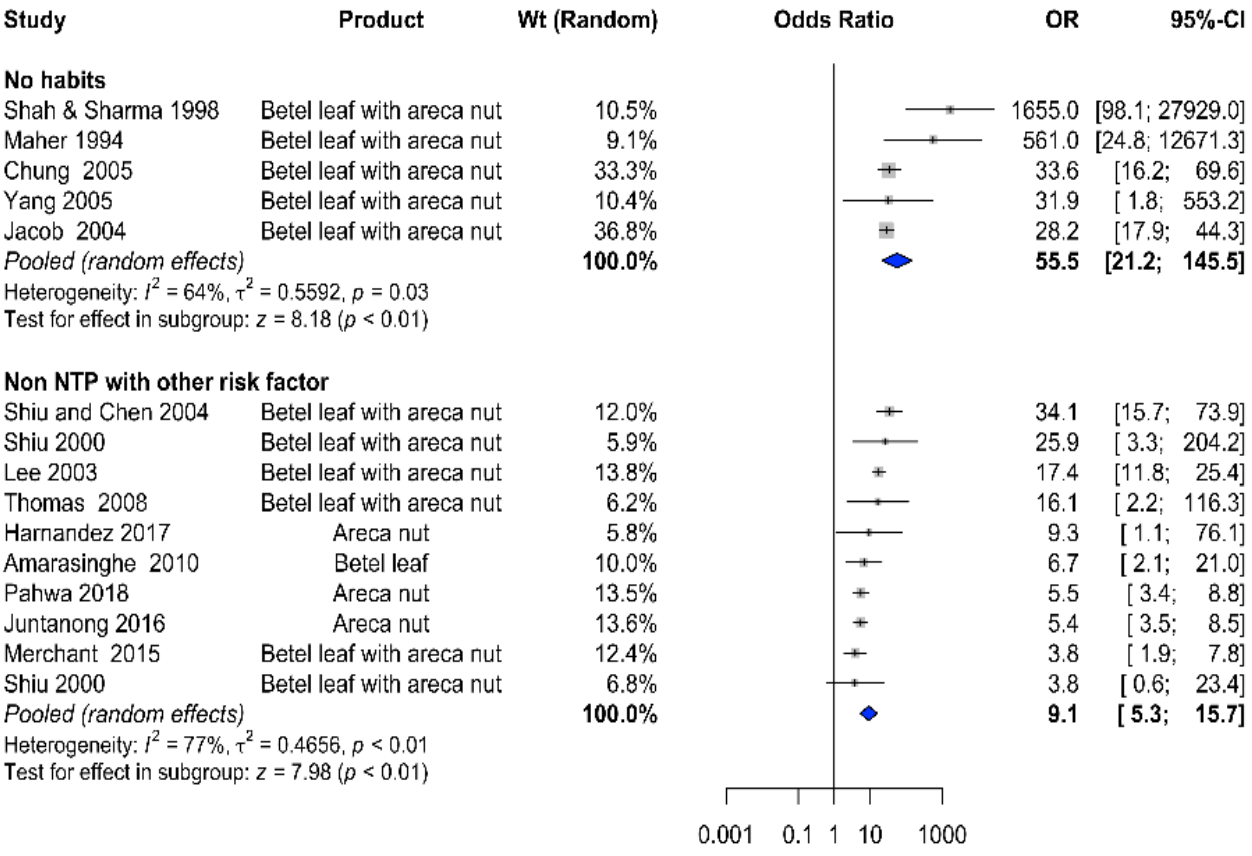


Figure S 7.14 Association of OPMD by country

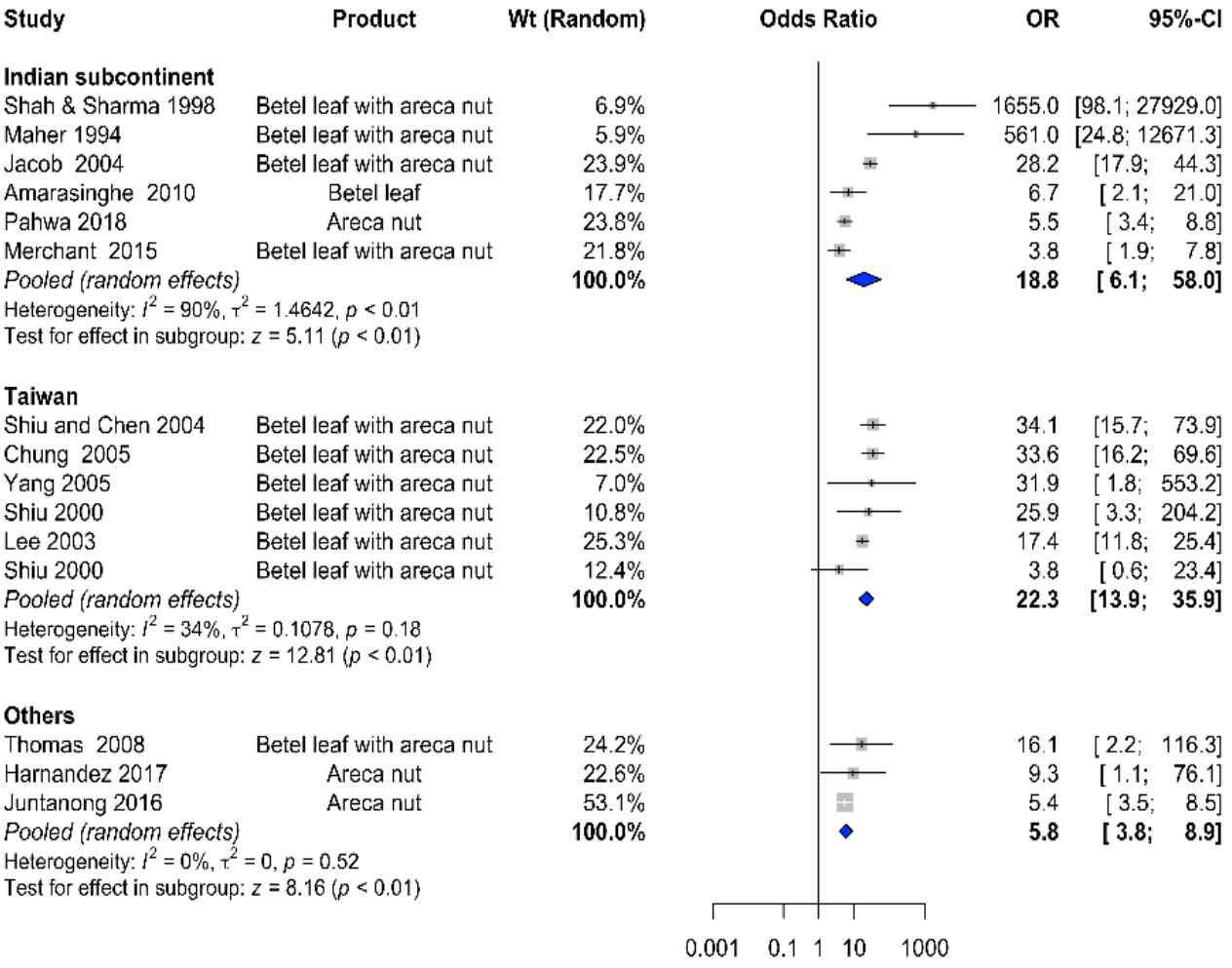


Figure S 7.15 Association of OPMD by Exclusive user

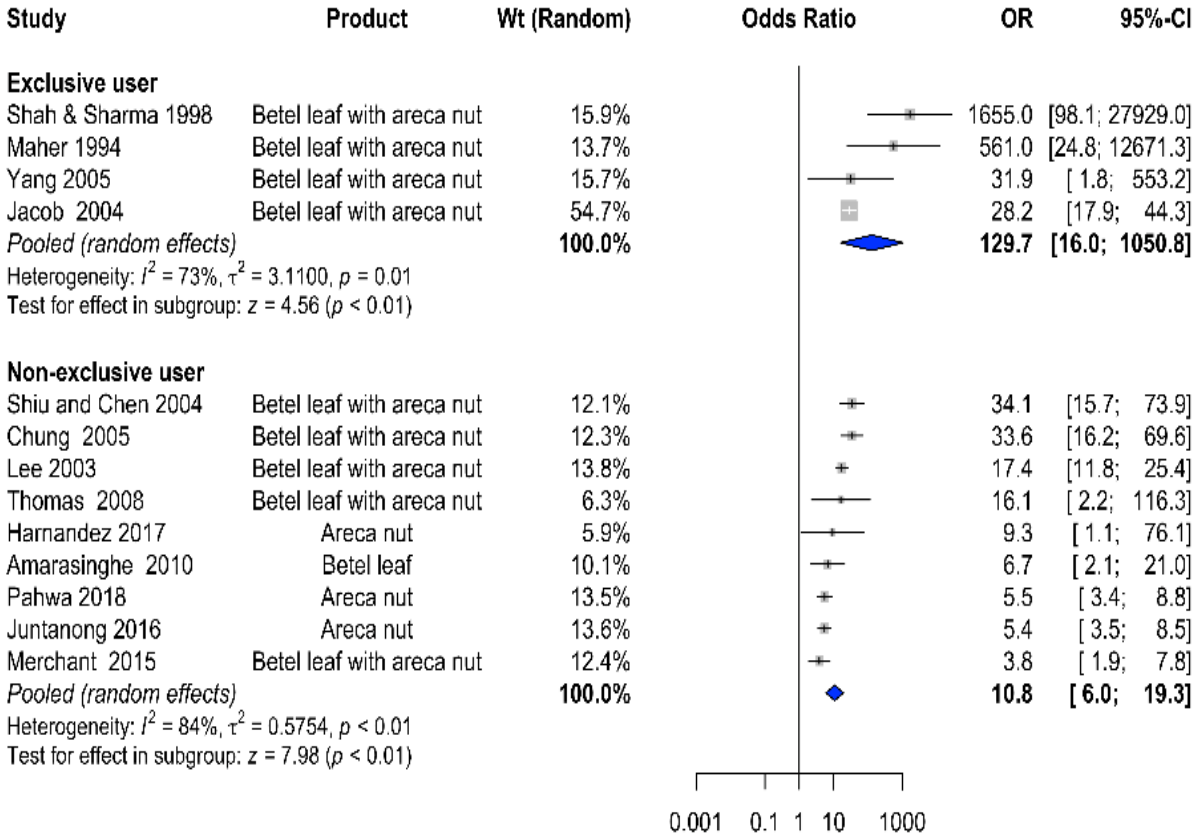


Figure S 7.16 Association of OPMD by Publication Year

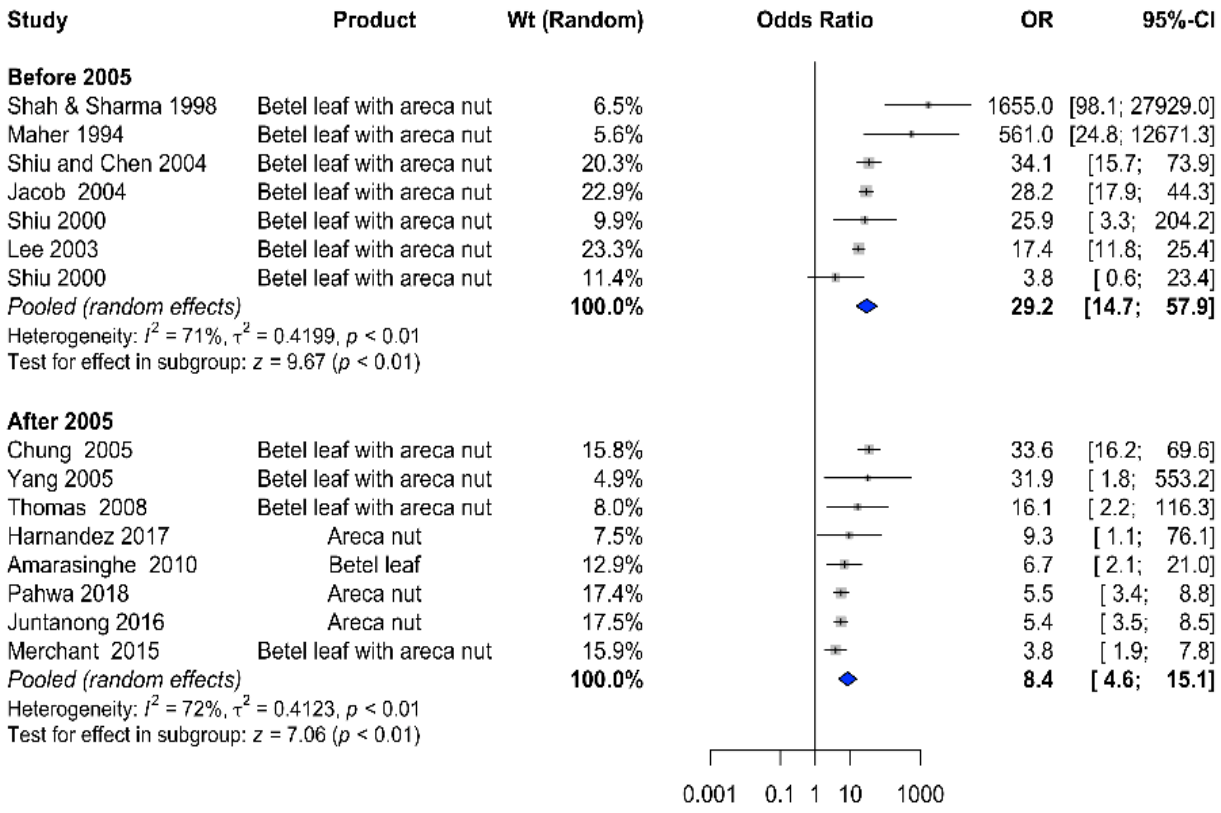


Figure S 7.17 Association of OPMD by User Type

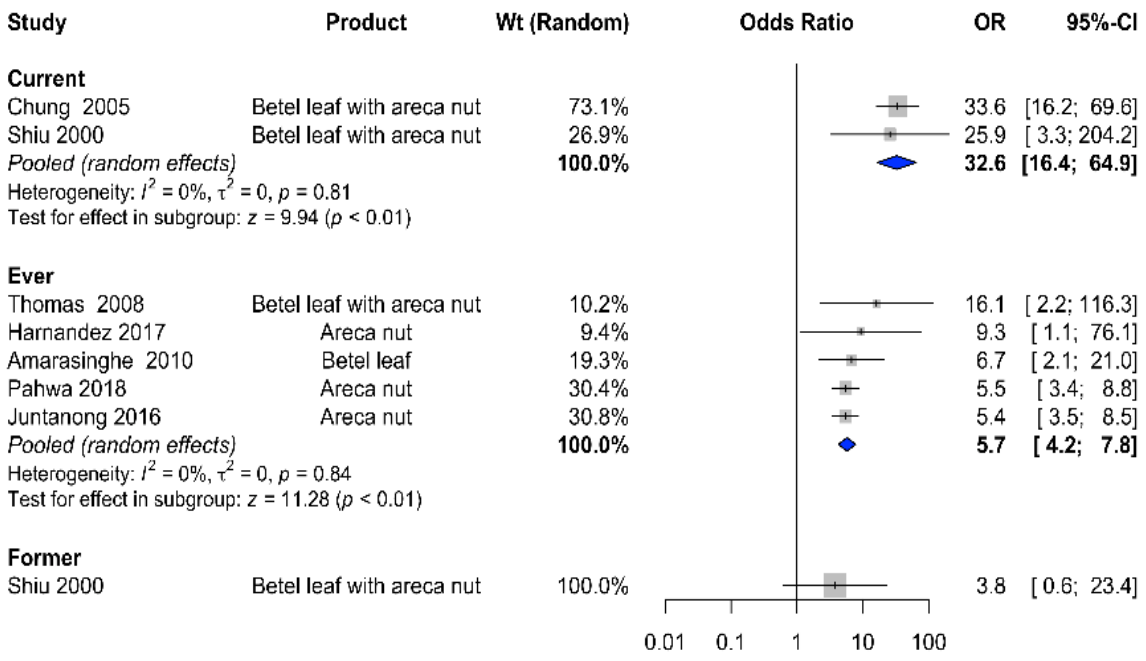


Figure 8: Funnel Plot

Figure S8.1: Funnel Plot of published studies of association of oral cancer and NTP

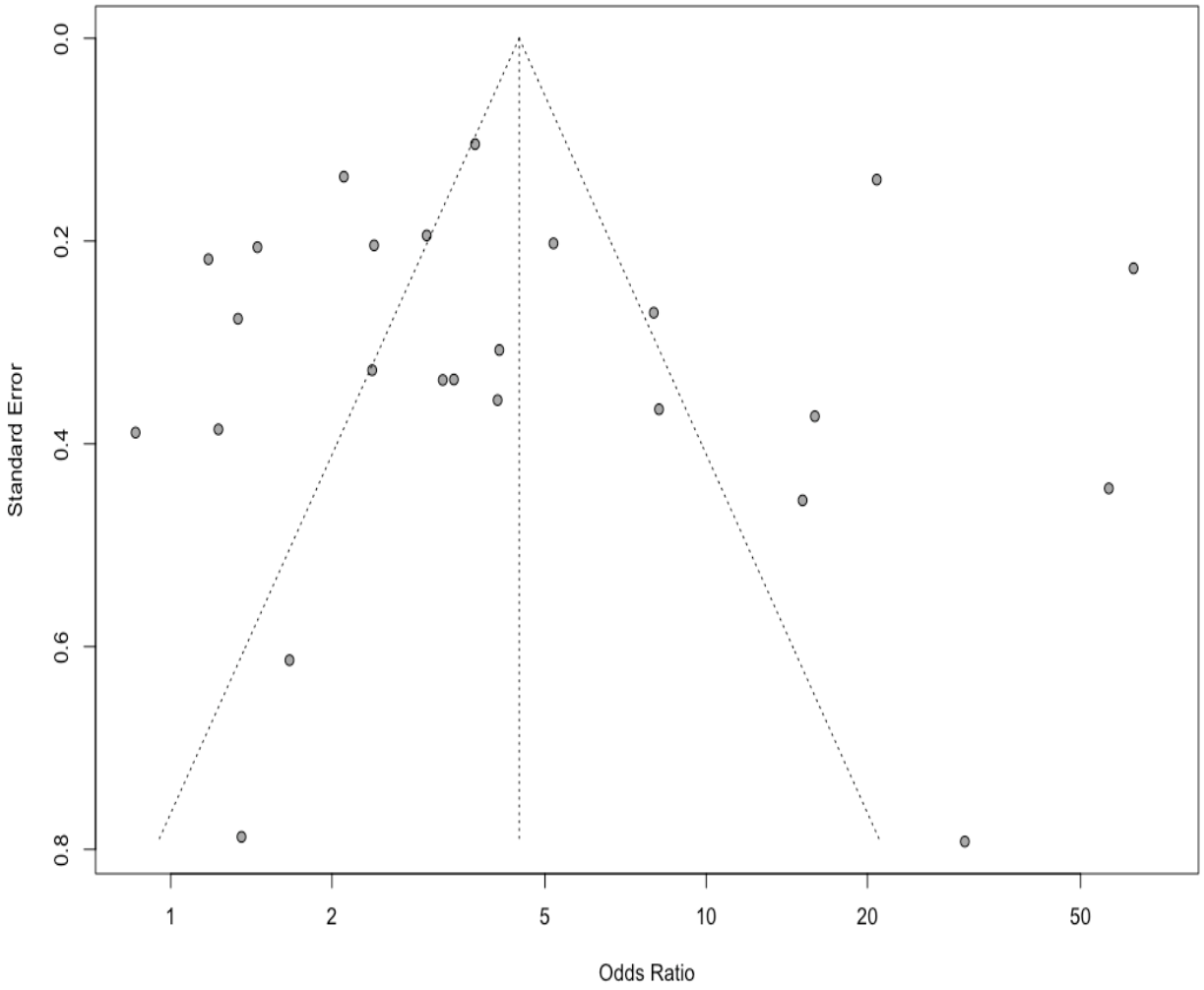
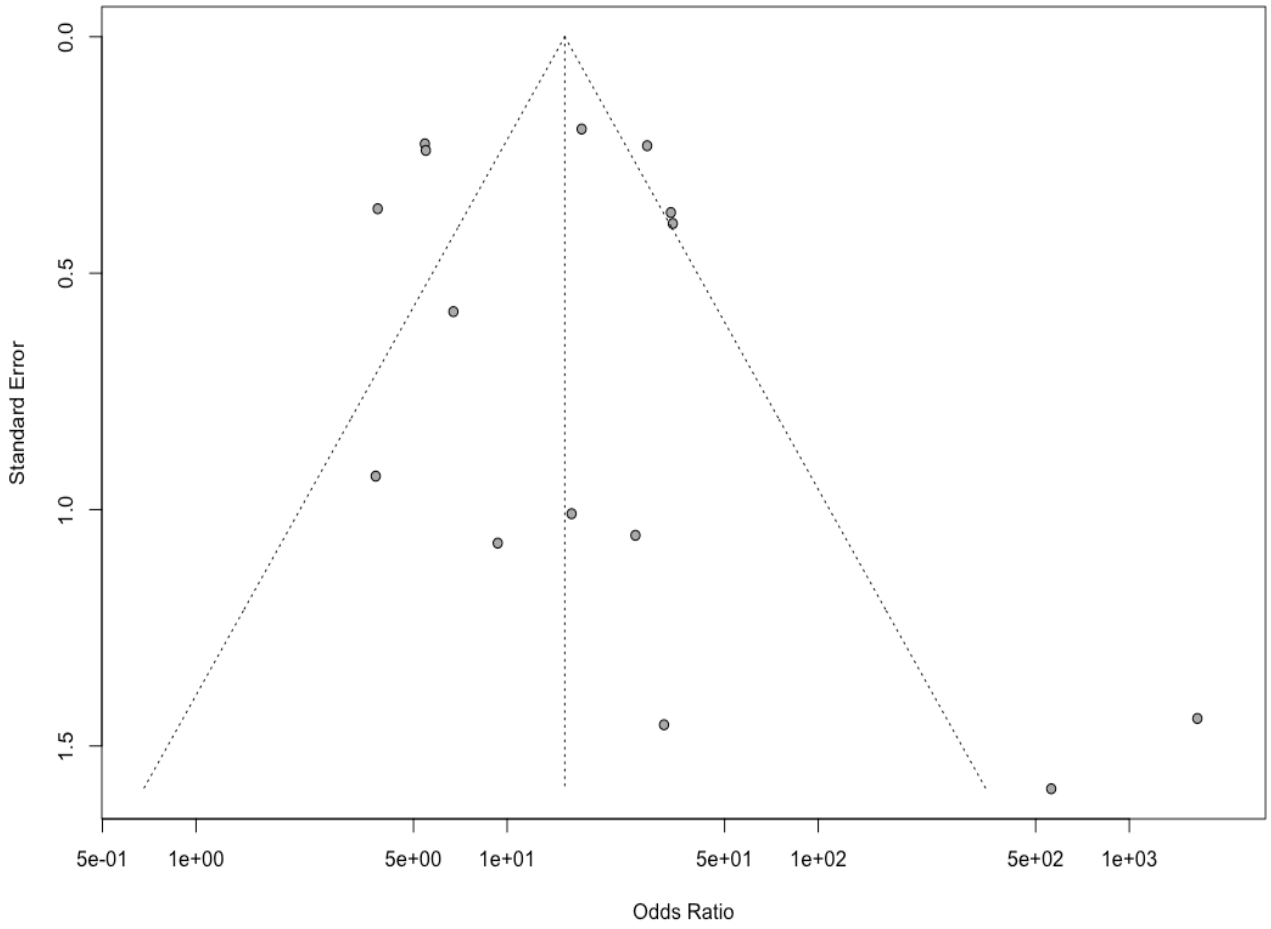


Figure S8.2: Funnel Plot of published studies of association of OPMD and NTP



9 Risk of Bias assessment

Table S5: Risk of bias Assessment of studies included in the review.

Case-control studies										
S.No.	**Study ID**	**Selection (S1)**	**Selection (S2)**	**Selection (S3)**	**Selection (S4)**	**Comparability (C1)**	**Exposure (E1)**	**Exposure (E2)**	**Exposure (E3)**	**Total score (9)**
1.	Mahapatra et al. 2015	1	1	0	1	1	1	1	1	7
2.	Nandakumar et al. 1990	1	1	0	1	2	1	1	0	7
3.	Jacob et al. 2004	1	1	1	1	2	1	0	0	7
4.	Shah and Sharma 1998	1	1	0	1	1	1	1	0	6
5.	Dikshit et al. 2000	1	1	1	1	1	1	0	1	7
6.	Lee et al. 2003	1	1	0	1	1	1	0	0	5
7.	Shih et al. 2022	1	1	0	1	1	1	1	0	6
8.	Cher et al. 2002	1	1	0	1	1	1	1	0	6
9.	Wu et al. 2006	1	1	0	1	1	1	0	0	5
10.	Merchant et al. 2000	1	1	0	1	1	0	1	0	5
11.	Balram et al. 2002	1	1	0	1	1	1	1	0	6

12.	Ko et al. 1995	1	1	0	1	1	1	0	0	6
13.	Hirayama et al. 1996	1	1	0	1	1	1	1	0	6
14.	Meher et al. 1994	1	1	0	1	1	1	0	1	6
15.	Shiu et al. 2000	1	1	0	1	1	1	1	0	6
16.	Loyha et al. 2012	1	1	0	1	1	1	1	1	7
17.	Akhtar et al. 2012	1	1	0	1	1	1	1	0	6
18.	Yuan et al. 2011	1	1	0	1	1	1	1	0	6
19.	Lee et al. 2005	1	1	0	1	1	1	1	1	7
20.	Thomas et al. 2007	1	1	0	1	1	1	0	0	5
21.	Shanta et al. 1962	1	1	1	1	1	1	0	0	6
22.	Mehrotra et al. 2012	1	1	1	1	1	1	1	0	7
23.	Chiang et al. 2008	1	1	0	1	1	1	0	0	5
24.	Jussawalla et al. 1981	1	1	0	1	1	1	1	1	7
25.	Wasnik et al. 1998	1	1	0	1	1	1	0	1	6
26.	Lu et al. 1996	1	1	1	1	1	1	1	0	7
27.	Madani et al. 2012	1	1	0	0	1	1	1	1	6
28.	Yina Hu. et al.2020	1	1	0	1	1	1	1	0	6
29.	Amarsinghe et al. 2010	1	1	1	1	1	1	1	1	8
30.	Thomas et al. 2008	1	1	1	1	1	1	1	0	7

31.	Jafarey et al. 1976	1	1	1	1	1	1	1	0	7
32.	Yang et al. 2005	1	1	1	1	1	1	0	1	7
33.	Kiett hub thew et al. 2001	1	1	1	1	1	1	1	0	7
34.	Shiu and chan2004	1	1	0	1	1	1	1	1	7
35.	Muwonge et al. 2008	1	1	1	1	2	1	1	0	8
36.	Znaor et al. 2003	1	1	0	1	2	1	1	1	8
37.	Yeh et al. 2023	1	1	0	1	2	1	1	1	8
39.	Wange et al. 2022	1	1	0	1	1	1	1	1	7
40	Edirisinghe et al. 2022	1	1	1	1	2	1	1	1	9
Cohort study										
S. No	**Study ID**	**Selection (S1)**	**Selection (S 2)**	**Selection (S 3)**	**Selection (S 4)**	**Comparability (C 1)**	**Outcome (O 1)**	**Outcome (O 2)**	**Outcome (O 3)**	**Total Score (9)**
1	Lin J W et al. 2011	1	1	0	0	2	0	0	1	5
2	Klongnoi 2022	1	1	1	1	2	0	0	0	6
Cross-sectional studies										
S. No	**Study ID**	**Selection (S1)**	**Selection (S 2)**	**Selection (S 3)**	**Selection (S 4)**	**Comparability (C 1)**	**Outcome (O 1)**	**Outcome (O 2)**	**Total score (10)**	
1	Rimal et al. 2019	1	1	1	0	1	0	1	5	
2	Chung et al. 2005	1	1	1	1	2	0	1	7	
3	Chuang et al. 2019	1	1	1	1	2	2	1	9	
4	Hernandez et al. 2017	1	1	1	1	2	1	1	8	

5	Pahwa et al. 2018	0	1	1	1	1	2	1	7	
6	Juntanong et al. 2016	1	1	1	1	1	0	1	6	
7	Yasin et al. 2022	1	0	1	2	0	1	1	6	

10. List of articles excluded from this review.

Table S 6.1: Reason for exclusion: Studies with wrong exposure.

S. No	Title	Year of publication	Journal	Authors
	Epidemiological and clinical correlates of oral squamous cell carcinoma in patients from north-west Pakistan.	2019	JPMA. The Journal of the Pakistan Medical Association	Ahmed et al.
2.	Oral cancer: Clinicopathological features and associated risk factors in a high-risk population presenting to a major tertiary care center in Pakistan.	2020	PloS one	Anwar et al.
3.	Tobacco (kretek) smoking, betel quid chewing and risk of oral cancer in a selected Jakarta population.	2014	Asian Pacific journal of cancer prevention : APJCP	Amtha R et al.
4.	Cancer and mortality among users and nonusers of snus.	2008	International journal of cancer	Roosaar A et al.
5.	Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in Karunagappally, Kerala, India: Karunagappally cohort study.	2011	Cancer science	Jayalekshmi PA et al.
6.	Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study.	1995	International journal of cancer	Idris AM et al.
7.	Novel risk factors for primary prevention of oesophageal carcinoma: a case-control study from Sri Lanka.	2018	BMC cancer	Talagala IA et al.
8.	Is workplace screening for potentially malignant oral disorders feasible in India?	2010	Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology	Warnakulasuriya S et al.
9.	Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India.	1990	Journal of epidemiology and community health	Sankaranarayanan R et al.
10	Intervention study for primary prevention of oral cancer among 36 000 Indian tobacco users.	1986	Lancet (London, England)	Gupta PC et al.

S. No	Title	Year of publication	Journal	Authors
11.	Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden.	2005	Acta oto-laryngologica	Rosenquist K et al.
12.	Tobacco usage in patients with head and neck carcinomas: a follow-up study on habit changes and second primary oral/oropharyngeal cancers.	1983	Journal of the American Dental Association (1939)	Silverman S Jr et al.
13.	Smoking and chewing of tobacco in relation to cancer of the upper alimentary tract.	1955	British medical journal	SANGHVI LD et al.
14.	Tobacco and oral health.	1992	Dental world (London, England)	S et al.
15.	Smokeless tobacco: betel quid chewing among adult women in Lao People's Democratic Republic.	1997	Tobacco control	Asma S et al.
16.	Upper alimentary tract cancer in Natal Indians with special reference to the betel-chewing habit.	1969	British journal of cancer	Schonland M et al.
17.	Smokeless tobacco: a problem for health professionals and educators.	1986	Journal of the Medical Association of Georgia	West JT
18.	Nass use, cigarette smoking, alcohol consumption and risk of oral and oesophageal precancer.	1992	European journal of cancer. Part B, Oral oncology	Evstifeeva TV et al.
19.	Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial.	2005	Lancet (London, England)	Sankaranarayanan R et al.
20.	Prevalence of oral lesions in relation to habits: Cross-sectional study in South India.	2006	Indian journal of dental research: official publication of Indian Society for Dental Research	Saraswathi TR et al.
21.	Oral leukoplakia in relation to tobacco habits. A ten-year follow-up study of Bombay policemen.	1972	Oral surgery, oral medicine, and oral pathology	Mehta FS et al.
22.	Oral squamous cell carcinoma and associated risk factors in Jazan, Saudi Arabia: a hospital-based case control study.	2015	Asian Pacific journal of cancer prevention: APJCP	Quadri MF et al.
23.	Effect of betel chewing on the oral mucosa.	1969	British journal of cancer	Tennekoon GE et al.
24.	Prevalence of oral cancer and potentially malignant lesions among shammah users in Yemen.	2007	Oral oncology	Scheifele C et al.

S. No	Title	Year of publication	Journal	Authors
25.	Oral cancer risk factors among Mexican American Hispanic adolescents in South Texas.	2009	Journal of dentistry for children (Chicago, Ill.)	Shetty K et al.
26.	Chewing tobacco, alcohol, and the risk of erythroplakia.	2000	Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	Hashibe M et al.
27.	Oral leukoplakia and adolescent smokeless tobacco use.	1991	Oral surgery, oral medicine, and oral pathology	Creath CJ et al.
28.	[Snufftaking and oral cancer. A retrospective study].	1978	Tandlakartidningen	AxÃ©ll T et al.
29.	[Cancer risk with the use of smokeless tobacco (snuff and chewable tobacco)].	1988	Den Norske tannlaegeforenings tidende	Dahl JE et al.
30.	Oral leukoplakia status six weeks after cessation of smokeless tobacco use.	1999	Journal of the American Dental Association (1939)	Martin GC et al.
31.	Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India.	2001	British journal of cancer	Phukan RK et al.
32.	Oral cancer via the bargain bin: The risk of oral cancer associated with a smokeless tobacco product (Naswar).	2017	PloS one	Khan Z et al.
33.	Keeping chewing tobacco in the cheek pouch overnight (night quid) increases risk of cheek carcinoma.	1996	European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	Ghosh S et al.
34.	Risk factors for esophageal cancer in Coimbatore, southern India: a hospital-based case-control study.	2004	Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology	Chitra S et al.
35.	The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia.	2000	International journal of cancer	Lagergren J et al.

S. No	Title	Year of publication	Journal	Authors
36.	Primary prevention trial of oral cancer in india: a 10-year follow-up study.	1992	Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology	Gupta PC et al.
37.	Tobacco and betel nut chewing behaviour and its association with potentially malignant disorders in Chennai	2019	Indian J. Public Health Res. Dev.	Aparnaa, M. et al.
38.	PREVALENCE OF ORAL POTENTIALLY MALIGNANT AND MALIGNANT LESIONS AND TOBACCO USE AMONG THE OLDER ADULTS ATTENDING A SCREENING CLINIC IN NOIDA (INDIA): A CROSS-SECTIONAL STUDY	2019	J. Geriatr. Oncol.	Nethan, S.T et al.
39.	Invited commentary: Smokeless tobacco-an important contributor to cancer, but more work is needed	2016	Am. J. Epidemiol.	Freedman, N.D.
40.	Risk factors for head and neck squamous cell carcinomas amongst patients attending a tertiary care centre of Assam	2016	Clin. Epidemiol. Global Health	Mahanta, B.N. et al.
41.	Risk assessment of smokeless tobacco among oral precancer and cancer patients in eastern developmental region of Nepal	2015	Int. J. Oral Maxillofac. Surg.	Rimal, J. et al.
42.	Tobacco or oral health	2005	Bull. WHO	Reibel, J.
43.	Cancer from snuff?	2003	Krebs durch schnupftabak?	Pfaue, D. et al.
44.	Re: Turkish smokeless tobacco 'Maras Powder'	1999	Prev. Med.	Erenmemisoglu, A.
45.	Correlation of histopathological patterns of OSCC patients with tumor site and habits.	2022	BMC oral health	Yasin MM and Abbas Z and Hafeez A

Table S 6.2: Reason for exclusion – Studies with wrong outcome

S. No	Title	Year	Journal	Authors
1.	[wareness and knowledge of oral cancer among 1 483 residents in Beijing].	2020	Beijing da xue xue bao. Yi xue ban = Journal of Peking University. Health sciences	Zhou XH et al.
2.	Oral cancer incidence rates from 1997 to 2016 among men in Taiwan: Association between birth cohort trends and betel nut consumption.	2020	Oral oncology	Su SY et al.
3.	A Survey of Areca (Betel) Nut Use and Oral Cancer in the Commonwealth of the Northern Mariana Islands.	2020	Hawai'i journal of health & social welfare	Narayanan AM et al.
4.	Tobacco or oral health: past progress, impending challenge.	2000	Journal of the American Dental Association (1939)	Jones RB
5.	Carcinoma and dysplasia in oral leukoplakias in Taiwan: prevalence and risk factors.	2006	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	Lee JJ et al.
6.	Population-based screening program for reducing oral cancer mortality in 2,334,299 Taiwanese cigarette smokers and/or betel quid chewers.	2017	Cancer	Chuang SL et al.
7.	Evaluation of risk factors of oral cancer.	2011	Mymensingh medical journal: MMJ	Ekramuddaula et al.
8.	Oral cancer incidence disparity among ethnic groups on Guam.	2005	Pacific health dialog	Haddock RL
9.	The use of tobacco-free betel-quid in conjunction with alcohol/tobacco impacts early-onset age and carcinoma distribution for upper aerodigestive tract cancer.	2011	Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology	Lee CH et al.
10.	The incidence and risk of developing a second primary esophageal cancer in patients with oral and pharyngeal carcinoma: a population-based study in Taiwan over a 25 year period.	2009	BMC cancer	Lee KD et al.
11.	Intervention study for primary prevention of oral cancer among 36 000 Indian tobacco users.	1986	Lancet (London, England)	Gupta PC et al.
12.	Lips as red as blood: areca nut lip staining.	2013	JAMA dermatology	Bicknell LM et al.

S. No	Title	Year	Journal	Authors
13.	Oral verrucous carcinoma. Incidence in two US populations.	1998	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	Bouquot JE
14.	The new pan-Asian paan problem.	2001	Lancet (London, England)	Mack TM
15.	Possible aetiology of oral cancer in Papua New Guinea.	1985	Papua and New Guinea medical journal	MacLennan R and et al.
16.	Tobacco chewing in India.	2008	International journal of epidemiology	Sauvaget C et al.
17.	Individual and Integrated Effects of Potential Risk Factors for Oral Squamous Cell Carcinoma: A Hospital-Based Case-Control Study in Jazan, Saudi Arabia.	2018	Asian Pacific journal of cancer prevention: APJCP	Alharbi F et al.
18.	Oral cancer in northern Thailand.	1990	Experimental pathology	Reichart PA et al.
19.	Prevalence of quid-induced lichenoid reactions among western Indian population.	2015	Journal of experimental therapeutics & oncology	Solanki J and Gupta S
20.	Incidence and patterns of second primary malignancies following oral cavity cancers in a prevalent area of betel-nut chewing: a population-based cohort of 26,166 patients in Taiwan.	2011	Japanese journal of clinical oncology	Chen PT et al.
21.	Study of oral epithelial atypia among Sudanese tobacco users by exfoliative cytology.	2003	Anticancer research	Ahmed HG et al.
22.	Prevalence of Oral mucosal lesions and their association with Pattern of tobacco use among patients visiting a dental institution.	2019	Indian journal of dental research : official publication of Indian Society for Dental Research	Verma S et al.
23.	The relation between smokeless tobacco and cancer in Northern Europe and North America. A commentary on differences between the conclusions reached by two recent reviews.	2009	BMC cancer	Lee PN et al.
24.	Prevalence of oral cancer among patients using different forms of tobacco - A retrospective study	2019	Drug Invent. Today	Nandhini, T et al
25.	Prevalence of oral cancer at a tertiary care hospital in Northern India	2017	J. Oral Maxillofac. Surg.	Gupta, A. et al.
26.	Smokeless tobacco uses and public health in countries of South-East Asia region	2014	Indian J. Cancer	Singh, P.K.

S. No	Title	Year	Journal	Authors
27.	Prevalence and type of tobacco habits and tobacco related oral lesions among Wayanad tribes, Kerala, India	2013	Indian J. Public Health Res. Dev.	Deepa, K.C. et al.
28.	Risk factors for nasal malignancies in German men: The South-German Nasal cancer study	2012	BMC Cancer	Greiser, E.M. et al.
29.	Social inequalities, tobacco chewing, and cancer mortality in south India: a case-control analysis of 2,580 cancer deaths among non-smoking non-drinkers	2012	Cancer Causes Control	Gajalakshmi, V et al.
30.	Paan - Social norm or health hazard?	2011	Pharm. J.	Ahmed, F. et al.
31.	Study on effects of tobacco (smokeless and chewed) and arecanut in Indian population not having overt oral malignancy	2011	Eur. J. Cancer	Sonkar, A.A. et al.
32.	Oral and pharyngeal cancer in Yemen: A retrospective registry-based study	2011	Oral Oncol.	Halboub, E. et al.
33.	Incidence of oral cancer in South Karnataka Regional Cancer Centre (2000-2010)	2011	Oral Oncol.	Elengkumaran, S. et al.
34.	Risk assessment of tobacco types and oral cancer	2010	Am. J. Pharmacol. Toxicol.	Madani, A.H. et al.
35.	Cancer in Northeast India - A study in demography and aetiology of carcinoma of hypopharynx and larynx with special reference to the betel-nut chewing habit	1984	INDIAN MED. GAZ.	Baruah, B.D.
36.	Evidence of areca nut consumption in the United States mainland: a cross-sectional study.	2022	BMC public health	Tami-Maury I et al.

Table S 6.3: Reason for exclusion – Others

S. No	Title	Year	Journal	Authors	Reason for exclusion
1.	Tobacco use and oral cancer: a global perspective.	2001	Journal of dental education	Johnson N	Review article
2.	A correlation between oral mucosal lesions and various quid-chewing habit patterns: A cross-sectional study.	2019	Journal of cancer research and therapeutics	Avinash Tejasvi ML et al.	Studies with wrong population
3.	Oral Screening for Pre-cancerous Lesions Among Areca-nut Chewing Population from Rural India.	2015	Oral health & preventive dentistry	Chatterjee R et al.	Studies with wrong population
4.	Betel nut chewing behaviour and its association with oral mucosal lesions and conditions in Ghaziabad, India.	2014	Oral health & preventive dentistry	Prasad S et al.	Studies with wrong population
5.	Synergistic effects of betel quid chewing, tobacco use (in the form of cigarette smoking), and alcohol consumption on the risk of malignant transformation of oral submucous fibrosis (OSF): a case-control study in Hunan Province, China.	2015	Oral surgery, oral medicine, oral pathology and oral radiology	Liu B et al.	Studies with wrong population