**Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Study period** | **Study design** | **Exposure status** | **Inclusion of cigarette/ alcohol users** | **Outcome** | **Odds Ratio/ Relative Risk (95% CIs)** | **Comments** | **Quality assessment (NOS)a** | **Reference** |
| CANCERS |
| India | 2001–2004 | Case–control | SLT with or without additives | No/No | Oral cancer | 0.49 (0.32–0.75) | Exclusive SLT users | Selection\*\*\*\*Comparability\*\*Exposure\* | [[36]](https://paperpile.com/c/bdxIpu/R10mW)  |
| India | 1996–1999 | Case–control | Ever SLT users | Yes/Yes | Oral cancer | 7.31 (3.79–14.1) | Never drinkers adjusted for smoking | Selection\*\*\*\*Comparability\*\*Exposure\* | [[37]](https://paperpile.com/c/bdxIpu/P0H8S) |
| 9.19 (4.38–19.28) | Never smokers adjusted for alcohol |
| India | 1982–1992 | Case–control | Tobacco quid chewing | Yes/No | Oral cancer | 5.80(3.60–9.34) | Adjusted for smoking | Selection\*\*\*Comparability\*Exposure\* | [[38]](https://paperpile.com/c/bdxIpu/9fZsP) |
| Pharyngeal cancer | 1.20(0.80–1.80) |
| Lung cancer | 0.70(0.40–1.22) |
| India | Not clear | Case–control | Chewing tobacco | No/No | Oral cancer | 10.75 (6.58–17.56) | Exclusive SLT users | Selection\*\*Comparability\*Exposure0 | [[39]](https://paperpile.com/c/bdxIpu/Iloxi) |
| India | 1990–1997 | Cohort | Current SLT users | No/No | Oral cancer | 5.50 (3.30–9.17) | Exclusive SLT users | Selection\*\*\*\*Comparability\*Outcome\*\* | [[40]](https://paperpile.com/c/bdxIpu/oeuTx) |
| Former SLT users | 9.20 (4.60–18.40) |
| India | 1990–1997 | Cohort | Current SLT user | Yes/Yes | Oral cancer | 2.40(1.70–3.39) | Adjusted for smoking and alcohol | Selection\*\*\*\*Comparability\*Outcome\*\*\* | [[41]](https://paperpile.com/c/bdxIpu/NNuZN) |
| Former SLT users | 2.10(1.30–3.39) |
| India | May, 2005 | Case–control | Ever SLT users | No/No | Oral cancer | 4.23 (3.11–5.75) | Exclusive SLT users | Selection\*\*\*Comparability\*\*Exposure0 | [[42]](https://paperpile.com/c/bdxIpu/tDOdd) |
| Pharyngeal cancer | 2.42 (1.74–3.37) |
| Laryngeal cancer | 2.80(2.07–3.79) |
| Oesophageal cancer | 1.55 (1.15–2.07) |
| India | 1968 | Case–control | Tobacco | Yes/No | Oral cancer | 4.63 (3.50–6.14) | Exclusive chewers and non-chewers data available | Selection\*\*\*Comparability\*\*Exposure0 | [[43]](https://paperpile.com/c/bdxIpu/4sMZh) |
| Pharyngeal cancer | 3.09 (2.31–4.13) |
| Laryngeal cancer | 2.29 (1.72–3.05) |
| Oesophageal cancer | 3.82(2.84–5.13) |
| India | 2005–2006 | Case–control | Tobacco flakes | Yes/Yes | Oral cancer | 7.60(4.90–11.79) | Adjusted for smoking and alcohol | Selection\*\*\*\*Comparability\*\*Exposure\* | [[44]](https://paperpile.com/c/bdxIpu/4OoC9) |
| Gutkha | 12.70(7.00–23.04) |
| Mishiri | 3.00(1.90–4.74) |
| India | Not clear | Case–control | Chewing tobacco | Yes/Yes | Oral cancer | 5.00(3.60–6.94) | Adjusted for smoking and alcohol | Selection\*\*\*\*Comparability\*Exposure\* | [[45]](https://paperpile.com/c/bdxIpu/XZBqG) |
| India | 1982–1984 | Case–control | Chewing tobacco | Yes/No | Oral cancer | 10.20(2.60–40.02) | Adjusted for smoking | Selection\*\*\*Comparability\*\*Exposure\* | [[46]](https://paperpile.com/c/bdxIpu/BwPWr) |
| India | 1980–1984 | Case–control | SLT users | No/No | Oral cancer | 1.99 (1.41–2.81) | Exclusive SLT users | Selection\*\*Comparability0Exposure\* | [[47]](https://paperpile.com/c/bdxIpu/oj03T) |
| India | 1952–1954 | Case–control | Chewing tobacco | No/No | Oral cancer | 4.85 (2.32–10.14) | Exclusive SLT users | Selection\*\*\*Comparability\*\*Exposure0 | [[48]](https://paperpile.com/c/bdxIpu/kil4V) |
| Pharyngeal cancer | 2.02 (0.94–4.33) |
| Laryngeal cancer | 0.76 (0.37–1.56) |
| India | 1983–1984 | Case–control | Snuff (males only) | Yes/Yes | Oral cancer | 2.93 (0.98–8.76) | Adjusted for smoking and alcohol; adjusted effect size is only among males | Selection\*\*\*Comparability0Exposure\* | [[49]](https://paperpile.com/c/bdxIpu/vXidK) |
| India | Not given | Case–control | Tobacco chewing | Yes/Yes | Oropharyngeal cancer | 7.98 (4.11–13.58)b | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure0 | [[50]](https://paperpile.com/c/bdxIpu/8ICak) |
| India | 1991–2003 | Case–control | Chewing tobacco | No/No | Oral cancer | 5.88 (3.66–7.93) | Exclusive SLT users | Selection\*\*\*\*Comparability\*\*Exposure\*\* | [[51]](https://paperpile.com/c/bdxIpu/1Mr11) |
| India | 1950–1962 | Case–control | Tobacco with or without paan or lime | Yes/No | Oral and oropharyngeal cancer | 41.90 (34.20–51.33) | Exclusive chewer data available; data of habit was not available for the whole cohort | Selection\*\*Comparability\*\*Exposure0 | [[52]](https://paperpile.com/c/bdxIpu/Y3Nat) |
| Pakistan | 1996–1998 | Case–control | Naswar | Yes/Yes | Oral cancer | 9.53 (1.73–52.50) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\* | [[53]](https://paperpile.com/c/bdxIpu/oMNU2) |
| Paan with tobacco | 8.42 (2.31–30.69) |
| Sweden | 1973–2002 | Cohort | Snus | Yes/Yes | Oral and pharyngeal cancer combined | 3.10 (1.50–6.41) | Adjusted for smoking and alcohol | Selection\*\*Comparability\*\*Outcome\*\*\* | [[54]](https://paperpile.com/c/bdxIpu/C52Ku) |
| India | 1993–1999 | Case–control | Chewing tobacco | Yes/Yes | Oral cancer | 5.05 (4.26–5.99) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\* | [[55]](https://paperpile.com/c/bdxIpu/IlcrJ) |
| Pharyngeal cancer | 1.83 (1.43–2.34) |
| Oesophageal cancer | 2.06 (1.62–2.62) |
| Norway | 1966–2001 | Cohort | Chewing tobacco plus oral snuff | No/No | Oral cancer | 1.10 (0.50–2.42) | Adjusted for smoking, might be confounded by alcohol use | Selection\*\*\*Comparability\*Outcome\*\*\* | [[56]](https://paperpile.com/c/bdxIpu/REEoc) |
| Oesophageal cancer | 1.40(0.61–3.21) |
| Pancreatic cancer | 1.67 (1.12–2.49) |
| Lung cancer | 0.80 (0.61–1.05) |
| Sweden | 1988–1991 | Case–control | Oral snuff | Yes/Yes | Oral cancer | 1.40(0.80–2.45) | Adjusted for smoking and alcohol | Selection\*\*Comparability\*\*Exposure\* | [[57]](https://paperpile.com/c/bdxIpu/EoXty) |
| Laryngeal cancer | 0.90(0.50–1.62) |
| Oesophageal cancer | 1.20(0.70–2.06) |
| Pharyngeal cancer | 0.70(0.40–1.22) |
| Sweden | 1969–1992 | Cohort | Snus | No/No | Oral cancer | 0.80(0.40–1.60) | Exclusive SLT users | Selection\*\*\*Comparability\*Outcome\*\*\* | [[58]](https://paperpile.com/c/bdxIpu/ZWqaK) |
| Lung cancer | 0.80(0.50–1.28) |
| Pancreatic cancer | 2.00 (1.20–3.33) |
| Sweden | 2000–2004 | Case–control | Oral snuff | Yes/Yes | Oral cancer | 0.70 (0.30–1.63) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\*\* | [[59]](https://paperpile.com/c/bdxIpu/4dFrQ) |
| Sweden | 1980–1989 | Case–control | Oral snuff | Yes/Yes | Oral cancer | 0.80(0.50–1.28) | Adjusted for smoking and alcohol | Selection\*\*Comparability\*\*Exposure\*\*\* | [[60]](https://paperpile.com/c/bdxIpu/1Rqi8) |
| USA | 1972–1983 | Case–control | Oral snuff | Yes/Yes | Oral cancer | 0.80(0.40–1.60) | Not clear if adjusted for smoking and alcohol | Selection\*\*Comparability0Exposure\* | [[61]](https://paperpile.com/c/bdxIpu/G8sHT) |
| Chewing tobacco | 1.00(0.70–1.43) |
| USA | Not given | Case–control | SLT use | Yes/Yes | Oral cancer | 0.90 (0.38–2.13) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\* | [[62]](https://paperpile.com/c/bdxIpu/dl1jG) |
| Pharyngeal cancer | 1.59 (0.84–3.01) |
| Laryngeal cancer | 0.67 (0.19–2.36) |
| India | 2001–2004 | Case–control | Chewing tobacco | No/No | Pharyngeal cancer | 3.18 (1.92–5.27) | Exclusive SLT users | Selection\*\*\*Comparability\*\*Exposure\* | [[63]](https://paperpile.com/c/bdxIpu/U34lk) |
| Laryngeal cancer | 0.95 (0.52–1.74) |
| Pakistan | 1998–2002 | Case–control | Snuff dipping | No/No | Oesophageal cancer | 4.10(1.30–12.93) | Adjusted for areca nut | Selection\*\*\*Comparability\*\*Exposure\*\* | [[64]](https://paperpile.com/c/bdxIpu/lBFNX) |
| Quid with tobacco | 14.20(6.40–31.50) |
| India | 2008–2012 | Case–control | Nass chewing | No/No | Oesophageal cancer | 2.88 (2.06–4.03) | Exclusive SLT users | Selection\*\*\*Comparability\*\*Exposure\*\* | [[65]](https://paperpile.com/c/bdxIpu/xARyY) |
| Gutkha chewing | 2.87 (0.87–9.47) |
| India | 2007–2011 | Case–control | Oral snuff | Yes/Yes | Oesophageal cancer | 3.86 (2.46–6.06) | Adjusted for smoking and alcohol | Selection\*\*Comparability\*\*Exposure\* | [[66]](https://paperpile.com/c/bdxIpu/iCvu2) |
| India | 2011–2012 | Case–control | Chewing tobacco | Yes/Yes | Oesophageal cancer | 2.63 (1.53–4.52) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\* | [[67]](https://paperpile.com/c/bdxIpu/hkSgX) |
| Sweden | 1995–1997 | Case–control | Oral snuff | Yes/Yes | Oesophageal – Adeno- carcinoma | 1.20(0.70–2.06) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*\*Exposure\* | [[68]](https://paperpile.com/c/bdxIpu/n4IGH) |
| Squamous cell carcinoma | 1.40(0.90–2.18) |
| Sweden | 1969–1993 | Cohort | Oral snuff | Yes/No | Oesophageal – Adeno-Carcinoma | 1.30(0.80–2.11) | Adjusted for smoking | Selection\*\*Comparability\*Outcome\*\* | [[69]](https://paperpile.com/c/bdxIpu/C9Ssl) |
| Squamous cell carcinoma | 1.20(0.80–1.80) |
| Sweden | 1974–1985 | Cohort | SLT users | No/NA | Lung cancer | 0.90 (0.20– 4.05) | Adjusted for age, region of origin | Selection\*\*\*Comparability\*Outcome\*\* | [[70]](https://paperpile.com/c/bdxIpu/w9dAP) |
| Morocco | 1996–1998 | Case–control | SLT users | Yes/No | Lung cancer | 1.05 (0.28–3.94) | Adjusted for smoking | Selection\*\*Comparability\*\*Exposure\*\* | [[71]](https://paperpile.com/c/bdxIpu/cvBlL)  |
| USA | 1977–1984 | Case–control | SLT users | Yes/No | Oesophageal cancer | 1.20(0.10–14.40) | Adjusted for smoking | Selection\*\*\*Comparability\*\*Exposure\*\* | [[72]](https://paperpile.com/c/bdxIpu/AfmcU) |
| USA | 1986–1989 | Case–control | SLT users | Yes/No | Pancreatic cancer | 1.40(0.50–3.92) | Adjusted for smoking | Selection\*\*\*Comparability\*Exposure\*\* | [[73]](https://paperpile.com/c/bdxIpu/qhQWD)  |
| USA | 2000–2006 | Case–control | Chewing tobacco | Yes/Yes | Pancreatic cancer | 0.60 (0.30–1.20) | Adjusted for smoking and alcohol | Selection\*\*\*\*Comparability\*\*Exposure\* | [[74]](https://paperpile.com/c/bdxIpu/IW9dZ)  |
| Oral snuff | 0.50(0.10–2.50) |
| Pakistan | 2014–2015 | Case–control | Ever use of naswar | Yes/Yes | Oral cancer | 21.20(8.40–53.8) | Adjusted for smoking; restricted control for alcohol due to cultural sensitivity | Selection\*\*\*\*Comparability\*\*Exposure\*\*\* | [[75]](https://paperpile.com/c/bdxIpu/5LY8V) |
| India | March–July, 2013  | Case–control | Gutkha | Yes/Yes | Oral cancer | 5.10 (2.00–10.30) | Adjusted for smoking and alcohol | Selection\*\*\*Comparability\*Exposure\*\* | [[76]](https://paperpile.com/c/bdxIpu/sUX7V) |
| Chewing tobacco | 6.00 (2.30–15.70) |
| Supari with tobacco | 11.40 (3.40–38.20) |
| Quid with tobacco | 6.40(2.60–15.50) |
| Pakistan | 1996–1998 | Case–control | Quid with tobacco | Yes/Yes | Oral cancer | 15.68 (3.00–54.90) | Adjusted for smoking and alcohol | Selection\*\*Comparability\*Exposure\*\*\* | [[77]](https://paperpile.com/c/bdxIpu/KmkBV) |
| **CARDIOVASCULAR DISEASES (ischaemic heart disease and stroke)** |
| 52 countries | 1999–2003 | Case–control | Chewing tobacco | Yes/Yes | Myocardial infarction | 1.57 (1.24–1.99) | Adjusted for smoking, diet, diabetes, abdominal obesity, exercise, hypertension | Selection\*\*\*\*Comparability\*\*Exposure\* | [[35]](https://paperpile.com/c/bdxIpu/HVW9h) |
| Pakistan | 2005–2011 | Case–control | Dippers (Naswar) | No/NA | Myocardial infarction | 1.46(1.21–1.78) | Adjusted for age, gender, region, ethnicity, diet, socioeconomic status | Selection\*\*\*\*Comparability\*\*Exposure\*\* | [[78]](https://paperpile.com/c/bdxIpu/uFggT)  |
| Chewers (Paan/ Supari/ Gutkha) | 1.71 (1.46–2.00) |
| Bangladesh | 2006–2007 | Case–control | Ever SLT users | Yes/NA | Myocardial infarction, Angina pectoris | 2.80 (1.10–7.30) | Adjusted for age, gender, smoking, hypertension | Selection\*\* Comparability\*\* Exposure\*\* | [[79]](https://paperpile.com/c/bdxIpu/4teMq) |
| Bangladesh | 2010 | Case–control | Ever SLT users | No/NA | Myocardial infarction, Angina pectoris | 0.77 (0.52–1.13) | Adjusted for age, gender, area of residence, hypertension, diabetes, stress | Selection\*\*\* Comparability\*\* Exposure\* | [[80]](https://paperpile.com/c/bdxIpu/8mHbM) |
| India | 2013 | Case–control | Current SLT users | Yes/Yes | Stroke  | 1.50 (0.80-2.79) | Adjusted for age, smoking, alcohol, diabetes, hypertension | Selection\*\* Comparability\*\* Exposure\* | [[81]](https://paperpile.com/c/bdxIpu/3SK2Z) |
| Sweden  | 1989–1991 | Case–control | Current snuff users | No/NA | Myocardial infarction | 0.89 (0.62-1.29) | Adjusted for age | Selection\*\*\*\* Comparability\*\* Exposure\* | [[82]](https://paperpile.com/c/bdxIpu/y91Z6) |
| Sweden  | 1991–1993 | Case–control | Current snuff users | No/NA | Myocardial infarction | 0.58 (0.35-0.94) | Adjusted for heredity, education, marital status, hypertension, diabetes, cholesterol | Selection\*\*\*\* Comparability\*\* Exposure\*\* | [[83]](https://paperpile.com/c/bdxIpu/eaylW) |
| Sweden  | 1985–2000  | Case–control  | Current snuff users | No/NA  | Stroke  | 0.87 (0.41–1.83)  | Adjusted for education, marital status, diabetes, hypertension, cholesterol | Selection\*\*\*\* Comparability\*\* Exposure\*\* | [[84]](https://paperpile.com/c/bdxIpu/OhHQF) |
| Sweden  | 1998–2005 | Case–control | Current snuff users  | No/NA | Myocardial infarction | 0.73 (0.35–1.50)  | Adjusted for age, hospital catchment area | Selection\*\*\* Comparability\*\* Exposure\*\* | [[85]](https://paperpile.com/c/bdxIpu/KlvIw) |
| Former snuff users | 1.20 (0.46–3.10) |
| Sweden | 1988-2003 | Cohort | Current use of snuff | No/NA | Ischaemic heart disease  | 0.77 (0.51-1.15)  | Adjusted for age, socioeconomic status, residential area, self-reported health, longstanding illnesses, physical activity | Selection\*\*\* Comparability\*\* Outcome\*\*\* | [[86]](https://paperpile.com/c/bdxIpu/rpUeq) |
| Stroke | 1.07 (0.65-1.77) |
| Sweden | 1978–2004 | Cohort | Ever snuff users | No/NA | Myocardial infarction | 0.99 (0.90–1.10) | Adjusted for age, BMI, region of residence | Selection\*\* Comparability\*\* Outcome\*\*\* | [[87]](https://paperpile.com/c/bdxIpu/Tqkqz) |
| Sweden  | 1985–1999  | Case–control  | Current snuff users  | No/NA  | Myocardial infarction  | 0.82 (0.46–1.43)  | Adjusted for BMI, leisure time, physical activity, education, cholesterol | Selection\*\*\*\* Comparability\*\* Exposure\* | [[88]](https://paperpile.com/c/bdxIpu/kcojj) |
| Former snuff users | 0.66 (0.32–1.34) |
| Sweden  | 1978–2003  | Cohort  | Ever snuff users | No/NA  | Stroke  | 1.02 (0.92–1.13)  | Adjusted for age, BMI, region of residence | Selection\*\* Comparability\*\* Outcome\*\*\* | [[89]](https://paperpile.com/c/bdxIpu/CPdVM) |
| Sweden  | 1998–2005  | Cohort  | Current snuff users  | No/NA  | Ischaemic heart disease  | 0.85 (0.51–1.42)  | Adjusted for age, hypertension, diabetes, cholesterol | Selection\*\*\* Comparability\*\* Outcome\* | [[90]](https://paperpile.com/c/bdxIpu/0k18N) |
| Former snuff users | 1.07 (0.56–2.04) |
| Current snuff users | Stroke | 1.18 (0.67–2.08)  |
| Former snuff users | 1.35(0.65–2.82) |
| Sweden  | 1991–2004  | Cohort  | Current snuff users | No/NA  | Myocardial infarction  | 0.75 (0.30–1.87)  | Adjusted for age, marital status, occupation, diabetes, BMI, hypertension, physical activity | Selection\*\*\* Comparability\*\* Outcome\*\* | [[91]](https://paperpile.com/c/bdxIpu/FaJPA) |
| Stroke | 0.59 (0.20–1.50) |

1. *BMI* body mass index, *NA* not applicable, *NOS* Newcastle-Ottawa Scale, *SLT* smokeless tobacco
2. aNOS for assessing the quality of non-randomised studies in meta-analyses based on selection, comparability, and exposure/outcome. Number of stars (\*) indicates the number of criteria met for each of these three categories
3. bEffect sizes are for oral and pharyngeal cancers combined and were included in the meta-analysis for oral cancer only